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

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Commercial in confidence data

NB. Data and analysis supplied that are commercial in confidence/academic in confidence, and any further discussion of this material, are underlined in the full version of this report, and have been deleted from this version. The text is annotated to show where these deletions occur.

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Aim

The aim of this systematic review and economic evaluation is to assess the clinical-effectiveness and cost-effectiveness of pegylated and non-pegylated interferon alfa and ribavirin for the treatment of adults with histologically mild chronic hepatitis C infection (HCV). This independent assessment will be used by the National Institute for Health and Clinical Excellence (NICE) to issue guidance to the health service in England and Wales.

Epidemiology and background

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

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

Currently, patients who present with histologically mild HCV are monitored with repeat biopsies every few years. Anti-viral treatment is only initiated when fibrosis and inflammation levels are indicative of moderate to severe disease. NICE has previously issued guidance on the use of anti-viral treatment in moderate to severe HCV. In 2000 guidance was published on the use of 'conventional' non-pegylated interferon alfa 2a and 2b (IFN) in combination with ribavirin (RBV). In 2003 the guidance was updated to include pegylated interferon alfa 2a and 2b (PEG), again with RBV. Randomised controlled trials (RCTs) of PEG + RBV in patients with moderate to severe HCV report that between 54% to 61% of patients can be successfully treated, depending on regimen. In sub-groups of patients with favourable genotypes 2 and 3, sustained virological response rates are in excess of 80%.

Anti-viral treatment in patients with histologically mild HCV has not been assessed at a policy level before. This assessment therefore compares treatment of patients early on, when liver disease is mild, with a policy of 'watchful waiting' whereby treatment is offered when the infection has advanced.

Methods

We conducted a systematic review and economic evaluation. A sensitive search strategy was designed and applied to a number of electronic bibliographic databases (e.g. Medline, Cochrane, NHS Economic Evaluation Database). Bibliographies of retrieved papers were screened, where possible, for relevant studies. Manufacturer and sponsor submissions to NICE were also searched.

To be included in the clinical-effectiveness component of the review, studies had to report an RCT, or systematic review of RCTs. Studies had to report evaluation of pegylated interferon alfa 2a or 2b either as dual therapy with ribavirin, or monotherapy for those unable to tolerate ribavirin. Studies of non-pegylated interferon alfa 2a or 2b with ribavirin were also eligible. Only studies reporting ≥70% of adult patients at baseline with histologically mild HCV were eligible. Outcomes include sustained viral, biochemical and histological response rates; health related quality of life, adverse events, and costs per Quality Adjusted Life Year (QALY). The trials were reviewed in a narrative synthesis, but meta-analysis was not undertaken due to heterogeneity in the interventions and comparators evaluated.

To be included in the cost-effectiveness review studies had to report a full economic evaluation of the cost-effectiveness of (pegylated or non-pegylated) interferon treatment for adults with mild chronic hepatitis C compared to treatment once the disease has progressed to moderate or severe HCV, or compared to best supportive care.

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

- Early anti-viral treatment, for all patients with mild chronic HCV,
- Delayed anti-viral treatment (watchful waiting), provided only to those patients who progress to moderate to severe disease
- No anti-viral treatment, but provision of best supportive care.

Findings are presented in terms of incremental cost per QALY gained. Watchful waiting, the current recommended strategy, is compared to best supportive care. Early treatment, the proposed strategy, is compared to watchful waiting (with the same agent. E.g. early treatment with IFN + RBV is compared to watchful waiting with IFN + RBV).

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

Results – clinical-effectiveness

A total of 2863 references to studies of the clinical effectiveness of treatments for HCV were screened. Of these 21 were included in this report:

- Eight of the 21 were RCTs of anti-viral treatment in patients with histologically mild HCV. These were included in the primary analysis.
- Two were RCTs of monotherapy in mild HCV patients.
- Eleven were studies which reported within-trial effects of anti-viral treatment in patients with mild HCV and patients with moderate to advanced disease. These were included in this report as context.

Of the eight RCTs in the primary analysis, three evaluated pegylated interferon, PEG 2a in combination with RBV. Two of these compared different regimens of PEG + RBV, whilst the third compared PEG + RBV with IFN + RBV (in HIV/HCV co-infected patients). Five of the eight RCTs evaluated IFN in combination with RBV, compared to either IFN monotherapy or no treatment. All trials were based on middle-aged (mean age range 36-49 years), adult patients. The majority of trials included patients who were treatment naïve and without co-morbidities (e.g. haemophilia) or co-infection (e.g. hepatitis B or HIV). Only one study included patients who were co-infected with HCV and HIV. Treatment lasted from 24-48 weeks, and follow-up was 24 weeks post treatment. In general, the RCTs were of good methodological quality, although reporting of randomisation methods and the blinding of assessors was generally poor.

Virological response

In two PEG RCTs, treatment for 48 weeks with PEG 2a + RBV was significantly more effective than the same treatment for 24 weeks (SVR at 48 weeks range 52-63%, $p \leq 0.002$). In the third PEG trial, treatment with PEG + RBV resulted in a significantly higher SVR than treatment with IFN + RBV. All five IFN trials reported significantly higher SVR rates with IFN + RBV (range 33-69%) compared to either IFN monotherapy (range 18-23%) or no treatment (zero response).

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

In the three PEG 2a + RBV trials:

- Higher SVRs were seen in genotype non-1 patients compared with genotype 1 patients, regardless of length of therapy.
- Genotype 1 patients treated with PEG + RBV for 48 weeks had significantly higher response rates than patients on the same therapy for only 24 weeks. Treatment duration did not have a significant effect on virologic response for patients with genotype 2 or 3.
- Patients with genotype 1 and low baseline viral load treated for 48 weeks had significantly higher SVRs than genotype 1 patients with high baseline viral load. In patients with genotypes 2 or 3, there was little additional benefit in extending treatment to 48 weeks, regardless of viral load.

- Patients with genotype non-1 aged 40 years or younger had a 26% higher probability of achieving an SVR compared with patients who were older than 40 years (RR, 1.26; 95% CI, 1.02-1.55).
- One trial reported results for sub-groups of patients with varying stages of fibrosis. In general, SVR's were higher in patients with mild HCV (fibrosis score F0 or F1, scored using the Knodell system) compared to those with bridging fibrosis/cirrhosis (F3 or F4) (it was not reported whether this difference was statistically significant). In mild HCV patients with genotypes 2 or 3, there was a small net loss of benefit when treatment was extended to 48 weeks.

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

In the five IFN + RBV trials:

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

Health related quality of life

Published data on health-related quality of life (HRQOL) was only available for one of the RCTs (comparing IFN + RBV versus no treatment) using the Short Form-36 (SF-36).

- At 24 weeks after the end of treatment, there was a mean improvement from baseline in seven out of eight of the SF-36 subscales in patients with an SVR. Significant improvement was reported for bodily pain, general health and vitality ($p=0.01$ compared with controls).
- Mean improvements were also observed in five of eight subscales in treatment failures (non-responders and relapsed patients).

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

Adverse events

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

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

Monotherapy

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

Sub-groups of mild and moderate to severe patients

Of the 11 studies in this category:

- Three evaluated PEG, and the remaining nine evaluated IFN. Studies ranged from international multi-centre RCTs to small scale RCTs. Doses and regimens varied considerably.
- In general, higher SVRs were observed for patients classified as having mild fibrosis at baseline, compared to those classified as advanced fibrosis/cirrhosis (n= 7 studies). However, this was only statistically significant in one study, with the remaining studies not reporting any significance values.
- In five studies no or minimal fibrosis was significantly and independently associated with SVR, as assessed in multivariate logistic regression analyses.

Results – cost-effectiveness

Systematic review of cost-effectiveness studies

A total of 316 cost-effectiveness publications were identified. Sixty five of these were full economic evaluations. Six of these were included, of which only one evaluated PEG. All six reported Markov models, four of which reported various iterations of a common model. All studies indicate that anti-viral treatment is effective in terms of improved life expectancy and quality-adjusted life expectancy compared to no anti-viral treatment. Those studies which have compared the effects of immediate versus delayed treatment (i.e. watchful waiting) have generally shown that early intervention

is cost-effective for genotype non-1 patients. Early treatment is less likely to be cost-effective for genotype 1 patients.

SHTAC cost-effectiveness analysis

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

- Watchful waiting with IFN + RBV versus best supportive care = £ 3,097 to £6,585
- Early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £5,043 to £8,092
- Watchful waiting with PEG 2a + RBV versus best supportive care = £3,052
- Early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £5,900
- Watchful waiting with PEG 2b + RBV versus best supportive care = £ 2,534
- Early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £ 5,774

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

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

- Watchful waiting with IFN + RBV versus best supportive care = £7,766 to £19,022
- Early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £ 9,021 to £15,954
- Watchful waiting with PEG 2a + RBV versus best supportive care = £6,867
- Early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £ 10,270
- Watchful waiting with PEG 2b + RBV versus best supportive care = £4,670
- Early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £8,324

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

- Watchful waiting with IFN + RBV versus best supportive care = £1,558 to £3,105
- Early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £3,528 to £ 5,050
- Watchful waiting with PEG 2a + RBV versus best supportive care = £1,326

- Early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £3,725
- Watchful waiting with PEG 2b + RBV versus best supportive care = £1,387
- Early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £4,320

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

The cost-effectiveness of applying early stopping rules for patients not demonstrating a viral response after 12 weeks treatment was also modelled. Costs for the watchful waiting strategies typically reduce by around £700 and for early treatment fall by around £3,000. There is less of an impact in terms of QALYs. Early stopping strategies are also modelled according to genotype. The order of reduction in lifetime costs is slightly lower for genotype 1 patients than for the mixed cohort of genotype 1 and genotype non-1. The greatest reductions in cost are realised by applying a 24 week duration of treatment to genotype non-1 patients. Costs for watchful waiting reduce by approximately £1,000 and for early treatment by approximately £4,000.

Uncertainty in model structure and key input parameters was explored in univariate sensitivity analyses:

- A number of scenarios to explore differences in SVR for non-pegylated interferon alfa compared to pegylated interferon alfa were conducted.
  - The SVRs for pegylated interferon alfa used in the model were replaced by lower values. These were based on the SVR reported for non-pegylated interferon in the UK Mild HCV trial and odds ratios for SVR with pegylated interferon alfa-2b and non-pegylated interferon alfa taken from a large multi-centre RCT. The incremental cost-effectiveness ratios for watchful waiting and early treatment with pegylated interferon alfa are much greater than under the base case. The incremental cost-effectiveness ratio for early treatment with pegylated interferon alfa-2a compared to non-pegylated interferon is £23,252. This contrasts to a value of approximately £2,000 for the base case with the low SVR for non-pegylated interferon.
  - The second scenario used a similar approach, but increased the difference between the SVR for pegylated interferon and non-pegylated interferon, based on outcomes for patients receiving higher doses of ribavirin. The ICERs were lower than for the previous analysis but were still greater than for the base case.
- Changing the discount rates (from 6% to 3.5%) has a greater effect on the watchful waiting strategy than on early treatment. This has the effect of increasing the impact of costs borne in the future.
- Increasing the disease progression rates increases the cost-effectiveness of all strategies.
- Varying the health state utilities used in the model has a different impact between the early and delayed treatment strategies. There is little impact on the ICERs for the delayed treatment strategies, but an increase for the early treatment strategies.

The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis. Early treatment with pegylated

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

Conclusion

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

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.
ALT	Alanine aminotransferase. An enzyme that indicates liver inflammation.
Ascites	Large accumulation of fluid in the abdominal cavity
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	The phase of progressive disease whereby the liver is no longer able to account for damage caused by scarring (fibrosis) and inflammation. Ascites, variceal haemorrhage and hepatic encephalopathy are complications that can occur during decompensation.
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
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.
Histological Response	Defined as a decrease of at least 2 points in the total score on the Ishak Histological Activity Index, where a score of 0 indicates no inflammatory changes and no fibrosis and a score of 22 indicates multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation, and cirrhosis.
HIV	Human Immunodeficiency Virus recognised as the agent that induces AIDS
HRQOL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio

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
interferon	There are several forms of interferon. Unless otherwise stated it is used in this report to refer to interferon alfa.
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 health and clinical Excellence
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	Out-patient
OR	Odds ratio
PSA	Probabilistic sensitivity analyses
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)
SUHT	Southampton University Hospitals Trust (SUHT)
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

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

2 BACKGROUND

2.1 Description of underlying health problem

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

2.1.1 Background

Hepatitis C, first described in 1989, is a slowly advancing, insidious, disease arising from transmission of the blood-borne Hepatitis C Virus (HCV). The symptoms vary according to the severity of infection, with worsening liver damage a feature of disease progression. Acute infection is cleared by around 20% of patients, with the remainder developing chronic HCV. In the early stages of chronic infection symptoms are generally mild although there may be a reduction in quality of life (e.g. tiredness, malaise, cognitive impairment). As the disease progresses, liver injury gradually occurs, in terms of tissue scaring (fibrosis) and inflammation, although this may not be noticed by the individual. Around 30% of people will become cirrhotic within 20 years. In worst cases, cirrhosis may progress to decompensated liver disease where liver function can no longer be sustained because of fibrosis and inflammation. Decompensation is characterised by ascities, variceal bleeding, and hepatic encephalopathy. Such patients will require liver transplant to survive, although the transplanted liver is highly likely to become infected and they will require prophylaxis and continued anti-viral treatment. A small proportion of people (1-4%) will develop hepatocellular carcinoma. Factors associated with accelerated disease progression include male gender, older age at infection, and excessive alcohol use (see Section 2.1.4 for further detail on progression rates and associated factors).

The most common source of transmission in the UK unsafe drug use, which accounts for around 90% cases. Many of these infections can be attributed to current or recent

injecting drug use. However, some people may have become infected as a result of transient, experimental, phases of drug use in their earlier lives. The latter in particular may be under-reported due to poor recall (particularly if injecting took place several decades ago), as well as reporting bias (i.e. not wishing to disclose prior drug use due to social stigma). Some people, particularly immigrants, may have been infected abroad due to re-use of syringes and needles for therapeutic injections by medical personnel (e.g. Romania, where 4.5% are chronically infected with HCV). The World Health Organisation supported Safe Injection Global Network (SIGN) estimate that each year re-use of dirty injection equipment causes an estimated 2.3 - 4.7 million infections with HCV.

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

There are six major genotypes, and several sub-types of HCV, 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 most common 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%). Type 3 is most common in injecting drug users[1;4], and type 1 in patients with haemophilia, infected via contaminated blood products[1]. As will be reported in Section 4.1.2, genotype is a key predictor of the effectiveness of anti-viral treatment. Patients with genotypes 1, 4 and 5 tend to respond less well than patients with genotypes 2 and 3.

2.1.2 Defining Mild Hepatitis C

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

2.1.2.1 Use of biopsy

Liver biopsy is commonly performed to ascertain the severity of HCV and to enable the clinician and the patient to agree the best course of action. The Royal College of Physicians and the British Society of Gastroenterology in their clinical guidelines

(2001)[5] state that the decision to offer treatment should be influenced by histological findings. They recommend that treatment can be reasonably withheld in patients with mild disease on liver biopsy but that these patients should be reviewed every 6 months, with repeat liver biopsy every 2-3 years or if there is a significant change in liver function tests (i.e. 2-3 times normal levels). If the biopsy shows evidence of progressive liver disease, treatment should then be considered. The guidelines also recommend that liver biopsy should be performed in all patients found to be viraemic, whether or not liver function tests are abnormal (e.g. ALT).

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

Opposition to the use of biopsy, stems from a number of arguments. Firstly, biopsy can be a painful procedure, causing a great deal of discomfort to the patient. It is suggested that this might act as a barrier for patients coming forward for investigation and treatment, and that it contributes towards the relatively low number of patients treated in the UK[7;8]. Wider availability and acceptance of non-invasive liver tests might encourage more people to undergo assessment, and increase the current low uptake of treatment (see Section 2.2.2).

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

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

Fourthly, histopathological analysis of biopsy samples can be subject to poor inter-observer reliability, although this may be an idiosyncrasy of biopsy classification systems, rather than the biopsy itself (see Section 2.1.2.2). Some histopathologists suggest it is misleading to apply numerical scores to subjective interpretations of liver damage.

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

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

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

- The most appropriate timing of therapy. The extent of disease progression (e.g. fibrosis) will guide decisions as to whether anti-viral treatment should be commenced immediately or whether a period of watchful waiting is necessary. This will enable patients to plan ahead with the knowledge that at some point they may have to undergo treatment, which may impact on their domestic circumstances and their ability to work[15;16]. This may apply particularly to those with genoptypes other than 2 or 3. In those with 2 or 3, treatment with existing combination therapy is very successful. Those with other genotypes such as 1, but who do not at present have moderate or severe liver damage, might prefer to wait for more effective combinations of drugs to come along.
- Expectations of the outcome of therapy. The degree of fibrosis has been shown to be an independent predictor of the response to anti-viral treatment[17;18]. The lower the degree the higher the sustained viral response.
- The presence of absence of steatosis (fatty liver). A recent UK study found this to be present in 50% of liver biopsies[19], and a review of 22 recent studies reported prevalence of between 40% and 70%. It's significance in the advancement of HCV is underpinned by studies such as Fartoux and colleagues (2005)[20] who found it to be an independent factor predictive of progression of fibrosis.
- Other potential confounding liver diseases such as steatohepatitis and haemochromatosis, or iron accumulation which can impact on prognosis[15].

Replacing liver biopsy requires validated and effective alternative methods to gauge the extent of HCV related liver damage. Non-invasive biochemical tests are in development, although some clinicians may not yet be convinced of their advantage over biopsy, and the tests may not yet be readily available in the UK (see Section 2.1.2.4).

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

2.1.2.2 Biopsy classification systems

The severity of HCV infection is usually determined by classification of liver biopsy samples as being mild, moderate or severe. Two components of a biopsy sample are

used to determine severity. The first is fibrosis, the level of scarring that has occurred in the liver. The extent of fibrosis is expressed as a 'stage' which determines the position of the patient on the continuum of disease progression between its initiation (no fibrosis), and its final stage (decompensated cirrhosis). The second is necro-inflammation of the liver. This is expressed in terms of the 'grade' of disease activity, which is the rate at which the disease stage is changing. The inflammatory activity increases and decreases as the disease flares and subsides, or may remain constant.

There are a number of commonly used systems for classifying liver biopsy samples. Some share common characteristics and are derived from the same systems. Desmet (2003)[21] provides an overview of the many different scoring systems available. The three most commonly cited are the Knodell Histological Activity index (HAI), 1981; The Ishak revised Histological Activity index (HAI) 1995, and the METAVIR system. (see Appendix 1 for further details).

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

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

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

[Academic-in-confidence item on comparability of scoring systems removed]

2.1.2.3 Staging fibrosis

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

Given the evolutionary development of biopsy classification systems over the last 25 years, and the fact that a number of different systems have been used in the clinical trial literature, the question of their comparability arises. For example, how does an Ishak fibrosis score of 1 compare with a Metavir fibrosis score of 2? Kleiner (2005)[15] compares five commonly used staging systems for chronic hepatitis C (see Table 1). As clinical guidelines[5] suggest that mild HCV is defined by an Ishak fibrosis score of less than or equal to 2/6, it can be determined that an Ishak 2 is comparable with less than or equal to 2 on the Batts and Ludwig (1995) system, and less than or equal to 1 on the Metavir, Scheuer and Knodell systems. A prospective biopsy study conducted at St. Mary's Hospital, London confirms this, demonstrating a significant correlation between biopsies scored with both the Ishak and Metavir systems ($r=0.96$, $p<0.00001$)[26].

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

Kleiner's thresholds of disease severity concurs with Dienstag (2002)[16] who reports the consensus to be the presence of septal/bridging fibrosis as the traditional indication for anti-viral therapy (i.e. Ishak fibrosis score ≥ 3, Metavir fibrosis score ≥ 2). Patients below these thresholds can therefore be considered as having mild HCV by virtue of ineligibility for treatment.

2.1.2.4 Non-invasive biochemical markers of disease severity

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

- There are limitations with liver biopsy (for reasons outlined in Section 2.1.4) including the assertion that biopsy might not give a representative picture of liver pathology. For example, Poynard and colleagues (2004)[27] noted that only 14% of biopsies were of size greater or equal to 25mm.
- Panels of tests gave the best results, but many of these were complex. Some simple panels were useful in reducing the proportion of patients who needed biopsy, by identifying those at the severe fibrosis and who would therefore be eligible for treatment, and those with very mild disease who then would not.

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

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

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

New algorithms are being developed. Rosenberg and colleagues (2004)[28] examined a group of nine serum markers, and developed an algorithm based on four factors (age, hyaluronic acid, tissue inhibitor of matrix metalloproteinase 1, and amino-terminal propeptide of type III collagen). This combination had very good sensitivity and specificity for significant fibrosis.

2.1.2.5 Summary

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

Table 1 - A comparison of commonly used staging systems for chronic hepatitis C

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

(Taken from Kleiner, 2005)[15]

2.1.3 Incidence and prevalence

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

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

Table 2 - Laboratory reports England and Wales, by sex, 1992 - 2003

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

(Source Health Protection Agency website - accessed 8/7/05)

Data from the UK Trent HCV Study group show that the total number of anti-HCV positive patients recorded in the region (an assumed total population of 5.12 million) between 1991 and 1998 was 2546, representing a population-based prevalence of 0.05%[1]. This figure should be regarded as an under-estimate, 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. In common with the HPA figures, the study reported an annual increase in referred patients of 23.4% of patients between 1991 and 1997.

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

It is difficult to estimate the proportion of infections which could be considered as being mild since this currently requires verification by a liver biopsy. The number of

infections which have been identified and verified histologically is likely to be relatively low. As patients with mild HCV are unlikely to experience hepatic symptoms they are probably not aware of their infection and few will present to health services. Perceptions of liver biopsy as being a painful and potentially risky procedure may be an additional barrier to establishing the proportion of histologically mild patients.

In the Trent cohort study[1] a biopsy was performed on 52.4% (588 of 1122) of the cohort, 397 of whom were scored using the Knodell classification system (see Section 2.1.2.2 for more details of this and other systems). 240 (60%) had a total Knodell score of less than six (out of 20), with 200 having a fibrosis stage score of 0, and 122 with a stage score of 1 (the threshold for mild disease in this system is ≤1/4). Only 33 (8%) had cirrhosis. Therefore, 322 (81%) of those biopsied could be classed as having histologically mild HCV. A 2004 publication from the Trent cohort study reported disease progression rates for a sample of 214 untreated patients assessed via paired biopsies (see Section 2.1.4 for further details of this study). One hundred and eighty three patients (85%) were classified as having mild HCV based on an Ishak fibrosis score of 0-1 on the index biopsy. This is a relatively high proportion, although it should be noted that it is based on a cohort of patients presenting to various health services and who were not eligible for, or who did not wish to receive, treatment. They are therefore not necessarily representative of the undiagnosed population of people infected. In contrast, Booth and colleagues estimated in 2001 that only 25% of all patients presenting to health services have mild HCV[5].

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

2.1.4 Disease progression

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

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

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

Either study design can estimate the risk of progression for underlying factors, but the paired biopsy sample method provides a stronger indication of the relationship between stage of fibrosis and subsequent disease progression. Studies commonly

combine the two methods, reporting the paired biopsy sample group as a subset of the single-sample.

2.1.4.1 Paired biopsy studies

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

In Ryder and colleagues' study[34], 214 untreated patients in the Trent region of the UK were prospectively examined, of whom 183 (85%) had mild fibrosis (Ishak F0 or F1). The median inter-biopsy interval was 2.5 years. During this time 122 (57%) of patients experienced no change in fibrosis, 22 (10%) improved by one or more stages, and 70 (33%) progressed at least one stage in fibrosis. Twenty three (11%) progressed by at least two stages. When restricting the sample to only those with histologically mild disease the proportions are slightly lower, with 25% progressing at least one fibrosis stage, and 9% progressing by at least two[a]. The overall rate of progression was 0.17 Ishak stages per year, based on the assumption of linearity in progression. The authors conclude that histologically mild HCV is progressive. The overall rate of progression was low, but was accelerated in older patients, and those with any fibrosis on their index biopsy.

Collier and colleagues (2005)[35]reports a prospective study based on a cohort of patients in Cambridge. 612 patients had undergone a biopsy, of whom they present data for 105 paired samples, separated by an average of 41 months. At index biopsy most patients (80%) had moderate to severe disease (stage F2 or worse. The classification system is not reported, but fibrosis was scored between 0 and 5). It appears therefore, that the proportion of patients in this study with histologically mild HCV is relatively low. Fibrosis stage remained the same in the majority of the sample. Improvement by one or more stages was experienced by 37 (35%) patients, whilst worsening by one or more stage was seen in 23 (22%). Progression rates are given for the 20% or so of patients with initially mild fibrosis. Only a small proportion of these progressed. The calculated rate of progression for all patients in the sample was 0.15 stages per year. In summary, this study seems to suggest that disease progression is generally uncommon in the short-term. The proportion of patients with initially mild disease is too low to be able to provide definitive estimations of progression in this sub-group.

In Wright's study, a cohort of 1606 patients at St Mary's Hospital, London with at least one biopsy are reported. The mean Ishak fibrosis score was 2.72 (SD 1.7), whilst the median was 2 (0-6). The rate of fibrosis progression was non-normal with a marked right skew. The mean time to cirrhosis was 15 years, with a median of 35. A sub-set of 137 patients who had more than one biopsy is reported (after a mean of 33 months). The majority had mild disease on index biopsy. Fibrosis progression is presented only as a rate rather than proportion, and they too suggest an average rate of 0.15 stages of fibrosis per year. Based on the sub-group results, it was suggested that

[a] Dr Stephen Ryder, personal communication

HCV is a slowly progressive disease, although this might be an artefact of the relatively short inter-biopsy interval. Wider intervals are recommended.

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

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

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

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

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

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

2.1.4.2 Single sample studies

In this type of study, the researchers have examined data for patients who have had a only one liver biopsy. They estimate the duration of infection retrospectively from such data as the person can remember, or sometimes from the date of a specific high risk event such as blood transfusion. This may be unreliable due to the uncertainty of the source of infection and recall errors. It also assumes linearity in progression.

Poynard and colleagues 2001[36] and 2003[37], report single biopsy sample studies. The 2001[36]publication reports a total of 2313 patients with HCV, 62% of whom were histologically mild (Metavir F0-F1). Fibrosis progression rates are reported for each individual Metavir stage. For all stages there were four periods of linear progression: very slow (first 10 years), slow (following 15 years), intermediate (the following 10

years) and fast progression for the last five years. Three independent factors were associated with a faster progression rate: age at infection, alcohol consumption (50g or more per day), and male gender ($p<0.001$). They conclude that fibrosis progression is mostly regular from stage to stage, with progressive accelerations. Progression accelerates at 50 years of age, whatever the duration of infection.

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

Finally, Alberti and colleagues (2004)[38] review observational prospective studies, finding that in patients with histologically mild HCV progression tends to be faster in those with elevated ALT levels (see Section 2.2.1).

2.1.4.3 Disease progression - summary

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

2.1.5 Co-infection / co-morbidities

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

Mohsen and colleagues (2002)[3] reviews the international literature on the epidemiology of HIV-HCV co-infected patients. They included 12 HCV sero-prevalence studies carried out in HIV-1 infected people in Europe and the United States. HCV prevalence ranged from 7% to 57%, largely influenced by risk factors in the study populations. Prevalence was highest in people with a history of injecting drug use (>80%). In each of the two of haemophiliac studies, prevalence of HCV was 98%.

Evidence also suggests an increased rate of liver disease progression in HCV-HIV co-infected people. Graham and colleagues[39] conducted a meta-analysis of 8 cohort studies, and report a pooled relative risk (RR) of 2.92 (95% confidence interval 1.70-5.01) for decompensated liver disease or histological cirrhosis. Mohsen and colleagues (2003)[40] report a study of 153 HCV infected and 55 HCV-HIV co-infected

patients were identified from two London hospitals. The estimated median fibrosis progression rate was 0.17 units/year in HIV-HCV co-infected and 0.13 in HCV mono-infected patients respectively (p=0.01). This equates to an estimated time from HCV infection to cirrhosis of 23 and 32 years, respectively. HIV positivity was also one of a number of factors independently related to fibrosis progression. A retrospective analysis of 4852 patients with chronic liver disease of a variety of causes by Poynard and colleagues (2003)[40] also confirms the role of co-infection in disease progression (see Section 2.1.4 for further detail).

In terms of co-morbidities a significant proportion of haemophiliacs in the UK are infected with HCV, due to contaminated blood products prior to the introduction of blood screening. It is estimated that 4,865 haemophiliacs have been exposed to HCV, of whom around 1900 are living today with chronic hepatitis C[b].

2.1.6 Health related quality of life

As many people do not display obvious symptoms, it could be assumed that the burden of ill-health associated with HCV is minimal. However, non-specific symptoms including fatigue, irritability, depression, nausea, headache, muscle ache, anorexia, abdominal discomfort, and right upper quadrant pain have been reported[41-43]. Clinicians point out that patients' awareness that they carry a transmissible disease and the perceived risk of passing the disease to others can also significantly affect their quality of life. Although this psychological effect has not been specifically evaluated, it is a major motivator for patients to seek treatment. There is also some evidence to suggest cognitive impairment in patients with mild disease, a so-called 'brain fog'[44;45].

The perception that chronic HCV infection has a marginal impact on health-related quality of life (HRQOL) has been challenged in recent years. Studies evaluating HRQOL in HCV patients have used 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[46]. The SF-36 is generally supplemented with several disease-specific scales to characterise particular problems experienced by patients (e.g., health distress, limitations caused by HCV infection) [47].

A study which examined the HRQOL of patients with HCV 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[48]. However, a different conclusion was reached by a study conducted in Egypt[49]. HRQOL data were collected from 1,286 people living in a remote village unaware of their serological status, using the SF-12 and a visual analogue scale (VAS). The prevalence of HCV infection was 146 (11.4%). There was no reduction in HRQOL for those with HCV compared to those without. The authors suggest this might be due to a general lower morbidity rate among people with HCV in rural Egypt, and a

[b] Dr John Morris, Haemophilia Society, personal communication

higher morbidity rate amongst those not infected (e.g. due to relatively poor standard of living in rural areas). There are significant differences in the social, economic and demographic characteristics of the sample with that of studies conducted in Western countries which may explain the findings.

One study found that HRQOL is impaired irrespective of the degree of liver inflammation, or the mode of acquisition, suggesting that chronic infection with HCV in itself gives rise to symptoms that reduce the quality of life[50]. However, economic evaluations of anti-viral treatment have employed higher baseline utility scores for people with mild HCV than those with moderate HCV (see Section 5.2.3.2). This suggests that patients with mild HCV infection experience less morbidity than those with moderate disease (but who have not yet developed cirrhosis). For mild HCV patients utility estimates varied from 0.77 to 0.98 (with 0 = death, and 1 = perfect health). For moderate disease the range was 0.66 to 0.92. These scores tend to be based on estimates given by clinicians, rather than patients themselves. Nonetheless, despite the disparity between these studies, mild HCV infection does not necessarily mean absence of morbidity.

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

2.2 Current service provision

2.2.1 Service delivery

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

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

- District general and university-associated hospitals that have a gastroenterologist with a primary interest in liver disease.
- Teaching hospitals with a major interest in liver disease that do not undertake liver transplantation
- Liver transplant centres (n=7).

They estimate that there are around 10-15 hospitals that would qualify as a hepatology centre, and propose a set of criteria for qualification.

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

2.2.2 Anti-viral treatment

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

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

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

The licensed indications for pegylated and non-pegylated interferon alfa 2a and 2b, are provided in Appendix 2.

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

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

2.2.3 Use of biopsy

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

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

2.2.4 Injecting drug users

For current injecting drug users the BSG 2001 guidelines suggest that anti-viral treatment is not appropriate, for various reasons (e.g. poor compliance, risk of re-

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

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

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

2.2.5 Patients with persistently normal ALT

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

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

Alberti (2004)[38] reviews observational prospective studies and outcome modelling projections of disease progression in histologically mild HCV patients. Studies indicate that the risk of liver disease progression towards severe fibrosis/cirrhosis is minimal at 10-15 years in people with persistently normal ALT, around 5-10% in patients with elevated ALT and F0 (no fibrosis) on the initial biopsy, but >30-40% in people with elevated ALT and F1 (portal fibrosis) on the initial biopsy.

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

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

2.3 Description of new intervention

The proposal is to extend anti-viral treatment to patients with mild HCV. NICE's 2003 guidance on pegylated interferon alfa in patients with moderate to severe HCV is due to be updated in 2006. However, consideration is to be given to a part-update to reflect results of two clinical trials evaluating anti-viral therapy in patients with mild HCV. Since anti-viral treatment in patients with mild HCV has never been appraised before at a policy level, it is necessary to assess the clinical and cost-effectiveness of both the current standard treatment, pegylated interferon alfa, and the previous standard, non-pegylated interferon alfa. This was specified in both the scope for the appraisal issued by NICE, and our published peer-reviewed research protocol[c].

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

[c] These can be downloaded from www.nice.org.uk

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

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

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

3 METHODS

We conducted a systematic review and economic evaluation to assess the clinical and cost effectiveness of anti-viral treatment for mild HCV. The review was guided by the general principles for conducting a systematic review proposed by the NHS CRD[62]. Peer-review comments were sought from a panel of experts, as well as NICE. The review followed the methods outlined in our published peer-reviewed research protocol[d].

3.1 Search strategy

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

- Cochrane Systematic Reviews Database
- Cochrane Central Register of Controlled Trials

[d] This can be downloaded from www.nice.org.uk

- NHS CRD (University of York) databases: DARE (Database of Abstracts of Reviews of Effects), Health Technology Assessment (HTA) database, NHS EED (Economic Evaluations Database)
- Medline (Ovid)
- PreMedline
- PubMed
- Embase (Ovid)
- EconLit
- National Research Register
- ISI Web of Science - Science Citation Index
- ISI Web of Knowledge Proceedings
- BIOSIS
- Clinical trials.gov
- Current Controlled Trials.

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

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

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

We also searched the following websites for completed or on-going studies, and background material:

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

- Health Protection Agency
- Department of Health (England)

3.2 Inclusion and exclusion criteria

Each study was screened on the basis of title and/or abstract for inclusion by one reviewer. A random 10% sample of these was screened independently by a second reviewer. Publications for those marked as relevant were then ordered for further screening. An inclusion worksheet was used (see Appendix 7). Further details on the criteria are set out below.

3.2.1 Interventions

Studies reporting the following interventions were included:

- Pegylated interferon
  - Dual therapy (pegylated interferon alfa-2a / pegylated interferon alfa-2b and ribavirin).
  - Monotherapy* (pegylated interferon alfa-2a / pegylated interferon alfa-2b)

- Non-pegylated interferon
  - Dual therapy (interferon alfa-2a / interferon alfa-2b and ribavirin)

* for patients who are unable to tolerate ribavirin

- Comparisons
  - Best standard care, including either treatment without any form of interferon therapy (e.g. best supportive care), or (for pegylated interferon) treatment with non-pegylated interferon (i.e. interferon alfa-2a / interferon alfa-2b) where evidence allows.

3.2.2 Patients

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

As discussed in Section 2.1.2.1, the result of a liver biopsy is generally the most accepted way of gauging disease severity. Clinical guidelines issued by The Royal College of Physicians/ British Society of Gastroenterology provide the following definition of mild HCV:

"Histological appearances are classified as mild if the fibrosis score (stage) is less than or equal to 2/6, and if the necroinflammatory score (grade) is less than or equal

to 3/18 (Ishak). If the fibrosis score is 3–5/6 and/or the necroinflammatory score is greater than 3/18, the appearances are described as moderate. If the fibrosis score is 6/6, the biopsy is cirrhotic irrespective of necroinflammatory score" [5]

The scope for this appraisal, issued by NICE, adopts this definition but notes that other classification systems are in use (e.g. METAVIR, Knodell) (see Section 2.1.2.2). In order to be as inclusive as possible we did not restrict inclusion to any particular classification system.

In setting the inclusion criteria there were a number of uncertainties. Firstly, clinical hepatology experts consulted suggested that choosing a threshold, in terms of fibrosis scores, between mild and moderate HCV can be arbitrary. For example, whilst some might consider an Ishak fibrosis score of ≤ 1, as defining mild HCV, others might consider a slightly higher threshold of less than or equal to 2. However, advice from histopathologists and a published comparison of fibrosis scoring thresholds of widely used biopsy classification systems helped to provide some clarity around this issue (see Section 2.1.2.3).

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

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

Taking all of the above into account we used the following criteria. For a trial to be classed as including patients with mild HCV, no less than 70% of enrolled patients* had to be classed as mild on initial biopsy. Table 3 reports the fibrosis thresholds employed:

Table 3 - Fibrosis thresholds

Classification system	Fibrosis threshold
Knodell	≤ 1/5
Ishak	≤ 2/6
METAVIR	≤ 1/5
Scheuer	≤ 1/5
Batts and Ludwig, 1995	≤ 2/5

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

* However, a trial with less than 70% of mild patients may be considered for inclusion if outcomes are reported for the sub-group of patients with mild HCV as well as moderate to severe HCV.

3.2.3 Types of studies

We included systematic reviews of randomised controlled trials (RCTs) and Phase II/III RCTs comparing the different drugs with placebo, each other, or best supportive care will be included in the review of clinical-effectiveness. Also included were full economic evaluations of the specified interventions in patients with chronic mild HCV. For studies reporting health related quality of life and epidemiology/natural history we included a range of study designs (e.g. cohort studies, cross-sectional surveys). Studies published as abstracts or conference presentations were included in the primary analysis of clinical and cost-effectiveness.

3.2.3.1 Outcomes

The following outcome measures were included

- virological response (12 weeks treatment, end of treatment; and end of follow-up)
- histological improvement (e.g. inflammation/fibrosis – on biopsy)
- biochemical response (e.g. liver function – alanine aminotransferase)
- adverse effects of treatment
- survival
- health related quality of life

3.3 Data extraction strategy

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

3.4 Quality assessment strategy

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

3.5 Methods of analysis/synthesis

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

4 CLINICAL EFFECTIVENESS

4.1 Results

4.1.1 Quantity and quality of research available

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

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

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

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

- Including patients with histologically mild HCV
- Reporting an RCT or systematic review
- Evaluating pegylated interferon alfa / non-pegylated interferon alfa
- Reporting a relevant outcome measure

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

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

Without further detail we were unable to judge what proportion of the patients included in these trials could be classed as having mild HCV, in accordance with our criteria reported in Section 3.2.2.

We were unable to retrieve full reports for two unclassified studies.

- Section 4.1.1.1 and Section 4.1.2 present details of eight RCTs of anti-viral combination therapy in patients with mild HCV.
- Section 4.1.3 presents brief details of two RCTs of monotherapy in mild HCV patients.
- Section 4.1.4 presents brief details of 11 studies of reporting the effectiveness of anti-viral therapy in sub-groups of patients with mild HCV, and moderate to severe HCV.

4.1.1.1 Trials of anti-viral treatment in mild HCV patients

Overview of the trials

Eight RCTs of anti-viral treatment in mild hepatitis C patients were identified and included.[63-70] Five of the studies evaluated (non-pegylated) interferon alfa-2b (IFN α-2b),[63-65;67;70] whilst three studies evaluated pegylated interferon alfa-2a (PEG α-2a).[66;68;69] The five interferon studies compared IFN α-2b in combination with ribavirin (RBV) to either no treatment,[65] or IFN α-2b monotherapy.[63;64;67;70] Three of these employed the standard 3MU dose of IFN, given three times a week,[64;65;70] and two used higher doses of 5MU[63] or 6MU,[67] again given three times a week.

The dose of Peg IFN α-2a was the same in all three studies (180μg once weekly), but the comparative intervention arms differed. Zeuzem and colleagues[66] incorporated three arms, evaluating PEG α-2a in combination with RBV for 24 weeks versus the same treatment for 48 weeks versus no treatment. Hadziyannis and colleagues[69] included four treatment arms of PEG α-2a plus RBV, assessing a low (800mg/d) versus high (1000-1200mg/d) dose of RBV as well as treatment duration (24 weeks versus 48 weeks) in a factorial design. The third study, by Chung and colleagues[68] was a direct comparison of PEG α-2a with IFN α-2a (6MU followed by 3MU three times per week) both in combination with RBV in ascending doses (600-1000mg/d) in patients co-infected with HIV/HCV.

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

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

All the trials were based on middle-aged (mean age range 36-49 years) adult patients, with the proportion of male participants ranging from 40-82%. Patients were treatment naïve in all but one study (Cheng and colleagues[67]) which included patients

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

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

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

Many of the trials stipulated certain laboratory readings in their exclusion criteria, most of which related to conditions which are consistent with decompensated liver cirrhosis. Six trials[63;64;66-69] excluded patients with thrombocytopenia, requiring platelet counts ranging from less than 90,000 to less than 100,000 cells/mm^3. Five[64;66-69] excluded patients with neutropenia where neutrophil counts ranged from less than 1,500 cells/mm^3 to less than 2,000 cells/mm^3. Three[63;64;67] excluded patients with low white blood cell counts ranging from less than 3,000 to less than 4,000 cells/mm^3. Six[63;64;66-69] excluded patients with anaemia who had haemoglobin ranging from

below 11.5 to 12 g/dl for women and below 13 g/dl for men. One trial[63] excluded patients with serum albumin less than 35 g/l, and two trials[66;69] excluded participants with serum creatinine levels over 1.5 times the upper limit of normal.

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

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

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

Table 4- Key characteristics of included studies – participants and outcomes

Study	Methods	Key inclusion/exclusion criteria	Other patient characteristics	Outcomes
Cheng et al., 2002[67]	*Design*: single-centre, double-blind RCT *Number of centres*: 1 *Sponsor*: Schering-Plough and National Cheng-Kung University Hospital, Taiwan *Country*: Taiwan *Interventions*: IFN α-2b + RBV vs IFN α-2b + placebo for 24 weeks *Follow-up*: 24 weeks post-treatment *No. participants*: 52	*Inclusion criteria*: • Adult patients who had previously responded to IFN-α and subsequently relapsed • HCV RNA positive • Positive antibody to HCV antibody test • Using effective contraception	• Fibrosis system: Knodell • Mean fibrosis stage: 0.5 Group 1, 0.2 Group 2 • Liver biopsy taken: before and at end of treatment • Mean HCV RNA, MEq/ml: ~ 7.5 • Average age ~ 44 years • Gender: 79% male • Genotypes: 42% 1b, 6% 1a+2, 42% 2a+c, 4% 2b, 6% 2 (not sub-typed) • Mode of infection: not reported • Ethnicity: not reported	*Primary outcomes*: • SVR *Secondary outcomes*: • Biochemical response (normalisation of ALT values) • Change in liver histology • Adverse events
Chung et al., 2004[68]	*Design*: multicentre, open-label RCT *Number of centres*: 21 *Sponsor*: National Institutes of Health *Country*: USA *Interventions*: Peg IFN α-2a + RBV vs IFN α-2a + RBV for 48 weeks *Follow-up*: 24 weeks post-treatment *No. participants*: 133	*Inclusion criteria*: • Treatment naïve adult patients • HCV RNA positive • HIV positive • Biopsy findings consistent with a diagnosis of chronic hepatitis C • Normal or elevated ALT levels • Cirrhosis acceptable provided there was no evidence of hepatic decompensation	• Fibrosis system: Ishak • Median fibrosis stage: 2.0 Group 1, 2.0 Group 2 • Liver biopsy taken: ≤48 weeks before study entry • Mean HCV RNA, x10^6 IU/ml: 6.2 • Average age ~ 45 years • Gender: 82% male • Genotype 1: 78% • Mode of infection: not reported • Ethnicity: 48% white, 33% black, 14% Hispanic, 5% other	*Primary outcomes*: • Virologic response at week 24 of treatment *Secondary outcomes*: • SVR • Histologic response • Adverse events
Hadziyannis et al., 2004[69]	*Design*: multicentre, double-blind RCT *Number of centres*: 99 *Sponsor*: Roche *Country*: USA	*Inclusion criteria*: • Treatment naïve adult patients • HCV RNA positive • Biopsy findings consistent with a diagnosis of chronic hepatitis C	• Fibrosis system: Knodell • Fibrosis stage 0,1: 75% • Liver biopsy taken: ≤15 months before study entry • Mean HCV RNA, x10^3 copies/ml:	*Primary outcomes*: • SVR *Secondary outcomes*: • Adverse events

	Interventions: Peg IFN α-2a + RBV (low dose), 24 weeks Peg IFN α-2a + RBV (standard dose), 24 weeks Peg IFN α-2a + RBV (low dose), 48 weeks Peg IFN α-2a + RBV (standard dose), 48 weeks *Follow-up*: 24 weeks post-treatment *No. participants*: 1284	• Raised ALT within previous 6 months • Compensated liver disease	~ 5944 • Average age ~ 42 years • Gender: 65% male • Genotypes: 58% 1, 42% non-1, 16% 2, 38% 3 • Mode of infection: 36% IDU, 18% transfusion, 33% unknown/other • Ethnicity: 89% white, 3% black, 7% Asian, 1% other	
Mangia et al., 2001[63]	*Design*: multicentre, open-label RCT *Number of centres*: 9 *Sponsor*: not stated *Country*: Italy *Interventions*: IFN α-2b + RBV vs IFN α-2b for 12 months *Follow-up*: 6 months post-treatment *No. participants*: 192	*Inclusion criteria*: • Treatment naïve patients • HCV RNA positive • Histopathological evidence of chronic hepatitis (liver biopsy taken ≤6 months before enrolment) • Raised ALT for at least 6 months	• Fibrosis system: Scheuer • Fibrosis stage 0,1: 77% • Liver biopsy taken: ≤6 months before enrolment • HCV RNA, number of equivalent genomes/ml: ~ 6.4 $x10^6$ • Average age ~ 47 years • Gender: 67% male • Genotypes: 47% 1b, 34% 2a, 14% 3, 5% other • Mode of infection: 21% IDU, 6% transfusion, 73% community acquired • Ethnicity: not reported	*Primary outcomes*: • SVR *Secondary outcomes*: • Biochemical response (normalisation of ALT values) • Adverse events
Reichard et al., 1998[70]	*Design*: multicentre, double-blind RCT *Number of centres*: 5 *Sponsor*: Schering-Plough *Country*: Sweden *Interventions*: IFN α-2b + RBV vs IFN α-2b + placebo for 24 weeks *Follow-up*: 24 weeks post-	*Inclusion criteria*: • Adult patients (age >18 years or <70 years) • HCV RNA positive • Biopsy findings consistent with a diagnosis of chronic hepatitis C (biopsy taken in preceding 12 months) • Positive antibodies to HCV	• Fibrosis system: Batts & Ludwig • Mean fibrosis stage: ~ 1.5 • Liver biopsy taken: ≤12 months before study entry and at week 24 • Geometric mean HCV RNA, $x10^6$ Eq/mL: ~ 3.6 • Average age ~ 39 years • Gender: 62% male	*Primary outcomes*: • SVR *Secondary outcomes*: • Biochemical response • Change in liver histology • Adverse events

	treatment *No. participants*: 100	antibody test • Persistently raised aminotransferases for at least 6 months	• Genotypes: 17% 1a, 19% 1b, 3% 1 (not sub-typed), 5% 1a+b, 1% 2a, 17% 2b, 1% 2a+b, 33% 3a, 2% 4 (not sub-typed), 1% 4c+d, 1% 5a • Mode of infection: 51% IDU, 16% transfusion, 33% unknown • Ethnicity: not reported	
Verbaan et al., 2002[64]	*Design*: multicentre, double blind RCT *Number of centres*: 15 *Sponsor*: Schering-Plough *Country*: Sweden *Interventions*: IFN α-2b + RBV vs IFN α-2b + placebo for 52 weeks *Follow-up*: 26 weeks post-treatment *No. participants*: 116	*Inclusion criteria*: • Treatment naïve patients (18-60 years) with histologically mild chronic HCV infection • Knodell fibrosis stage ≤1, Knodell activity score ≥1 and ≤6 • HCV RNA positive (liver biopsy taken within previous 12 months) • Raised ALT for at least 6 months	• Fibrosis system: Knodell • Mean fibrosis stage: 0.4 Group 1, 0.3 Group 2 • Liver biopsy taken: not reported • Viral load, mean HCV RNA bDNA version 3, copies/ml: 2.34 x 10^6 Gp 1, 9.16 x 10^5 Gp 2 • Average age ~ 37 years • Gender: 59% male • Genotypes: 35% 1a, 14% 1b, 16% 2b, 32% 3a, <1% 4, 2% missing/unknown • Mode of infection: 60% IDU, 9% transfusion, 7% other, 24% unknown • Ethnicity: not reported	*Primary outcomes*: • SVR *Secondary outcomes*: • Change in liver histology • Adverse effects
Wright et al., 2005[65]	*Design*: multicentre, open-label RCT *Number of centres*: 13 *Sponsor*: HTA programme *Country*: UK *Interventions*: IFN α-2b + RBV vs no treatment for 48 weeks *Follow-up*: 24 weeks post-treatment *No. participants*: 196	*Inclusion criteria*: • Treatment naïve adult patients with mild chronic hepatitis C (Ishak necroinflammatory score ≤3, fibrosis score ≤2) • HCV RNA positive • Normal or raised ALT	• Fibrosis system: Ishak • Mean fibrosis stage: 1.01 for treatment group, 1.18 for control group. • Liver biopsy taken: ≤1 year prior to screening visit • Viral load, IU/mL: <4x10^5 57% treated patients, >4x10^5 43% treated patients; not reported for control patients • ALT: normal 38%/raised 62%	*Primary outcomes*: • SVR *Secondary outcomes*: • Quality of life • Adverse events

			treated patients; not reported for control patients • Average age ~ 40 years • Gender: 61% male • Genotypes: 52% 1, 48% non-1 • Mode of infection: 53% IDU, 16% transfusion, 31% unknown • Ethnicity: 90% white, 7% non-white, 3% not recorded	
Zeuzem et al., 2004[66]	*Design*: multicentre, open-label RCT *Number of centres*: 70 *Sponsor*: Roche *Country*: Australia, Europe, New Zealand, North and South America *Interventions*: Peg IFN α-2a + RBV (24 weeks) vs Peg IFN α-2a + RBV (48 weeks) vs no treatment *Follow-up*: 48 weeks (Group 1), 24 weeks (Group 2) post-treatment *No. participants*: 491	*Inclusion criteria*: • Treatment naïve, adult patients • HCV RNA positive • Positive antibody to HCV antibody test • Biopsy findings consistent with a diagnosis of chronic hepatitis C • Persistently normal ALT levels	• Fibrosis system: Ishak • Fibrosis stage: 69% stage 0 or 1, 20% stage 2; total mean = 1.4 • Liver biopsy taken: ≤36 months before study onset • Viral load, mean HCV RNA level: ~ 1190 x10^3 • ALT, maximum mean: ~ 24 IU/L • Average age ~ 43 years • Gender: 40% male • Genotypes: 68% 1, 32% non-1 • Mode of infection: 31% IDU, 23% transfusion, 14% other, 32% unknown • Ethnicity: 86% white, 8% black, 2% Asian, 4% other	*Primary outcomes*: • SVR *Secondary outcomes*: • Adverse events

IDU, injecting drug user; iv, intravenous

Table 5 - Quality assessment of mild HCV trials

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

Ad = adequate, In = inadequate, Par = partial, Rep = reported, Un = unknown, N/a = not applicable

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

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

4.1.2 Assessment of effectiveness

This section presents the results of the included RCTs in terms of primary and secondary outcomes: virological response and sustained virological response (SVR), biochemical response (ALT), histological response (change in fibrosis) and health-related quality of life.

4.1.2.1 Virological response

Table 6 reports SVRs for two of the three PEG trials. In the trial by Zeuzem and colleagues,[66] treatment for 48 weeks with Peg IFN α-2a was significantly more effective than the same treatment for 24 weeks (SVR 52% vs 30%, $p<0.001$), with a relative risk of 1.7 (95% CI 1.4 to 2.2). No patient in the untreated control group cleared HCV. The manufacturer's submission to NICE reports the SVR for the sub-group of patients with histologically mild HCV, based on Ishak fibrosis and necro-inflammation scores. This is slightly lower at 50% (n=55/110). A further analysis supplied by the manufacturer, restricting the criteria for histologically mild HCV on baseline fibrosis score only, yielded an SVR of 51% (n=97/188).

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

The third PEG study, by Hadziyannis and colleagues[69], only reported SVRs according to genotype and baseline viral load. Tabulated details can be found in Table 8 and Table 11. However, the authors report that PEG + RBV (standard dose 1000-12000mg per day) for 48 weeks produced an overall SVR of 63% (95% CI 59% to 68%).

Table 6 - Virological response (PEG trials)

Study **Outcome: virological response**	**Treatment arms**				
Zeuzem, 2004[66] **Multicentre, open label RCT**	**Peg IFN α-2a (180µg) + RBV (800mg), 24 wk (n=212)**	**Peg IFN α-2a (180µg) + RBV (800mg), 48 wk (n=210)**	**No treatment (n=69)**	**Risk diff (95% CI)**	**RR, 48 vs 24 wk (95% CI) + *p*-value†**
% with response (95% CI) SVR at follow-up	30% (24-36)	52% (45-59)	0	22 (13-31)	1.7 (1.4-2.2) $p<0.001$

Chung, 2004[68] **Multicentre RCT** **HIV/HCV co-infected patients**	**Peg IFN α-2a + RBV 48 wk n=66**	**IFN α-2a + RBV 48 wk n=67**	***p*-value†**
% with response (n/N) SVR at follow-up	27% (18/66)	12% (8/67)	$p=0.03$

† between-group comparison; RR = Relative Risk

Table 7 presents virologic response rates for the five IFN trials. All trials reported significantly higher SVR rates with IFN + RBV (range 33-69%) compared to either IFN monotherapy (range 18-23%) or no treatment (zero response). Of note is the relatively high SVR of 69% achieved by patients treated with only 24 weeks IFN + RBV in the study by Cheng and colleagues[67]. These patients were treated with a higher dose of IFN than is commonly used in practice. Also noteworthy is the relatively low SVR for patients treated with IFN + RBV in UK RCT by Wright and colleagues[65].

Table 7 - Virological response (IFN trials)

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

*Post-treatment cessation; RR, relative risk; †between-group comparison, * within-group comparison; ns = not significant

4.1.2.2 Virological response according to prognostic factors

Genotype

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

In the trial by Zeuzem and colleagues,[66] no patient in the untreated control group cleared HCV. Across all genotypes, patients treated with PEG + RBV for 48 weeks

Table 8 - Sustained virological response according to genotype (PEG trials)

Study Outcome: virological response	**Treatment arms**			
Zeuzem, 2004[66] Multicentre, open label RCT	**Peg IFN α-2a (180µg) + RBV, 24 wk (n=212)**	**Peg IFN α-2a (180µg) + RBV, 48 wk (n=210)**	**No treatment (n=69)**	**RR, 48wks vs 24wks (95% CI), *p*-value†**
% with response (95% CI)				
1	13% (8-19)	40% (32-49)	0	3.1 (1.9-4.9), $p<0.001$
non-1	65%	75%	0	not reported
2 or 3	72% (61-84)	78% (67-89)	0	1.1 (0.9-3.1), $p=0.452$
4	13%	56%	0	not reported
Hadziyannis, 2004[69] Multicentre, double blinded RCT	**Peg IFN α-2a 180µg + RBV 800mg 24 wk n=207**	**Peg IFN α-2a 180µg + RBV 1000 – 12000 mg 24 wk n=280**	**Peg IFN α-2a 180µg + RBV 800mg 48 wk n=361**	**Peg IFN α-2a 180µg + RBV 1000 – 12000 mg 48 wk n=436**
% with response (n/N)				
1	29% (29/101)	42% (50/119)	41% (103/250)	52% (141/271)
2 or 3	84% (81/96)	81% (117/144)	79% (78/99)	80% (122/153)
Chung, 2004[68] Multicentre RCT HIV/HCV co-infected patients	**Peg IFN α-2a + RBV 48 wk n=66**	**IFN α-2a + RBV 48 wk n=67**		***p*-value†**
% with response (n/N)				
1	14% (7/51)	6% (3/52)		
non-1	73% (11/15)	33% (5/15)		0.07

†between-group comparison; RR, relative risk.

had higher response rates than patients on the same therapy for only 24 weeks. However, this was only significant for genotype 1 patients (40% vs 13% respectively, relative risk 3.1 (95% CI 1.9-4.9), $p<0.001$). SVRs for patients infected with genotype 4 were similar to those infected with genotype 1. Treatment duration did not have a significant effect on virologic response for patients with genotype 2 or 3 (78% vs 72% for 48 and 24 weeks respectively, relative risk 1.1 (95% CI 0.9-3.1), $p=0.452$). Within treatment groups, higher SVRs were seen in genotype non-1 patients compared with genotype 1 patients, regardless of length of therapy.

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

In the trial of HCV/HIV co-infected patients by Chung and colleagues[68], the SVRs for non-1 genotypes treated with PEG + RBV were broadly similar to those achieved

by patients in the comparable arms of the two other PEG trials. However, for genotype 1 patients, rates were noticeably lower.

Table 9 - Sustained virological response according to genotype (IFN trials)

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

*Within-group comparison (favourable vs unfavourable baseline features in each treatment group); †between-group comparison; ¶$p<0.05$ for comparison with genotype 1

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

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

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

Viral load

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

Table 10 - Sustained virological response according to baseline viral load (IFN trials)

Study **Outcome: SVR by viral load**	**Treatment arms**					
Cheng, 2002[67], Double blind RCT	**IFN α-2b (6MU) + RBV 24 wks (n=26)**		**IFN α-2b (6MU) + placebo, 24 wks (n=26)**		***p*-value†**	
% with response (n/N) ≤3 MEq/ml >3 MEq/ml	 92% (12/13)‡ 46% (6/13)		 50% (6/12)‡‡ 0 (0/14)		 <0.05 <0.005	
Mangia, 2001[63] Multicentre, open label RCT	**IFN α-2b (5MU) + RBV (1000-1200mg) 48 wks (n=96)**	***p*-value***	**IFN α-2b (5MU) 48 wks (n=96)**	***p*-value***		
% with response (95% CI) Low[a] High[a]	 49% (32-64) 58% (45-70)	 *p*=0.39	 26% (13-40) 21% (10-31)	 *p*=0.52		
Reichard, 1998[70] Multicentre, double blind RCT	**IFN α-2b (3MU) + RBV (1000-1200mg) 24 wks (n=50)**		**IFN α-2b (3MU) + placebo 24 wks (n=50)**		***p*-value†**	
% with response (n/N) <1 x10^6 1-2.99 x10^6 3-7.99 x10^6 8-19.99 x10^6 ≥20 x10^6	 45% (5/11) 10% (1/10) 10% (1/10) 62% (8/13) 50% (3/6)		 45% (5/11) 23% (3/13) 0/13 13% (1/8) 0/5		 1.00 0.60 1.00 0.07 0.18	
Wright, 2005[65] Multicentre, open label RCT	**IFN α-2b (3MU) + RBV 48 wks (n=98)**		**No treatment (n=98)**		***p*-value***	
% with response <4 x 10^5 IU/mL[b] >4 x 10^5 IU/mL[b]	 34% 31%		 0 0		 *p*=0.82	

*Within-group comparison (favourable vs unfavourable baseline features in each treatment group); † between group comparison; [a]low viremia ≤200,000 equivalent genomes/ml, high viremia ≥200,000 equivalent genomes/ml; [b]1 IU is equivalent to approximately 5 RNA copies. ‡*p*<0.05 for comparison with HCV RNA level >3 MEq/ml; ‡‡*p*<0.005 for comparison with HCV RNA level >3 MEq/ml

The trial by Verbaan and colleagues[64] reports geometric mean viral load (equivalent genomes/ml) for sustained responders and non-responders within each treatment arm (IFN + RBV vs IFN + placebo), rather than the proportion of patients with low/high viremia who achieved a response. This study found that in the combination therapy group, mean viral load was lower among sustained responders compared to non-responders (4.6 x 10^5 vs 2.0 x 10^6 respectively, *p*=0.034). The same tendency was

seen within the IFN + placebo monotherapy group between sustained responders and those who did not clear the infection (5.9 x 10^5 vs 2.4 x 10^6 respectively, p=0.002).

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

Combined genotype and viral load

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

Table 11- Sustained virological response according to combined genotype and viral load (PEG trials)

Study **Outcome: SVR by genotype + viral load**	**Treatment arms**			
Zeuzem, 2004[66] **Multicentre, open label RCT**	**Peg IFN α-2a (180µg) + RBV, 24 wk (n=212)**	**Peg IFN α-2a (180µg) + RBV, 48 wk (n=210)**	**No treatment (n=69)**	
% with response				
Genotype 1				
low viral load[a]	16%	47%	0	
high viral load[a]	9%	27%	0	
Genotype non-1				
low viral load[a]	69%	79%	0	
high viral load[a]	59%	71%	0	
Genotype 2 or 3				
low viral load[a]	80%	81%	0	
high viral load[a]	64%	75%	0	
Genotype 4				
low viral load[a]	17%	67%	0	
high viral load[a]	0	33%	0	
Hadziyannis, 2004[69] **Multicentre, double blind RCT**	**Peg IFN α-2a 180µg + RBV 800mg 24 wk n=207**	**Peg IFN α-2a 180µg + RBV 1000 – 12000 mg 24 wk n=280**	**Peg IFN α-2a 180µg + RBV 800mg 48 wk n=361**	**Peg IFN α-2a 180µg + RBV 1000 – 12000 mg 48 wk n=436**
% with response (n/N)				
Genotype 1				
low viral load[b]	41% (21/51)	52% (37/71)	55% (33/60)	65% (55/85)
high viral load[b]	16% (8/50)	26% (12/47)	36% (68/190)	47% (88/186)
Genotype 2 or 3				
low viral load[b]	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)
high viral load[b]	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)

[a]low viral load ≤800,000 IU/mL, high viral load >800,000 IU/mL; [b] low viral load ≤2 x 10^6 copies/mL; high viral load >2 x10^6 copies/mL. ns, not significant.

In the PEG study by Zeuzem and colleagues,[66] baseline viral load (high viral load vs low viral load: odds ratio, 2.21 (95% CI 1.20-4.09)) significantly affected SVRs in

patients with genotype 1. In genotype 1 patients with a low baseline viral load, the unadjusted probability of achieving an SVR was 77% higher than in patients with a high viral load (unadjusted RR 1.77, 95% CI 1.12-2.82)). In contrast, baseline viral load did not have a significant effect on SVRs in patients infected with non-1 genotypes, although viral load did appear to influence SVRs in patients infected with genotype 4.

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

Table 12 - Sustained virological response according to combined genotype and viral load (IFN)

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

*Within-group comparison (favourable vs unfavourable baseline features in each treatment group); [a]low viremia ≤200,000 equivalent genomes/ml, high viremia ≥200,000 equivalent genomes/ml;

In the trial by Mangia and colleagues,[63] response rates for IFN + RBV therapy were higher than for IFN monotherapy regardless of the viral load or genotype. Within the combination treatment group, SVRs were similar irrespective of the level of viremia (*p*=ns), although SVRs were twice as high for patients with genotype 2 or 3 compared with genotype 1, 4 or 5 for both low and high viral load.

ALT level

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

Table 13 - Sustained virological response according to ALT level

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

*Within-group comparison (favourable vs unfavourable baseline feature in treatment group)

Age

Table 14 shows SVRs according to age, stratified into age less than or greater than 40 years. In the two trials where data are presented,[63;65] patients receiving combination therapy had higher SVRs than those receiving monotherapy or no treatment, regardless of age. In both trials age did not significantly influence the rate of sustained response within treatment groups.

Table 14 – Sustained virological response according to age (IFN)

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

*Within-group comparison (favourable vs unfavourable baseline features in each treatment group).

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

Gender

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

Histology

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

Table 15 - Sustained virological response according to gender

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

*Within-group comparison (favourable vs unfavourable baseline features in each treatment group).

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

Table 16 - Sustained virological response according to baseline liver histology (PEG)

Study **Outcome: SVR by histology**	**Treatment arms**			
Hadziyannis, 2004[69] **Multicentre, double blind RCT**	**Peg IFN α-2a 180µg + RBV 800mg** **24 wk** n=207	**Peg IFN α-2a 180µg + RBV 1000 – 12000 mg** **24 wk** **n=280**	**Peg IFN α-2a 180µg + RBV 800mg** **48 wk** **n=361**	**Peg IFN α-2a 180µg + RBV 1000 – 12000 mg** **48 wk** **n=436**
% with response (n/N) F3 or F4 Genotype 1 F3 or F4 Genotype 2 or 3 F0 or F1 Genotype 1 F0 or F1 Genotype 2 or 3	 26% (6/23) 75% (15/20) 29% (23/78) 87% (66/76)	 26% (7/27) 74% (29/39) 46% (42/91) 84% (88/105)	 28% (19/67) 70% (14/20) 45% (83/183) 81% (64/79)	 41% (32/78) 73% (24/33) 57% (110/193) 83% (100/120)

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

Mangia and colleagues[63] reported SVRs according to baseline fibrosis stage (stage 0 or 1 vs >1) and necro-inflammation grade (grade 1 or 2 vs 3), scored using the Scheuer criteria (Table 17). The histological staging significantly affected the sustained response in the combination therapy group, with SVRs being more than two times higher in patients with a lower fibrosis stage compared to a higher stage (63% vs 28% respectively, *p*=0.004).

Table 17 - Sustained virological response according to baseline liver histology (IFN)

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

*Within-group comparison (favourable vs unfavourable baseline features in treatment group).

4.1.2.3 Biochemical response (ALT)

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

Table 18 - Biochemical response (ALT normalisation)

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

†Between-group comparison.

Response was measured by reduction in ALT to normal levels. In all trials response rates subsided between end of treatment and follow-up. Both end of treatment and follow-up rates were significantly greater for IFN + RBV compared to IFN

monotherapy or IFN with placebo. The magnitude of response varied according to dose and regimen.

In the trial by Mangia and colleagues[63] the combined biochemical and virological response rate was more than 2.5 times higher ($p<0.0001$) in patients receiving IFN + RBV compared to patients receiving IFN alone. At the end of follow-up, normalisation of ALT values was associated with undetectable levels of serum HCV RNA in 71 out of 72 patients (98.6%) who had an SVR. Serum HCV RNA levels remained detectable after treatment, despite persistently normal serum ALT concentration, in 5 out of 77 patients (6.5%), of which three were combination therapy and two were IFN monotherapy.

4.1.2.4 Histological response

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

Table 19 - Histological response (PEG)

Study **Outcome: Histological response**	**Treatment arms**	
Chung, 2004[68] **Multicentre RCT** **HIV/HCV co-infected patients**	**Peg IFN α-2a + RBV** **48 wk** **n=66**	**IFN α-2a + RBV** **48 wk** **n=67**
No virologic response at wk 24 histologic response	(n=37) 9/26[a] (35%)	(n=57) 16/45[a] (36%)
Virologic response at wk 24 histologic improvement no change worsening disease	(n=39) 14/27[b] (52%) 11/27[b] (41%) 2/27[b] (7%)	

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

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

Three of the IFN trials reported changes in liver histology. There were no significant changes in fibrosis scores. In the trial by Verbaan and colleagues[64] for patients with a sustained response there was a significant improvement ($p\leq0.018$) in mean inflammation grade score irrespective of the treatment group. There was no significant change in non-responders. Verbaan and colleagues[64] also report that the low fibrosis stage (mean stage 0.3 and 0.4 for IFN + RBV, and IFN + placebo groups respectively) did not change in either group, irrespective of treatment results, but data are not presented.

Table 20 - Histological response (IFN trials)

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

*Within-group comparison (at entry vs follow-up); † between group comparison; ns, not significant.

4.1.2.5 Health-Related Quality of Life

Fully published data on the impact of treatment on health-related quality of life (HRQOL) are available for only one of the eight RCTs. This was the UK mild HCV trial.[65] (A conference abstract reports data for another trial – see below). The study compared IFN + RBV with no treatment. HRQOL was measured using the Short Form-36 (SF-36), a generic health status survey of general health items.

The SF-36 questionnaire was completed by participants at baseline and at 24 weeks post-treatment cessation, and their responses to eight concepts were reported, as well as summary physical component scores (PCS) and mental component scores (MCS). The eight concepts included: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Differences between baseline and post-week 24 scores for the eight concept scales and two summary scales were compared across three groups: sustained virological responders (SVRs), treatment failures (non-SVRs) including non-responders and relapsed patients, and the control group. Data were available for 75% of the SVRs, 65% of the non-SVRs, and approximately half (56%) of the control group.

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

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

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

In addition, HRQOL data from Zeuzem and colleagues' trial of PEG were presented in a conference abstract[71]. As these data have not yet been fully published, and therefore not subjected to appraisal, caution is advised in their interpretation. Briefly, the key findings were:

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

4.1.2.6 Adverse events

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

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

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

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

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

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

Only two trials[67;70] reported statistical tests for comparison between groups. Cheng and colleagues[67] reported a higher incidence of adverse events in combination therapy patients compared to monotherapy patients, being statistically significant for anorexia and insomnia ($p<0.05$). Reichard and colleagues[70] reported that nausea occurred in significantly more combination therapy patients compared to monotherapy ($p=0.02$). In addition, the total number of patients requiring dose discontinuation or reduction was also significantly greater in the IFN + RBV group ($p=0.03$).

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

Table 21 - Adverse events

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

Peg IFN trials									
Reported adverse events n (%) of patients affected	**Chung et al., 2004[68]**		**Hadziyannis et al., 2004[69]**				**Zeuzem et al., 2004[66]**		
	Peg IFN α-2a (180µg) + RBV (n=66)	**IFN α-2a (3-6 MIU) + RBV (n=67)**	**Peg IFN α-2a (180µg) + RBV 800mg, 24 wks (n=207)**	**Peg IFN α-2a (180µg) + RBV 1000-1200mg, 24 wks (n=280)**	**Peg IFN α-2a (180µg) + RBV 800mg, 48 wks (n=361)**	**Peg IFN α-2a (180µg) + RBV 1000-1200mg, 48 wks (n=436)**	**Peg IFN α-2a (180µg) + RBV, 24 w (n=212)**	**Peg IFN α-2a (180µg) + RBV, 48 wks (n=210)**	**No treatment (n=69)**
Discontinuation of treatment									
serious adverse event									N/A
adverse event[e]	8 (12)	8 (12)	10 (5)	13 (5)	59 (16)	67 (15)	15 (7)	38 (18)	N/A
other reason			14 (7)	22 (8)	148 (41)	141 (32)			N/A
Dose modification									
anaemia									N/A

adverse event[d] lab abnormality/other reason	3 (5)	3 (4)	102 (49)	149 (53)	221 (61)	325 (74)	65 (31) 52 (25)	102 (49) 92 (44)	N/A N/A
Hospitalisations	1 (<1)[f]		NR	NR	NR	NR	NR	NR	NR
Deaths	1 (<1)[f]		0	1 (<1)	1 (<1)	2 (<1)	0	0	1 (1)
Any adverse event[c]	NR	NR					209 (99)	207 (99)	53 (77)
severe adverse event	NR	NR	46 (22)	63 (23)	116 (32)	141 (32)	56 (26)	70 (33)	10 (14)
serious adverse event	NR	NR	7 (3)	19 (7)	33 (9)	44 (10)	18 (8)	34 (16)	4 (6)

NR, not reported; N/A, not applicable

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

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

[c]in the trials by Cheng,[67] Reichard[70] and Chung[68] specific adverse events were reported for each treatment group, but not the total number of patients who had an adverse event nor the total number of adverse events

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

[e]adverse event included laboratory abnormalities in all three Peg trials[66;68;69]

[f]did not specify which treatment group

4.1.2.7 Clinical effectiveness: summary

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

4.1.3 Monotherapy trials

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

Reddy and colleagues (2001)[72] randomised 159 patients to IFN 2a monotherapy (n= 33) or to three ascending doses of PEG 2a monotherapy (45µg n=20; 90µg n=20; 180µg n= 45; or 270µg, n=41). At baseline 144 (91%) of the patients were classed as 'non-cirrhosis' (≤ F2), and 15 (9%) were classed as having bridging fibrosis, according to the Ishak biopsy classification system. The majority of patients had

genotype 1 (74%). Only 3% of patients receiving IFN monotherapy had an SVR, compared to 10% to 29% of patients receiving various doses of PEG monotherapy (statistically significant for all comparisons with IFN monotherapy). SVRs increased in a dose-dependent manner between 45µg and 180µg with no further increase in response at the 270µg dose. SVRs were higher in the sub-group of patients with genotypes non-1. Rates reached as high as 67% for both the 90µg and 270µg PEG dose groups.

Lindsay and colleagues (2001)[73] randomised patients to IFN 2b (n=303) or to three doses of PEG 2b (0.5 µg/kg n=315; 1.0 µg/kg n= 297; 1.5 µg/kg n=304). This was an international multi-centre RCT conducted in USA, Europe and Australia. At baseline 164 (13%) of the patients were classified as having bridging fibrosis (F3), and 4% as having cirrhosis, according to the Knodell classification system. The mean fibrosis score was 1.4. According to the Knodell system, fibrosis scores of less than or equal to one indicate mild HCV. Although the mean baseline fibrosis score was just over this threshold the majority of patients (83%) were classified as having a fibrosis score less than F3, and therefore can be considered as having mild HCV (NB. The Knodell system has no F2 score, see Sections 2.1.2.2 and 2.1.2.3 for more detail on biopsy classification systems). The majority of patients were infected with genotype 1 (70%). Only 12% of patients treated with IFN achieved an SVR, compared to 18 to 23% of patients given various doses of PEG. Comparisons between PEG and IFN were statistically significant, but not for the 0.5 µg/kg group.

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

4.1.4 Studies reporting sub-groups of mild HCV patients

Although we did not include trials which comprised less than 70% of patients with mild HCV, we did consider such trials if they reported outcomes according to baseline fibrosis stage scores. This enabled us to gauge within-trial response rates for patients with mild HCV in comparison to response rates for patients with moderate to severe disease. We identified 11 such studies, three of which evaluated pegylated interferon alfa, and the remainder evaluating non-pegylated interferon alfa. Below we report brief characteristics and results for each study. Even though all are RCTs, caution is advised as, except for Poynard and colleagues[74] and Manns and colleagues[17e], they have not been subjected to full critical appraisal. Furthermore, none of the trials were specifically designed to evaluate differences in response according to baseline fibrosis. Their results are presented here as context within which to interpret the results of the RCTs reported in the previous sections.

4.1.4.1 Pegylated interferon alfa studies

Poynard and colleagues (2002) – Meta-analysis of pegylated interferon alfa 2b + ribavirin on fibrosis (incorporating Poynard and colleagues (2000)

[e] Full data extraction and critical appraisal of Poynard and colleagues and Manns and colleagues can be found in our previous assessment report[11]. This can be downloaded from www.ncchta.org

Poynard and colleagues (2002)[74] conducted a meta-analysis to estimate the impact of anti-viral treatment on liver fibrosis in patients who had achieved an SVR after anti-viral treatment, as well as those who didn't. This supersedes their earlier 2000 meta-analysis of 3 RCTS of non-pegylated interferon alfa and ribavirin (n=1509 patients)[75] In the 2002 publication, data from four similar pivotal RCTs that tested either IFN α-2b or PEG IFN α-2b regimens in HCV were combined. (One of which is Manns and colleagues' 2001 RCT of PEG 2b, reported below). These regimens could be either monotherapies or dual therapy combining RBV with IFN or PEG. The 'control' regimen was considered to be IFN 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. Liver biopsies were scored using the Metavir scoring system. Mean fibrosis stage varied between 1.3 and 1.5 depending on the study. This is slightly higher than the threshold for mild HCV in the Metavir system (≤ 1). However, the proportion of patients with a Metavir score of ≤ 1 varied between 68% to 78% across the studies. The majority of patients could therefore be considered as having mild HCV. This is endorsed by the authors who report that at baseline 2243 patients had no significant fibrosis (75%), defined as Metavir F0-F1.

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

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 α-2a or IFN α-2a.

A range of detailed results were presented. The key findings are summarised below:

- 1094 (36%) were sustained virological responders; 1452 (48%) were virological non-responders; 464 virologically relapsed (16%).
- The SVR varied according to treatment regimen, ranging from 5% to 63%. Lowest rates were observed in the older interventions evaluated, such as non-pegylated interferon alfa monotherapy (5% to 16%). Rates increased for different doses of PEG monotherapies (21% to 29%), followed by various regimens of IFN + RBV (34% to 51%), and reached their highest for various PEG + RBV doses (54% to 63%).
- Fibrosis stage improved in 20% of patients, stablised in 65%, and worsened in 15%, mostly in terms of a 1 point change. Improvements were generally higher among PEG + RBV treated patients, and lower among those given IFN monotherapy.

- All regimens significantly reduced fibrosis progression rates relatively to pre-treatment.
- There was significantly less worsening of fibrosis among patients who achieved SVR (7%) than among relapsers (17%) or non-responders (21%).
- Rates of fibrosis progression were lower after treatment in both virological responders and non-responders with no significant differences between different treatment regimens (but there was a significant difference between responders and non-responders).
- Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (F0/F1), SVR, age < 40 years, body mass index < 27 kg/m^2, no or mild baseline necroinflammatory activity (based primarily on necrosis), and viral load < 3.5 million copies/ml.

Manns and colleagues (2001) Pegylated interferon alfa 2b + Ribavirin

Manns and colleagues (2001)[17] report an international multi-centre RCT of PEG 2b + RBV compared to IFN + RBV (also included in Poynard's meta-analysis above). This was one of the pivotal registration trials included in our previous assessment report[f]. 1530 patients were assigned to:

- IFN (3 MU 3 x week), + RBV 1000-1200 mg/day for 48 weeks. N=505
- PEG (1.5 µg/kg 1x week) + RBV 800 mg/day for 48 weeks. The 'high PEG dose' group. N= 511
- PEG (1.5 µg/kg per week for 4 weeks, followed by 0.5 µ/kg per week for 48 weeks). The 'low PEG dose' group N=514.

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

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

[f] The report contains a full data extraction and critical appraisal of this RCT, and can be downloaded from www.ncchta.org

[g] Note that the Knodell system has no fibrosis score of 2. See Section 2.1.2.3 and Appendix 1 for further details.

Table 22 - Baseline fibrosis scores for Manns and colleagues PEG 2b trial

	High PEG dose N=511	**Low PEG dose** N=514	**IFN + RBV** N=505
Manufacturer's submission[76] (Metavir)			
F0	8	0	0
F1	321	343	330
F0 + F1	329	343	330
Manns and colleagues (2001)[17] (Knodell)			
No/minimal fibrosis	333	345	336
Bridging fibrosis/cirrhosis	136	146	132

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

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

Table 23 - SVRs for all patients, and by baseline fibrosis (Manns and colleagues)

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

† p=0.01 for comparison with IFN + RBV
†† p=0.73 for comparison with IFN + RBV
* p=0.04 for comparison with IFN + RBV
** p=0.65 for comparison with IFN + RBV
¶ P= 0.62 for comparison with IFN + RBV
¶¶ P=0.72 for comparison with IFN + RBV

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

Bruno and colleagues (2004) Pegylated interferon alfa 2b + ribavirin in genotype 1 patients

Bruno and colleagues (2004) report an RCT of PEG 2b in combination with ribavirin for initial treatment of patients with genotype 1. Patients received 48 weeks of PEG + RBV (80-100 depending on body weight for 8 weeks, followed by 50 for the next 40 weeks) (n= 163), or IFN 6 MU on alternate days (n=148). Both regimens contained ribavirin 1000-1200mg/day. The mean Ishak fibrosis score was 2.61 to 2.62 across the two study groups. Two hundred and one patients (65%) were classified as having mild HCV at baseline, based on an Ishak fibrosis score of either 1 or 2 (no patients with zero score are reported).

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

Table 24 - SVR by baseline fibrosis in Bruno and Colleagues (2004)

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

P=0.001

Although the authors do not tabulate SVRs by baseline fibrosis stage for the respective study groups, they do provide a bar chart of SVRs by baseline stage for the PEG + RBV group. In the text they report that 19 of 31 patients (61.3%) with stage 1 fibrosis had an SVR, and that only 1 of 14 patients (7.1%) with stage 6 fibrosis (cirrhosis) had an SVR. We estimated the SVRs for the intermediate stages by reading off the graph, as follows: stage 2 (58%), stage 3 (31%), stage 4 (21%), and stage 5 (19%). Multi-variate analysis also confirmed mild baseline fibrosis as an independent predictor of SVR.

4.1.4.2 (Non-pegylated) interferon alfa studies

August-Jorg and colleagues (2003), Re-treatment with interferon alpha 2b and ribavirin in interferon alpha monotherapy relapsers

August-Jorg and colleagues (2003)[77] report a small pilot RCT of 24 versus 48 weeks of IFN + RBV in patients who had relapsed following previous IFN monotherapy. Of the 19 patients assigned to the 24 weeks treatment, 9 (50%) were classed as having 'none/mild' fibrosis at baseline, with the remaining 9 classed as 'moderate / severe/

cirrhosis'. Of the 18 patients receiving 48 weeks treatment, the proportions were 8 (44%) and 9 (50%), respectively. Histology was classified using the Metavir system. Sustained responses (SR) were (10/19) 53% in the 24 week group, and 13/18 (72%) in the 48 week group. For the 24 week treatment group the SR was higher for the moderate to severe fibrosis group (7/10, 70%), compared to the none/mild fibrosis group (3/9, 33%). This pattern was reversed in the 48 week treatment group, where the SR in the none/mild fibrosis group was higher than in the moderate to severe fibrosis group (10/12, 83% vs 2/5, 40%). However, caution is advised as these are relatively small numbers of patients, and statistical significance values are not reported.

Berg and colleagues (2000) Induction treatment with interferon alfa 2a and ribavirin followed by interferon alone

Berg and colleagues (2000)[78] report results of an RCT evaluating induction therapy with IFN + RBV followed by IFN monotherapy in previously untreated patients. One hundred and eighty five patients recruited from University clinics in Germany were randomised to the following treatment groups:

- IFN 6MU 3 x week + RBV for 12 weeks (n=93)
- IFN 6MU 3 x week for 12 weeks (n=92)

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

All patients received a liver biopsy prior to therapy, with findings classified according to what appears to be the Metavir system (the authors cite papers by Hytiroglou and colleagues (1995)[79], and Desmet and colleagues (1994)[80] in relation to histological classification). The mean fibrosis stage at baseline in both treatment groups was 1.5. The proportion of patients classed as having fibrosis with numerous septa (stage 3) was 20 (11%), and the number with cirrhosis (stage 4) was 2 (1%).

A 12 week response was achieved by 61/93 (66%) of patients in the IFN + RBV group, compared to 44/92 (48%) in the IFN monotherapy group (p=0.015). An SVR was achieved by 24/93 (26%) in the IFN + RBV group, compared to 16/92 (17%) in the IFN group, although the difference was not significant (p=0.10). Table 22 presents the results of the sub-group analyses by mean baseline fibrosis stage, and proportion of patients with fibrosis scores ≤ 1 or >1 (the threshold for defining mild HCV).

Table 25 - SVR by baseline fibrosis in Berg and colleagues (2000)

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

± Mean ± SEM
n/N(%)

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

De Ledinghen and colleagues (2002a)[81] Daily or three times a week interferon alfa 2b plus ribavirin in patients not responding to previous interferon alfa

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

- 6MU IFN 3 x week for 24 weeks, followed by 3MU 3 x week for 24 weeks (Group A)
- 6MU IFN 3 x week + RBV for 24 weeks, followed by 3MU 3 x week + RBV 24 weeks (Group B)
- 3MU IFN daily + RBV for 24 weeks, followed by 3MU 3 x week + RBV for 24 weeks (Group C)

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

SVRs were achieved by 7 (6%), 27 (21%) and 33 (26%) of patients in groups A to C respectively. Differences between group B and A, and group C and A were statistically significant. SVRs were reported for sub-groups of patients, 'cirrhosis or bridging fibrosis' (n=125) and 'minimal or no fibrosis' at baseline (n = 186). Their definition of the latter includes patients with Metavir scores ≤ 2 which is one stage higher than the threshold used in this report for defining mild HCV (see Section 3.2.2). Table 20 presents the results.

Table 26 SVR by baseline fibrosis in De Ledinghen and colleagues (2002a)

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

In groups B and C SVRs were around 10% higher for the 'minimal or no fibrosis' sub-group than the 'cirrhosis or bridging fibrosis' sub-group. However, for Group A the difference was marginal. No significance values are presented between treatment groups or patient sub-groups. Logistic regression was performed to assess the association between a number of factors and SVR. In the univariate analysis Metavir fibrosis score F0, F1 or F2 vs F3 or F4 was not significantly related to SVR (p=0.06). However, it was significant in the multi-variate analysis (p=0.001).
In summary, this study shows that SVRs were generally higher for mild HCV patients treated with IFN + RBV for 24 weeks compared to those with moderate to severe HCV. However, the sub-group of patients with minimal or no fibrosis included a

substantial proportion of patients with Metavir fibrosis score 2, considered to be in the moderate category of disease severity, according to the definition of mild HCV used in this report.

De Ledinghen and colleagues (2002b) Daily or three times a week interferon alfa 2b plus ribavirin in previously untreated patients.

The purpose of this second trial by De Ledinghen and colleagues (2002b)[82] was to compare IFN monotherapy with the standard regimen of IFN given three times a week in combination with RBV, or an induction dose of daily IFN in combination with RBV in previously untreated patients.

- IFN (3MU 3 x week) for 48 weeks (Group A),
- IFN (3MU 3 x week) + RBV daily for 48 weeks (Group B),
- IFN 3MU daily + RBV daily for 12 weeks followed by 3MU 3 x week for 24 weeks (Group C).

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

SVRs were achieved by 23 (25%), 59 (52%), and 53 (46%) of patients in groups A to C respectively. Differences between group B and A, and group C and A were statistically significant. No statistically significant difference was observed between groups B and C. SVRs were reported for sub-groups of patients, 'cirrhosis or bridging fibrosis' (n=87) and 'minimal or no fibrosis' at baseline (n = 230). Their definition of the latter includes patients with Metavir scores ≤ 2 which is one stage higher than the threshold used in this report for defining mild HCV (see Section 3.2.2). Table 21 presents the results.

Table 27 SVR by baseline fibrosis in De Ledinghen and colleagues (2002b)

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

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

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

Di Bisceglie and colleagues (2001) Interferon alfa 2b and ribavirin in the re-treatment of non-responders to interferon alfa

Di Bisceglie and colleagues (2001) recruited patients who had not responded to a previous course of interferon monotherapy, from the liver clinic of Saint Louis University in the United States. A total of 124 patients were randomised to receive IFN + RBV for either 24 or 48 weeks. All patients received a biopsy prior to treatment, with samples classified according to the Scheuer system (see Section 2.1.2.3). The proportion of patients with a baseline fibrosis score of 1 was 24 (19%), compared to 32 (26%) for stage 2, (33%) for stage 3 and 27 (22%) for stage 4. A score of 1 or less indicates mild HCV on this system.

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

Gettachew and colleagues (2004) Interferon alfa 2b and ribavirin in previously treated /untreated Veterans

Gettachew and colleagues[83] report a small RCT of previously treated and untreated patients recruited from the Dallas Veterans Affairs Medical Center. The aim of the trial was to evaluate the effectiveness of high dose induction therapy with IFN in combination with RBV, compared to standard dose combination therapy.
Patients were randomly assigned to the following groups:

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

Patients with genotypes 2 and 3 were treated only for 24 weeks. The Knodell system was used to classify biopsy samples. At baseline the majority of patients (31/68%) had bridging fibrosis or cirrhosis (stages 3 to 4), with the remaining patients either having no or minimal fibrosis (stages 0-1) (10/22%), or unclassified (4/8%). This trial, therefore, had a high proportion of patients with advanced HCV related liver disease.

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

Table 28 SVR by baseline fibrosis and genotype in Gettachew and colleagues 2004

Sub-group	Total	High induction dose	Low dose
F stage 0-1	3/10 (30)	1/3 (33)	3/7 (43)
F stage 3-4	10/31 (32)*	5/17 (29.4)	4/14 (28.6)
SVR genotype 1	7/34 (20)	3/17 (17.6)	4/17 (23.5)
F stage 0-1	1/7 (14.3)	0/2 (0)	1/5 (20)
F stage 3-4	6/24 (25)**	3/14 (21)	3/10 (30)
SVR genotype 2A/2B 3A/2B	7/11 (64)	4/5 (80)	3/6 (50)
F stage 0-1	3/3 (100)	1/1 (100)	2/2 (100)
F stage 3-4	3/7 (42.8)***	2/3 (67)	1/4 (25)

n/N(%)
* p=1.00 (stage 3-4 vs stage 0-1)
** p=1.00 (stage 3-4 vs stage 0-1)
*** p=0.2 (stage 3-4 vs stage 0-1)

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

Mangia and colleagues (2002)[84] High versus low dose interferon alfa 2b plus ribavirin in previously untreated patients

The aim of this open-labelled RCT by Mangia and colleagues (2002)[84] was to compare a high dose of IFN (5MU) to the lower, standard dose (3MU) in patients recruited from seven community hospitals in the south of Italy. Both doses of IFN were administered in combination with ribavirin, for 12 months. A total of 298 patients were treated, 148 in the 5MU group and 150 in the 3mU group. The Scheuer system was used for classifying biopsy samples. At baseline 121 (41%) of the sample were classified as having a fibrosis score of ≤ 1 (indicating mild HCV). SVRs were 71/148 (48%) in the 5MU group, and 61/150 (40%) in the 3mU group. However, differences were not statistically significant (p=0.25). The effect of baseline histology was explored in univariate analysis. For stage 0 to 1 patients there were 67 sustained responders (50.7%) compared to 54 (32.5%) non-responders. For stages 2 to 3 the proportions were 65 (49%), and 112 (67.4%), respectively. The proportion of sustained responders with mild HCV was similar to those with moderate HCV. Differences between sustained responders and non-responders were statistically significant (p=0.002).

Poynard and colleagues (2000) pooled analysis of two pivotal interferon alfa 2b and ribavirin RCTs

Poynard and colleagues (2000)[85] present a pooled analysis of two multi-centre international RCTs of IFN + RBV in comparison to IFN monotherapy in previously untreated patients (Poynard and colleagues 1998[18], and McHutchison and colleagues 1998[86] – for full data extraction and critical appraisal of these trials please refer to our earlier assessment report[87], which can be downloaded from www.ncchta.org). The

purpose of pooling them was to increase the power of the analysis to ascertain, amongst other things, which factors were associated with SVR.

The total number of patients analysed was 1,744, all of whom were treatment naïve. The Metavir system was used to classify histological status, although the baseline histological profile of the sample is not reported. Four treatment groups are included, two evaluating IFN + RBV (48 and 24 weeks), and two evaluating IFN + placebo (48 and 24 weeks), SVRs for the four groups, respectively, were as follows: 41% (205/505), 33% (166 of 505), 16% (82 of 503), and 6% (13 of 231). Significant differences were found between all groups.

Table 24 shows the SVRs for the sub-group of patients with 'no or portal fibrosis' (stage 0 to 1) or 'septal fibrosis or more' (stage 2 to 4).

Table 29 SVR by baseline fibrosis in Poynard and colleagues 2000

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

n/N(%)

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

4.1.4.3 Summary

- The aim of this section was to briefly review RCTs/meta-analyses which reported within-trial SVRs according to sub-groups of patients with mild and moderate to severe HCV.
- We found 11 studies ranging from international multi-centre RCTs to small scale pilot RCTs. Three evaluated PEG, and the remaining eight evaluated IFN. The majority of report evaluations of PEG 2b / IFN 2b. Doses and regimens varied considerably.
- Around half of the studies included previously untreated patients. The other half included patients and re-treated following non-response or relapse to previous treatment.
- In general, higher SVRs were observed for patients classified as having mild HCV at baseline, compared to those classified as moderate to severe HCV (n= 7 studies). However, this was only statistically significant in one study, with the remaining studies not reporting any significance values. Another study reported no statistically significant difference in SVRs between mild and moderate to severe fibrosis.
- In five studies no or minimal fibrosis was significantly and independently associated with SVR, as assessed in multivariate logistic regression analyses.
- In a meta-analysis of RCTs, baseline fibrosis stage (F0/F1) was associated with absence of significant fibrosis after treatment.

5 ECONOMIC ANALYSIS

5.1 Introduction

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

- a systematic review of the literature on the cost-effectiveness of interferon-based treatments in adults with mild chronic hepatitis C (section 5.2);
- a review of the manufacturer submissions (cost-effectiveness section) to NICE (Sections 5.3 and **Error! Reference source not found.**);
- presentation of our economic model and cost-effectiveness evaluation (Section 0).

5.2 Systematic review of the literature

5.2.1 Methods for the systematic review

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

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

5.2.2 Results of the systematic review: cost-effectiveness

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

- Sixty five were identified as full economic evaluations. No systematic reviews of the cost-effectiveness of treating mild chronic hepatitis C were identified by the search.
- Thirty seven of the full economic evaluations were initially excluded as they were not concerned with anti-viral treatment of chronic hepatitis C or were evaluations in non-adult populations.
- The remaining twenty nine economic evaluations of anti-viral treatment of chronic hepatitis C were decision analyses using data on treatment effects derived from clinical trials, with the majority adopting a common natural history model[88].
- Only seven[12;88-93] were concerned with interferon treatment for patients with mild chronic hepatitis C. One of these[89] was excluded from this review as it was solely concerned with the incremental cost-effectiveness of dual therapy compared to monotherapy and did not evaluate interferon-based treatment compared to no

treatment or delayed treatment. While the remaining twenty two evaluations included patients with mild disease in the cohorts modelled, only one reported separate analyses by stage of disease[94]. This evaluation did not indicate the criteria for defining mild disease or the source of the effectiveness data used to model treatment for patients with mild disease and is not reviewed here.

- Only two of the six published evaluations for interferon treatment for patients with mild chronic hepatitis C in the review included pegylated interferon as an intervention.

Table 30 provides a summary of the characteristics and base case finding for the six published economic evaluations reporting the cost-effectiveness of interferon-based treatment for mild chronic hepatitis C (see also Appendices 18 to 23 for full data extraction and critical appraisal of each study). The studies are either United States or European/UK based (one of these[12] is the cost-effectiveness analysis of the UK Mild HCV Trial which is included in the assessment of effectiveness in Section 4.1.2), although the clinical literature used to derive estimates of the effectiveness of interferon-based treatment for mild chronic hepatitis C covers a wide range of countries and institutional settings. All studies that compared anti-viral treatment to best supportive care indicate that it is effective in terms of improved life expectancy and quality-adjusted life expectancy compared to no anti-viral treatment. Those studies which have compared the effects of early versus delayed treatment (i.e. watchful waiting) have generally shown that early intervention is cost-effective for genotype non-1 patients. Early treatment is less likely to be cost-effective for genotype 1 patients, due to the lower SVRs observed for this subgroup, and for whom the recommendation from these analyses has been to wait until moderate disease develops before starting treatment.

5.2.2.1 Estimation of outcomes within economic evaluations

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

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

Each of the models adopted for these evaluations allows the possibility of patients with progressive liver disease to undergo liver transplantation. Bennett et al[88] specified in their state transition model that transitions were allowed from the decompensated cirrhosis health states (ascites, variceal haemorrhage and hepatic encephalopathy) to liver transplantation but not from hepatocellular carcinoma. The majority of included papers followed this same assumption, either by directly

adopting the same decision model[90;92] or by citing this assumption within their tables of transition probabilities[91;93].

Table 30 - Characteristics of economic evaluations of interferon treatment for mild chronic hepatitis C

Author	**Bennett**[88]	**Davis**[90]	**Wong**[92]
Publication Year	1997	1998	2000
Country	USA	USA	USA
Study type	CEA model	CUA model	CUA model
Study population	Mild CHC	Mild CHC	Mild CHC with elevated ALTs
Intervention(s)	interferon alfa-2b monotherapy versus no anti-viral treatment.	interferon alfa-2b monotherapy for varying durations versus no anti-viral treatment.	Four strategies: 1) no anti-viral treatment 2) early treatment; 3) watchful waiting with treatment once cirrhotic; 4) watchful waiting with treatment once moderate. Treat with non-pegylated interferon alfa-2b dual therapy.
Treatment effect modelled	SVR (persistently normal serum ALT level for at least 6 months after completion of treatment). Same SVR (27%) applied to mild and moderate patients based on pooled results of five clinical trials[95-99].	SVR (persistently normal serum ALT level for at least 6 months after completion of treatment). SVR of 36.4% for 18-24 months and 15.3% for six month course were applied based on pooled results of two clinical trials[99;100].	SVR (not defined). SVR of 71.6% and 36.7% for women with genotype 2/3 and non-2/3 respectively. 62.5% and 27.7% for men with genotype 2/3 and non-2/3 respectively. Based on pooled results of two clinical trials[18;86]. Same SVR for early and delayed treatment.
Currency base		1995 US $	1998 US $
Base case results	35 year old with mild CHC gain 0.26 life years (discounted at 5%) with incremental cost of $490 (discounted at 5%) for interferon alfa-2b treatment compared to standard care. Discounted incremental QALYs not reported.	35 year old with mild CHC gains 0.98 QALYs from 6 months and 2.26 QALYs from 18-24 months treatment (discounted at 3%) with incremental lifetime cost of $609 and $1732, respectively (discounted at 3%) for interferon alfa-2b treatment compared to standard care. ICERs were $621 and $766 respectively.	Cohort with mean age of 40, over 20 years strategy 4 reduces cirrhosis to 18% compared to 28% no treatment and avoids treatment in 50% of cohort compared to strategy 2. Incremental QALYs for strategy 2 and strategy 4 vs no treatment are 1.1 and 0.6 respectively. Incremental costs are $7,000 and $6720.

Table 30 (continued) - Characteristics of economic evaluations of interferon treatment for mild chronic hepatitis C

Author	**Grieve and Roberts**[93]	**Salomon**[91]	**Grieve**[12]
Publication Year	2002	2003	2005
Country	Europe	USA	UK
Study type	CUA model	CUA model	CUA model
Study population	Mild CHC	Mild with elevated ALTs	Mild CHC
Intervention(s)	Immediate treatment with combination versus treatment on development of moderate CHC (current UK guideline).	Five strategies: 1) no anti-viral treatment 2) interferon alfa-2b monotherapy; 3) pegylated interferon alfa-2b monotherapy; 4) interferon alfa-2b dual therapy; 5) pegylated interferon alfa-2b 2b dual therapy.	Immediate treatment with non-pegylated interferon alfa-2b dual therapy versus treatment on development of moderate CHC (current UK guideline). Assume same response for mild and moderate patients.
Treatment effect modelled	SVR (not stated – definition for trial was absence of HCV RNA in the serum at 24 weeks post-treatment cessation[65]). SVR or 43% based on one clinical trial[18] assuming 50:50 ratio of genotype 1 and genotype non-1 patients. Assume same response for mild and moderate patients.	SVR (undetectable HCV-RNA in the serum for at least 6 months after treatment cessation). SVR of 31% (6%) for interferon dual (mono) and 42%(15%) for pegylated interferon dual (mono) therapy in genotype 1. SVR of 67% (26%) for interferon dual (mono) and 79% (47%) for pegylated interferon dual (mono) therapy in genotype non-1. Based on pooled results of five clinical trials[17;18;73;86;101].	SVR (not stated – definition for trial was absence of HCV RNA in the serum at 24 weeks post-treatment cessation[65]). SVR of 33% (18% genotype 1 and 49% genotype non-1) based on one clinical trial[65] for non-pegylated interferon. SVR for pegylated interferon (24% genotype 1 and 55% genotype non-1), based on odds ratio for SVR for PEG compared to IFN from one clinical trial[17].
Currency base	2001 Euros	US $	2002/03 UK £. Report 2002/03 US $ for comparison
Base case results	Cohort of 1,000 patients with mean age of 40 would experience 55 fewer deaths with early treatment. The gain in life expectancy is 1.2 years and 1.8 QALYs compared to delayed treatment. Incremental costs of early treatment were €14,882. ICERs quoted were €12,089 per life year gained and €8,490 per QALY gained.	Probability of developing cirrhosis over 30 years ranged from 13-46% in men and 1-29% in women. Substantial range in ICERs for dual therapy with pegylated interferon ($26,000 - $64,000 for G1 and $10,000 - $28,000 for non-G1 in men; $32,000 - $90,000 for G1 and $12,000 - $42,000 for non-G1 in women). Benefits largely depend on improved quality of life, not survival.	Genotype non-1 patients gain 0.61 QALYs with early treatment over delayed treatment. Incremental lifetime cost of £2,300 with non-pegylated interferon. £3,733/QALY for non-pegylated interferon alfa-2b dual therapy (£28,754 for pegylated interferon). Lower QALY gain for genotype 1 (0.18) for early treatment. Incremental lifetime cost of £4,000. ICERs are £23,029/QALY for non-pegylated interferon alfa-2b dual therapy (£36,440 for pegylated interferon)[h].

[h] These results differ from those in the on-line publication[12] and have been supplied by the lead author (Richard Grieve, personal communication).

Table 31 presents an outline of the approaches used to model disease progression and treatment effects in cost-effectiveness models for anti-viral treatment in mild chronic hepatitis C. Table 32 reports the transition probabilities adopted in the economic evaluations reviewed here, while Table 33 in Section 5.2.3.2 presents the health state utilities used in their models. All the evaluations have modelled disease progression for a specified cohort of patients starting with mild chronic hepatitis C. Definitions of mild disease vary between the included studies. While each study has based the definition of mild disease on histological measures they have varied as to whether they have used a purely fibrosis-based measure[91] or a combination of fibrosis and inflammation scores[12;88;90;92;93]. Moreover, different scoring systems have been adopted for defining severity of liver disease. However the fibrosis-based definitions used for mild disease under each of these scoring systems in the included studies are consistent with those indicated in the mapping presented by Kleiner[15], reproduced in this report in Table 2 (Section 2.1.6).

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

Salomon and colleagues[91] extracted data on fibrosis progression from intervention trials that included serial liver biopsies and cross-sectional studies that included fibrosis stage related to duration of infection[105-108]. These studies were used to estimate ranges for age- and sex-specific fibrosis progression rates to be used in simulation models. Predicted outcomes from the simulations were compared to epidemiological data on prevalence of HCV and mortality from hepato-cellular carcinoma in the USA. A subset of parameter values, which were selected on the basis of goodness of fit[109], were used in the economic model. The fibrosis progression rates adopted for the economic model increase with age, in contrast to those adopted in the previous evaluations in which progression rates were constant with respect to age.

Grieve and colleagues[12] used estimates for early transition probabilities (from mild to moderate disease and from moderate disease to cirrhosis) derived from re-analysis of a dataset used in a previously published retrospective cohort study[26]. Data on 373 cases who attended St Mary's Hospital, London, between 1st January 1990 and 30th June 2001 and who had at least one biopsy were analysed. Patients with HCC, other types of liver disease in addition to hepatitis C, HIV co-infection or treatment prior to first biopsy were excluded. For the purposes of modelling disease progression mild chronic hepatitis C was defined as Ishak fibrosis stages F0 to F2, moderate disease as stages F3 to F5 and cirrhosis as stage F6. Annual transition probabilities for forward transitions between consecutive states were estimated using maximum likelihood. Covariates associated with increased progression were male sex, older age at infection, and alcohol consumption greater than 40 units per week – no significant

association with viral genotype 1 was shown. As with the estimates developed by Bennett and colleagues[88], these early transition probabilities are constant with respect to time. The estimates of fibrosis progression developed for the cost-effectiveness analysis of the UK Mild HCV trial presented by Grieve and colleagues[12] are lower than those estimated by Bennett and colleagues[88] and adopted by Davis and colleagues[90] and Wong and colleagues[92] – and are lower than those applied in a preliminary analysis from the Mild Hepatitis C Trial team[93].

The other major difference between models adopted in the included studies is whether decompensated disease is modelled as a single entity[12;93] or by separate clinical manifestations (ascites, variceal haemorrhage and hepatic encephalopathy)[88;90-92]. This may have an impact on the clinical validity of the disease progression model, since large differences in mortality, quality of life and cost may be expected between the sub-states included under the heading of "decompensation" (see Table 32, Table 33, Table 36). However this is unlikely to have a substantial impact on the analysis of anti-viral treatment for people with mild CHC since the vast majority of their life expectancy will be spent in the early stages of liver disease. Assumptions over the rate of disease progression in the early stages of disease will have a far greater impact than decisions over the disaggregation of later disease states.

Table 31 - Model structure/ assumptions for cost-effectiveness models for anti-viral treatment of mild CHC

Author	Bennett[88]	Davis[90]	Wong[92]
New model	Yes	Adapted from Bennett and colleagues[88]	Adapted from Bennett and colleagues[88]
Number of states	11 Remission/SVR Mild CHC Moderate CHC CHC with cirrhosis Ascites Refractory ascites Variceal bleed HE HCC Liver transplant Death	11 Remission/SVR Mild CHC Moderate CHC CHC with cirrhosis Ascites Refractory ascites Variceal bleed HE HCC Liver transplant Death	11 Remission/SVR Mild CHC Moderate CHC CHC with cirrhosis Ascites Refractory ascites Variceal bleed HE HCC Liver transplant Death
CHC severity	Mild - Moderate PPI ≤ 1 & F≤ 1 F=3 or (F≤ 1 & (PPI ≥ 3 & PPI≤ 10) Cirrhosis F=4	Mild - PPI ≤ 1 & F≤ 1	Mild - raised ALT & PPI ≤ 1
Cycle length	1 year	1 year	1 year
Time horizon	Lifetime	Lifetime	Lifetime
Baseline cohort	35 years old with mild CHC	35 years old with mild CHC	40 years old, 35% female, 32% genotype 2/3
Genotype	No account taken of genotype	No account taken of genotype	SVRs vary by genotype and sex. Outcomes (life years and QALYs) reported by genotype, but not cost-effectiveness.

Notes:
PPI = peri-portal inflammation score (Knodell)
F = fibrosis score (Knodell)

Table 31 (continued) - Model structure/ assumptions for cost-effectiveness models for anti-viral treatment of mild CHC

Author	Grieve and Roberts[93]	Salomon[91]	Grieve[12]
New model	No - adapted from Dusheiko and Roberts[110]	No - adapted from Bennett and colleagues[88], but using METAVIR scoring system to define fibrosis stages	No - adapted from Grieve and Roberts[93]
Number of states	8 Remission/SVR Mild CHC Moderate CHC Cirrhosis Decompensated cirrhosis HCC Liver transplant Death	12 Remission/SVR F0 F1 F2 F3 F4 Ascites Variceal bleed HE HCC Liver transplant Death	8 Remission/SVR Mild CHC Moderate CHC Cirrhosis Decompensated cirrhosis HCC Liver transplant Death
CHC severity	Mild - NI≤ 3, F≤ 2, serum positive for HCV, with normal or raised ALT	Mild - F0 serum positive for HCV, with raised ALT	Mild - NI≤ 3, F≤ 2, serum positive for HCV, with normal or raised ALT
Cycle length	1 year	1 year	1 year
Time horizon	Lifetime	Lifetime	Lifetime
Baseline cohort	40 years old with mild CHC	40 years old (% female and % by genotype not reported) with raised ALT and no fibrosis	40 years old with mild CHC
Genotype	SVRs vary by genotype. Results not reported by genotype.	SVRs vary by genotype. Cost-effectiveness results reported by genotype and sex	SVRs vary by genotype. Cost-effectiveness results reported by genotype.

Notes:
NI = necro-inflammation score (Ishak)
F = fibrosis score (Ishak)
F0, F1, F2, F3, F4 = stages in METAVIR fibrosis scoring system (see Appendix I for definitions of fibrosis stages).

Table 32 - Transition probabilities used in published economic evaluations

Health state					
From	**To**	**Bennett[88], Davies[90], Wong[92]**	**Salomon[91]**	**Grieve and Roberts[93]**	**Grieve[12]**
Mild CHC	Remission	0.002	0.012	0.000	0.000
Mild CHC	Moderate CHC	0.041	Age / Male / Female[a] 40-49 / 0.054 / 0.028 50-59 / 0.125 / 0.065 60-69 / 0.221 / 0.114 70-79 / 0.301 / 0.154 >=80 / 0.301 / 0.210	0.060	0.025
Moderate CHC	Compensated cirrhosis	0.073		0.060	0.037
Moderate disease	Hepatocellular carcinoma	0.001	0.000	0.000	0.000
Compensated cirrhosis	Decompensated cirrhosis	Asc 0.025 VH 0.011 HE 0.004	0.040	0.040	0.039
Compensated cirrhosis	Hepatocellular carcinoma	0.015	0.021	0.000	0.014
Decompensated cirrhosis	Hepatocellular carcinoma	0.000	0.000	0.010	0.014
Decompensated cirrhosis	Liver transplant	0.031	0.031	0.030	0.020
Hepatocellular carcinoma	Liver transplant	0.000	0.000	0.000	0.00
Decompensated cirrhosis	Decompensated cirrhosis	Asc -> R Asc 0.067	NA	NA	NA

Health state					
From	**To**	**Bennett[88], Davies[90], Wong[92]**	**Salomon[91]**	**Grieve and Roberts[93]**	**Grieve[12]**
Decompensated cirrhosis	Death	Asc 0.110 R Asc 0.330 VH Yr 1 = 0.400 Yr 2 = 0.130 HE Yr 1 = 0.680 Yr 2 = 0.400	0.306	NR	0.130
Hepatocellular carcinoma	Death	0.860	0.433	NR	0.43
LT	Die	Yr 1 = 0.210 Yr 2 = 0.057		NR	Yr 1 = 0.150 Yr 2 = 0.030

Asc = ascites; R Asc = refractory ascites; VH = variceal haemorrhage; HE = hepatic encephalopathy
NA = not applicable; NR = not reported
[a] – the reported progression probabilities are for progression through METAVIR fibrosis stages. the mild and moderate disease health states each comprise two METAVIR stages (See Table 2, Section 2.1.6) these values for progression between fibrosis stages are not directly comparable with transition probabilities for movement between adjacent health states.

5.2.2.2 Estimation of costs within economic evaluations

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

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

Published economic evaluations – summary of methods

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

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

We undertook a literature search to identify studies reporting health state values/ utilities for individuals with chronic hepatitis C by stage of fibrosis. The details of databases searched and search strategy are documented in Appendix 5. The literature search identified two published studies reporting on health state values/utilities for patients with chronic hepatitis C by stage of fibrosis[111;112]. Health state values/ utilities used in previous economic evaluations of anti-viral treatment for patients with mild chronic hepatitis C are presented in section 5.2.3.2, along with further supporting information on quality of life for patients with progressive liver disease associated with chronic hepatitis C

5.2.3.1 Health state valuations

Chong and colleagues. Health state utilities and quality of life in Hepatitis C patients[111]

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

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

- SVR – negative qualitative PCR at least 6 months after treatment cessation (n=36);
- Mild or moderate CHC – liver biopsy showing METAVIR stage 0 through 3 (n=44);
- Compensated cirrhosis – liver biopsy or definite ultrasound/ CT scan showing cirrhosis but no clinical signs of decompensation;
- Decompensated cirrhosis – at least one event of variceal haemorrhage, ascites or hepatic encephalopathy (n=24);
- HCC – demonstrated by liver biopsy or CT scan (n=15, with 7 of these due to HCV, the rest with a mixture of aetiology);
- Liver transplant (n=30);
- No biopsy - without liver biopsy or biopsy more than 2 years old showing no cirrhosis (n=35).

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

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

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

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

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

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

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

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

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

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

The authors conclude that the study confirms previous research[50;115] which suggests that people with CHC have lower health-related quality of life than the general population. The absence of any consistent relationship between disease severity (as measured by ALT) and quality of life or health state values is also consistent with previous studies [50;115;116] – although the authors do not acknowledge this or refer to this previous research. They argue that previous decision analyses and economic models, incorporating expert panel-derived health state valuations, overstate the differences in utility values across stages and severity of disease – citing Chong and colleagues[111] in support of this argument.

5.2.3.2 Supporting information on quality of life associated with chronic hepatitis C

Table 33 reports the health state values/ utilities applied in previous economic evaluations of interferon treatment for patients with mild chronic hepatitis C. Bennett and colleagues[88] and Davis and colleagues[90] adopted the same model for their analysis, hence the same quality of life weights. Similarly, Salomon and colleagues[91] adopted quality of life weights derived by Wong for a previous decision analysis[117] which were also used in the subsequent evaluation of treatment for mild chronic hepatitis C by Wong and colleagues[92].

Table 33 - Health state values/ utilities used in previous economic evaluations of anti-viral treatment for mild chronic hepatitis C

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

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

† indicates that valuations were derived from ratings by an expert clinical panel
‡ indicates that valuations were derived from patient ratings of current health state. Responses to EuroQol (EQ-5D) questionnaire were transformed to utility values using a standard tariff[118]

NB. A utility value of 0 = death, utility value of 1 = perfect health

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

The clinician derived valuations are dissimilar to the patient-derived valuations reported from the UK Mild HCV trial which show a similar decrement in utility

through diseases stages from mild CHC to decompensation. The reduction in health state valuations is approximately 0.1 at each stage of disease. In contrast, the values adopted in previous economic evaluations showed a distinct reduction in utility when moving from compensated cirrhosis to decompensated disease. Chong and colleagues[111], similarly showed smaller decrements between disease states up to compensated disease, but a more substantial decrease between compensated cirrhosis and decompensated disease.

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

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

5.3.1 Estimation of benefits

5.3.1.1 Model structure/ structural assumptions

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

The model includes seven health states:

- Remission;
- Chronic hepatitis C (severity of disease defined by METAVIR fibrosis stages);
- Cirrhosis (METAVIR stage F4);
- Decompensated cirrhosis;
- Hepatocellular carcinoma;
- Liver transplantation;
- Death.

All patients start in the chronic hepatitis C health state – distributed roughly evenly (57% and 43% respectively) between the no fibrosis (F0) and minimal scarring (F1) stages which indicate mild disease using the METAVIR staging system. The natural history model has a proportion of patients progressing through increasing stages of fibrosis within the chronic hepatitis C health state toward the cirrhosis health state. Patients in these health states are not exposed to any condition-specific excess mortality and face only general population mortality risks. Patients who develop cirrhosis may progress to one of two health states (decompensated disease or hepatocellular carcinoma, both of which have an excess mortality risk) or may remain

in the cirrhotic state. Patients with decompensated disease may be eligible for liver transplantation. This is not an allowed transition for patients with hepatocellular carcinoma, where the majority of patients will have died within a year of entering this state.

The primary outcome modelled is sustained viral response – defined as undetectable HCV RNA in serum 24 weeks after the end of treatment. The benefits of treatment are assumed to result only from changing patients' virological status, in that an SVR is regarded as a cure. Patients achieving an SVR enter the remission health state where they face no risk of progressive liver disease and are subjected only to general population mortality risks. Moreover an SVR is associated with in increase in health-related quality of life, hence a higher utility value (see Section 5.3.1.3) and has a health state cost of zero.

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

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

5.3.1.2 Supporting data

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

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

<u>Pegylated interferon alfa dual therapy and non-pegylated interferon alfa dual therapy</u>
Two comparisons of pegylated interferon alfa and non-pegylated interferon alfa are reported:

- The first uses the early transition probabilities as reported by Salomon and colleagues[91] as estimates of fibrosis progression for patients with elevated ALTs. SVRs for pegylated interferon dual therapy in mild patients were derived for the sub-group of mild patients within the pegylated interferon alfa-2a trial by Zeuzem and colleagues[66] and for non-pegylated interferon were taken from the UK Mild HCV trial[65]. The lifetime treatment costs and health outcomes were estimated separately by genotype and sex. These results were combined by applying the

proportions of patients in each sex and genotype group included in the pegylated interferon alfa-2a trial[66].

- The second uses reduced fibrosis progression rates to estimate the cost effectiveness of intervention in patients with persistently normal ALTs. This is achieved by applying a relative rate estimate of 56%, derived from a longitudinal study of fibrosis progression in groups with elevated or normal ALTs[120], to the fibrosis progression rates taken from Salomon and colleagues[91]. It should be noted that this risk reduction has been applied across all METAVIR stages. However only patients in stages F0 to F2 were recruited to the study from which the relative risk was calculated. Otherwise the input data and calculations performed for this analysis are identical to those used for patients with elevated ALTs.

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

5.3.1.3 Health-Related Quality of life

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

Table 34 - Health state utilities for chronic hepatitis C

Health state	Chong and colleagues[111]	
SVR	0.86	
Mild CHC	F0 F1	0.79
Moderate disease	F2 F3	0.79
Compensated cirrhosis	F4	0.80
Decompensated cirrhosis	0.60	
Hepatocellular carcinoma†	0.72	
Liver transplant	0.73	

† n = 15; 7 with HCV, 4 with HBV, 3 with alcoholic liver disease and 1 with haemochromatosis.

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

5.3.2 Estimation of costs

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

The drug costs for non-pegylated interferon alfa dual therapy were based on a dosage of 3 million units three times per week (giving a weekly cost of £48.60) and 1000 mg of ribavirin daily (giving a weekly cost of £48.60). The treatment duration was 24 weeks for genotype 2/3, giving a total cost of £4,130, and 48 weeks for genotype 1, giving a total cost of £8,261. Drug costs for pegylated interferon alfa-2a were based on a dosage of 180 microgram/0.5 ml per week (giving a weekly cost of £132.00) and 800 mg of ribavirin daily (giving a weekly cost of £77). The treatment duration was 24 weeks for genotype 2/3, giving a total cost of £5,016, and 48 weeks for genotype 1, giving a total cost of £10,032. The submission contains no estimate of any additional costs arising from the assessment and monitoring of patients (including laboratory tests and investigations) during treatment.

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

Table 35 - Health state costs from Roche submission

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

Note the economics section of the Schering Plough submission to NICE on pegylated interferon alfa 2b is academic in confidence. Therefore our review of the submission (Section 5.4) will only appear in some versions of this report.

…[Academic in confidence material removed]

…[Academic in confidence material removed]…

5.3.2.1 Supporting data

…[Academic in confidence material removed]…

…[Academic in confidence material removed]…

5.3.2.2 Health-Related Quality of life

5.3.3 Estimation of costs

…[Academic in confidence material removed]…

Table 36 - Health state costs from Schering-Plough submission

State	Value	Source

[Academic in confidence material removed from table]

Non-pegylated interferon alfa 2b + ribavirin versus no treatment

Population	Incremental cost	Incremental QALYs	ICER
Overall			
Genotype 1			
Genotype 2 or 3			

Pegylated interferon alfa 2b + ribavirin versus non-pegylated interferon alfa + ribavirin

Population	Incremental cost	Incremental QALYs	ICER
Overall			
Genotype 1			
Genotype 2 or 3			

Table 37 –Cost-effectiveness of treatment with interferon alfa-2a (non-pegylated and pegylated). Patients with fibrosis scores of F0 (57%) and F1 (43%), age 45 (Roche submission)

Non-pegylated interferon alfa 2a + ribavirin versus no treatment

Population	Incremental cost	Incremental QALYs	ICER
Overall			
Genotype 1			
Genotype 2/3			

Pegylated interferon alfa 2a + ribavirin versus non-pegylated interferon alfa + ribavirin

Population	Incremental cost	Incremental QALYs	ICER
Overall			
Genotype 1			
Genotype 2/3			

SHTAC Cost-effectiveness analysis

5.4 SHTAC Cost-effectiveness model

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

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

5.4.2 Strategies/ comparators

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

- Dual therapy with pegylated interferon alfa and ribavirin;
- Monotherapy (pegylated interferon alfa) for those who cannot tolerate ribavirin;
- Dual therapy with non-pegylated interferon alfa and ribavirin.

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

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

5.4.3 Model type and rationale for the model structure

The principal outcome of interest in the clinical trials reviewed in Section 4 is the sustained virological response (SVR), defined as undetectable HCV-RNA in the

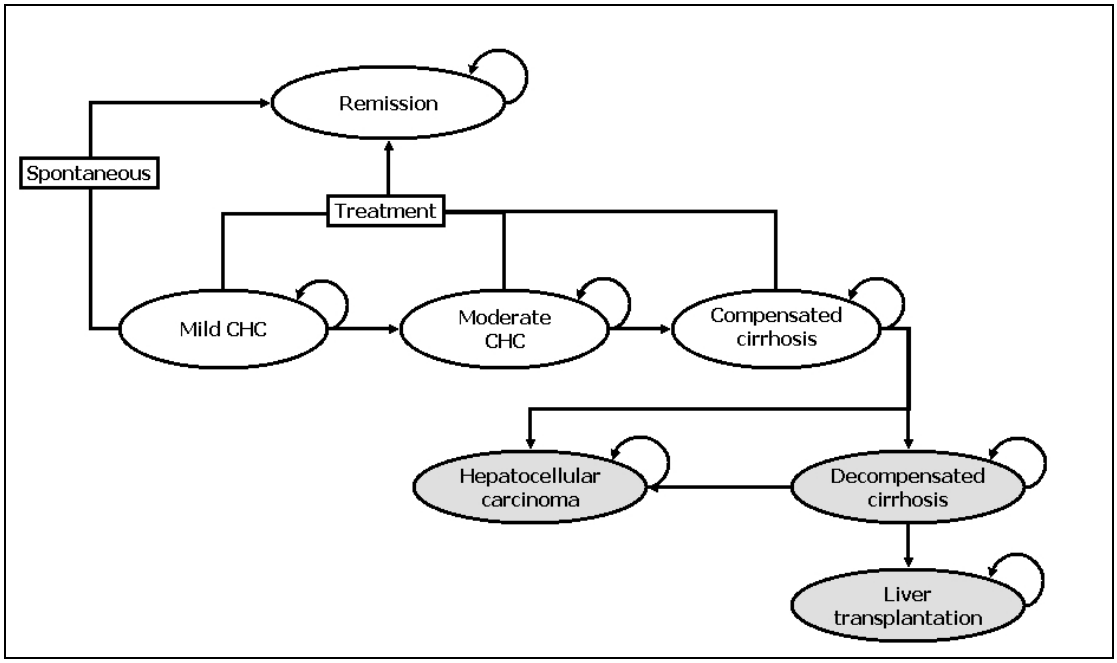
serum for at least 6 months after treatment cessation. To estimate the impact of this intermediate effect on final outcomes for patients we required an appropriate model of the natural history of chronic hepatitis C. We conducted a systematic search of the literature to identify source material on the natural history, epidemiology and treatment of chronic hepatitis C (see Appendix 6 for details of the databases searched and the search strategy). References identified by these searches, along with previous economic evaluations reviewed in section 5.2.2, informed the development of a Markov state transition model. We developed a new model, rather than adopting the model used in the previous NICE appraisal of pegylated interferon dual therapy[121]. The original model did not distinguish between mild and moderate/ severe chronic hepatitis C, would have required considerable adaptation in order to model early treatment against watchful waiting and adopted a fixed time horizon of thirty years. The underlying state transition model is the same, except that ascites, variceal bleed and hepatic encephalopathy (which were separate health states in the original model) have been collapsed into a single decompensated cirrhosis state and that background mortality transitions have been included for all states (in addition to the condition-specific mortality risks for those states that are associated with excess deaths).

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

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

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

Figure 1 - State transition diagram



Patients in each of the mild and moderate chronic hepatitis C health states, as well as compensated cirrhosis, face the same mortality risk as the general population. However, those with decompensated disease, hepatocellular carcinoma and who undergo liver transplantation face higher mortality rates than the general population. The shading of the ellipses for these health states indicates this. A dotted line has been drawn between hepatocellular carcinoma and liver transplantation to indicate that this transition is often not included in treatment models used for economic evaluations in chronic hepatitis C, and has been excluded from this analysis.

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

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

5.4.4 Baseline cohort of adult mild chronic hepatitis C patients

Baseline characteristics of adults with mild chronic hepatitis C are taken from the UK Mild HCV trial[65] with a mean age at infection of 25 and mean age at entry to the model of 40. Sixty percent of the cohort is male and 50% of the cohort is genotype 1. The majority of the remaining 50% of the cohort are of genotypes 2 and 3, which is consistent with the predominant genotypes in England and Wales (see Section 2.1.1).

5.4.5 Data Sources

5.4.5.1 Effectiveness data

We have reported on the findings from our systematic review on the clinical effectiveness of pegylated interferon alfa (Section 4.1) and also the findings of the review of natural history models and clinical effectiveness data used in economic evaluations of interventions (Section 5.2.2.1).

Table 38 reports the transition probabilities adopted in the natural history model for this economic evaluation. They represent the complete set of transition probabilities for the best supportive care comparator. None of these transition probabilities is affected by treatment.

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

Table 39 reports the treatment effects that have been applied to estimate the effectiveness of anti-viral dual therapy with interferon (pegylated and non-pegylated) and ribavirin in the treatment strategies being considered.

Table 38 – Transition probabilities for natural history model

Health state			
From	**To**	**Transition Probability**	**Source**
Mild disease	Mild disease	#	
	Moderate disease	0.025	Wright and colleagues[65], Grieve and colleagues[12]
Moderate disease	Moderate disease	#	
	Compensated cirrhosis	0.037	Wright and colleagues[65], Grieve and colleagues[12]
Compensated cirrhosis	Compensated cirrhosis	#	
	Decompensated cirrhosis	0.039	Fattovich and colleagues[119]
	Hepatocellular carcinoma	0.014	Fattovich and colleagues[119]
Decompensated cirrhosis	Decompensated cirrhosis	#	

	Hepatocellular carcinoma	0.014	Fattovich and colleagues[119]
	Liver transplant	0.020	Grieve and colleagues[12], Siebert and colleagues[126]
	Death	0.130	Fattovich and colleagues[119]
Hepatocellular carcinoma	Hepatocellular carcinoma	#	
	Death	0.430	Fattovich and colleagues[119]
Liver Transplantation	Liver Transplantation	#	
	Death	Yr 1 = 0.210 Yr 2 = 0.057	Bennett and colleagues[88]
Notes: # indicates that this is the default transition and is calculated as the complement of the other transition probabilities for each health state			

Table 39 - SVRs for interferon alfa dual therapy used for the base-case analysis in the cost-effectiveness model

SVRs used in model	Non-pegylated interferon alfa-2b	Pegylated interferon alfa-2a	Pegylated interferon alfa-2b
All patients	33%	59%	*
Genotype 1	18%	39%	*
Genotype non-1	49%	78%	*

*NB. SVRs for pegylated interferon alfa 2b will not appear in all versions of this report. They were based on adjusted SVRs from the Manns and colleagues RCT, as reported in the manufacturer's submission to NICE (academic in confidence).

SVRs for all patients, and by genotype, for non-pegylated interferon treatment of mild HCV have been taken from the UK Mild HCV trial (Wright and colleagues[65]). This trial evaluated interferon alfa-2b – no trials of interferon alfa-2a in mild patients were identified.

The SVRs for pegylated interferon in patients with mild disease are based on two sources. For pegylated interferon alfa-2b they have been taken from the Phase III trial of pegylated interferon alfa-2b by Manns and colleagues[17]. In this trial the SVR for the sub-group of patients with no or minimal fibrosis was 61% (for patients treated with high dose PEG – for more details of this trial see Section 4.1.4.1). The publication reporting the trial results does not give the SVR for the sub-group of patients with no or minimal fibrosis by genotype. For this analysis the SVRs by genotype, for patients with mild disease treated with pegylated interferon alfa-2b, were taken from the manufacturer's submission to NICE (Wong, J. Personal Communication). The proportions of genotype 1 and genotype non-1 patients in the trial were different to that assumed for the UK population of CHC patients (68% genotype 1 and 29% genotype 2/3 compared to the 50:50 ratio assumed for this analysis). The reported SVRs for each genotype were used to adjust the overall SVR for all patients for the genotype distribution in the UK. For pegylated interferon alfa-2a, SVRs were taken from the manufacturer's submission[127] which reported SVRs for

the sub-group of mild patients within the pegylated interferon alfa-2a trial by Zeuzem and colleagues[66]. The SVR for all patients was estimated based on the 50:50 ratio of genotype 1 and genotype non-1 assumed for the UK population of CHC patients.

Table 40 reports the treatment effects that have been applied to estimate the effectiveness of anti-viral monotherapy with interferon (pegylated and non-pegylated) in the treatment strategies being considered.

Table 40 - SVRs for interferon alfa monotherapy used for the base-case analysis in the cost-effectiveness model

SVRs used in model	Non-pegylated interferon alfa-2b	Pegylated interferon alfa-2a	Pegylated interferon alfa-2b
All patients	17%	41%	31%
Genotype 1	6%	31%	14%
Genotype non-1	28%	50%	47%

SVRs, by genotype, for non-pegylated interferon monotherapy have been taken from the trial by Lindsay and colleagues[73] (reviewed in Section 4.1.3) as have the SVRs for pegylated interferon alfa-2b. The SVRs for pegylated interferon alfa-2a have been taken from a trial reported by Reddy and colleagues[72]. Since the mix of genotypes in these trials did not match that assumed for the UK population of CHC patients, the SVRs for all patients have been adjusted assuming a 50:50 ratio genotypes 1 and non-1.

For these analyses we have assumed that, for both dual therapy and monotherapy, the same SVR applies for patients with mild disease receiving early treatment and those who wait to have active treatment once their disease has progressed to the moderate/ severe stage. In the trials reviewed in Section 4.1.4 it appears that, where differences in SVRs have been reported, they tend to show higher responses in patients with mild disease. However, the majority have not reported tests of the statistical significance of these differences. Where statistical analyses have been reported these have been inconsistent, with one trial reporting a significant difference and another reporting a non-significant difference. Given the lack of prospective RCT data on responses for patients receiving early treatment compared to watchful waiting, and the lack of strong within-trial evidence of differences in response between patients with mild and those with moderate disease, we adopted a conservative assumption that the same SVR would apply in both treatment strategies.

5.4.5.2 Health state values/ utilities

The health state utilities adopted in the cost-effectiveness model are those estimated for the UK Mild HCV trial[65] (Table 41). Patients in the trial completed the EQ-5D at baseline, during treatment and during follow-up. The baseline assessments were used to estimate health state utility for patients with mild disease and the estimate for utility associated with SVR was based on responses at 24 and 48 weeks. Responses at weeks 12 and 24 for the treatment group of patients in the trial were used to estimate utilities for patients during treatment. A separate observational study recruiting 302 patients with varying severity of liver disease associated with chronic hepatitis C was undertaken to develop utility estimates for moderate disease and compensated

cirrhosis[12]. Values derived from a UK study of costs and outcomes following liver transplantation were used for the decompensated cirrhosis, hepatocellular carcinoma health state[128].

Table 41 – Health state utilities

Health State	Utility
SVR (from mild disease)	0.82
SVR (from moderate disease)	0.72
Mild CHC	0.77
Treatment for mild CHC	0.66
Moderate CHC	0.66
Treatment for moderate CHC	0.55
Cirrhosis	0.55
Decompensated cirrhosis	0.45
Hepatocellular carcinoma	0.45
Liver transplantation	0.45

5.4.5.3 Discounting of future benefits

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

5.4.5.4 Cost data

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

5.4.5.5 Intervention costs

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

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

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

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

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

In addition to the excess costs of health service contacts for patients undergoing treatment, drug costs also need to be estimated. Drug unit costs were taken from the British National Formulary, number 50 (September 2005).

Drug costs for non-pegylated interferon alfa-2b (Viraferon) were calculated for a dosage of 3 million units, self-administered by patients three times per week using an injection pen. Cost per MU was estimated at £6, resulting in a weekly cost of £54. Total drug cost for 24 weeks of non-pegylated interferon alfa monotherapy are therefore £1,302 – cost for 48 weeks treatment £2,604.

Drug costs for ribavirin (Rebetol), used in dual therapy with pegylated interferon alfa-2b and non-pegylated interferon were calculated for a dosage of 1000mg per day, based on an average body weight of 79kg. A 168-tab packet of 200mg tablets costs £551.30, which corresponds to a weekly cost of £115. Combined with the costs estimated above this gives a total drug cost for combination therapy (non-pegylated interferon alfa-2b plus ribavirin) of £4,058 for 24 weeks of treatment for genotype 2/3 and £8,117 for 48 weeks of treatment for genotype 1.

Drug costs for pegylated interferon alfa-2b (ViraferonPeg) were calculated for a patient weighing 79kg (at a dosage of 1.5 micrograms / kg for dual therapy and 1.0

micrograms / kg for monotherapy). Weekly costs were estimated as the average of the unit cost for the appropriate dosage using a pre-filled pen and a vial (£109.62 for monotherapy and £158 for dual therapy). The total drug cost for a 24 week course of treatment for genotype 2/3 patients is £2,631 for monotherapy and for 48 weeks is £5,261. The total drug costs estimated for 24 weeks of dual therapy are £6,553 and £13,106 for 48 weeks of dual therapy.

Drug costs for pegylated interferon alfa-2a (Pegasys) were calculated for a dosage of 180 microgram/0.5ml, self-administered by patients once per week, corresponding to a weekly cost of £132. The total drug cost for a 24 week course of treatment for genotype 2/3 patients is £3,168 for monotherapy and for 48 weeks is £6,336. Drug costs for ribavirin (Copegus), for dual therapy with pegylated interferon alfa-2a were calculated for a dosage of 800mg per day for genotype 2/3 and 1000-1200mg per day (depending on body weight, 1000mg for weight <75kg and 1200mg for weight >=75kg) for genotype 1. A 168-tab packet of 200mg tablets costs £462.47. This corresponds to a weekly cost of £116 for genotype 1 (based on an average body weight of 79kg) and £77 for genotype 2/3. The total drug costs estimated for 24 weeks of dual therapy are £5,018 and are £11,886 for 48 weeks of dual therapy.

5.4.5.6 Health state costs

Health state costs for SVR, chronic hepatitis C, compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma have been taken from the observational study conducted during the UK mild HCV trial[65]. Costs for liver transplantation and post-liver transplantation taken from a Department of Health funded study of the costs of liver transplantation[129]. Costs for 2002/03 have been updated to 2003/04 costs using the Hospital and Community Health Services (HCHS) Pay and Prices Index[130].

Table 42 - Health state costs

Health state	Cost (£ per year) 2003/04 prices
SVR	267
Mild chronic hepatitis C	142
Moderate chronic hepatitis C	738
Compensated cirrhosis	1,171
Decompensated cirrhosis	9,385
Hepatocellular carcinoma	8,363
Liver transplantation	37,857
Post Liver transplantation	1,425

5.4.5.7 Discounting of future costs

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

5.4.5.8 Presentation of results

We report findings on the cost-effectiveness of interventions based on analysis of a cohort of patients having age, sex and genotype characteristics as reported in the UK Mild HCV trial, as discussed earlier (Section 5.4.4). For the interventions being assessed in this report comparisons for watchful waiting are made against best supportive care, while for early treatment the comparison is made against watchful waiting with the same anti-viral agent (i.e. for early treatment with non-pegylated interferon dual therapy the comparison is made against watchful waiting with non-pegylated interferon dual therapy). Comparisons are also made for early treatment compared to watchful waiting with different agents.

We report the results of these comparisons in terms of the incremental gain in quality adjusted life years (QALYs) and the incremental costs determined in the cohort analysis.

5.4.5.9 Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

Parameter uncertainty is addressed using probabilistic sensitivity analysis. Probability distributions are assigned to the point estimates used in the base case analysis. The point estimates for state transitions in the natural history and treatment effects are reported in Table 38 and Table 39 and for health state costs in Table 42. Distributions are also assigned to the health state utilities described in section 5.4.5.2 and these are sampled during the probabilistic analysis. Appendix 25 reports the variables included in the probabilistic sensitivity analysis, the form of distribution used for sampling and the parameters of the distribution.

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

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

The purpose of this analysis is to identify clearly the impact of this uncertainty and to test the robustness of the cost-effectiveness results to variation in structural assumptions and parameter inputs. Particular attention will be paid to key structural differences between models previously used in studies of the cost-effectiveness of anti-viral therapy (reviewed in Section 5.2.2) and the model adopted for this evaluation.

<u>SHTAC cost-effectiveness model – summary of methods</u>

- We devised a Markov state transition model to estimate the cost-effectiveness of alternative treatment strategies for adults with mild chronic hepatitis C, from the perspective of the NHS and personal social services. This was based on our systematic review of literature on natural history, epidemiology and health-related quality of life in chronic hepatitis C, as well as a systematic review of literature on clinical effectiveness and cost-effectiveness of anti-viral treatment.
- The treatment strategies evaluated are:
  - Early anti-viral treatment, for all patients with mild chronic hepatitis C, with either non-pegylated or pegylated interferon;

  - Watchful waiting with anti-viral treatment, provided only to those patients who progress to moderate/ severe disease, with either non-pegylated or pegylated interferon;
  - No anti-viral treatment and provision of best supportive care.
- The model includes eight health states (SVR, chronic hepatitis C, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death). 2 "tunnel" states within the chronic hepatitis C state distinguish severity of disease (i.e. mild or moderate/ severe).
- A cohort of patients pass through these states at different rates. The baseline cohort comprises patients with mild chronic hepatitis C, who have a mean age of 40 and 60% of whom are male. In this cohort 50% of patients are of Genotype 1 – the majority of the remaining 50% are genotype 2 and 3.
- The model has a lifetime horizon, with a cycle length of one year (with half cycle correction applied).
- The short term outcome of treatment is sustained viral response. Estimates of SVRs following treatment were extracted from published trials and from unpublished data in the manufacturers' submissions. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs for the baseline cohort comprising patients with mild chronic hepatitis C under each treatment strategy.
- Published quality of life weights estimated for a UK trial in patients with chronic hepatitis C were used to derive the QALYs associated with each treatment strategy.
- To assess costs associated with anti-viral treatment of chronic hepatitis C, resource use was estimated from clinical guidelines and advice from clinical practitioners. Drug costs were taken from the BNF. To estimate costs associated with the management of chronic hepatitis C values from a UK trial in patients with chronic hepatitis C were used.
- Costs were discounted at 6% and benefits at 1.5%.
- Uncertainty was explored through probabilistic and deterministic sensitivity analysis.

5.5 Cost-effectiveness results

Cost-effectiveness findings are presented separately for the alternative treatment strategies using non-pegylated interferon alfa dual therapy and pegylated interferon alfa dual therapy for a cohort of chronic hepatitis C patients having the age, sex and genotype characteristics reported in the literature and described in Section 5.4.4. Discounted costs are presented along with life expectancy and quality-adjusted life expectancy for patients in the cohort. Findings are presented for the incremental cost per life year gained and for incremental cost per QALY.

5.5.1 Base case results

5.5.1.1 Interferon alfa dual therapy (48 weeks treatment)

Costs and outcomes modelled for non-pegylated and pegylated interferon alfa dual therapy for patients with mild hepatitis C are presented in Table 43. The assumed treatment duration for all patients in the base case is 48 weeks, regardless of genotype (the effect of adopting alternative durations of treatment is explored in Section 5.5.1.2). This table reports total costs (anti-viral treatment and supportive care), health outcomes (in terms of life years and QALYs for each treatment strategy) and the

incremental cost per QALYs ratios for each intervention relative to their closest comparator. Costs are discounted at 6% and health outcomes discounted at 1.5%.

The table contains two entries for non-pegylated interferon alfa-2b dual therapy. The first entry represents the model prediction using the 33% SVR observed in the UK Mild HCV trial[65]. A second set of estimates for non-pegylated interferon alfa dual therapy have been derived from the model using the overall SVR reported in the Manns and colleagues[17] trial. The overall SVR reported by Manns and colleagues[17] for non-pegylated interferon alfa dual therapy was 47%, with a SVR of 49% for patients with no or minimal fibrosis.

Table 43 – Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) and ribavirin (48 weeks treatment)

Treatment Strategy		SVR	Cost	LY	QALY	Cost per QALY
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.33	£ 8,532	28.18	20.55	£ 6,585[a]
	Early treatment		£ 13,476	28.20	21.16	£ 8,092[b]
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.49	£ 7,942	28.30	20.80	£ 3,097[a]
	Early treatment		£ 12,581	28.34	21.72	£ 5,043[b]
Pegylated Interferon Alfa 2a	Watchful waiting	0.59	£ 8,346	28.38	20.94	£ 3,052[a]
	Early treatment		£ 14,834	28.41	22.04	£ 5,900[b]
Pegylated Interferon Alfa 2b	Watchful waiting	*	£ 8,438	28.47	21.13	£ 2,534[a]
	Early treatment		£ 16,205	28.52	22.48	£ 5,774[a]

Notes: [a] – comparing watchful waiting to best supportive care
[b] – comparing early treatment to watchful waiting with the same agent

*NB. SVRs for pegylated interferon alfa 2b will not appear in all versions of this report. They were based on adjusted SVRs from the Manns and colleagues RCT, as reported in the manufacturer's submission to NICE (academic in confidence).

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

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

Under the base case assumptions on disease progression, in the watchful waiting strategy, only 60% of the cohort of patients who initially have mild disease will progress to moderate disease and therefore receive active anti-viral treatment. This difference in the proportion of the cohort undergoing active treatment means that, without taking into account the differential timing of anti-viral treatment in the two strategies, drug costs are 40% lower for the watchful waiting strategy than for early treatment. When the difference in timing of anti-viral treatment is taken into account,

the average discounted cost for 48 weeks of non-pegylated interferon alfa-2b dual therapy under watchful waiting is £2,217 compared to £8,117 for early treatment.

Table 43 shows that if the difference between SVRs for non-pegylated interferon dual therapy and pegylated interferon dual therapy are large, as is suggested by the comparison of the SVR reported from the UK Mild HCV trial (0.33) and those reported in trials sponsored by the drug manufacturers (0.59 to ***[Academic-in-confidence]***), then much of the additional cost of treatment with pegylated interferon is offset by reduced lifetime costs for supportive care. Since the SVR health state is only associated with health care costs in the year immediately following treatment response (due to costs of post-treatment follow-up, viral assays and management of treatment-related adverse events which may persist for a period after treatment ceases) it follows that the greater the SVR then the greater the potential saving in averted supportive care costs. When the SVR for non-pegylated interferon alfa that was observed in the Manns and colleagues[17] trial is used to estimate cost-effectiveness, with a smaller disparity between SVR for non-pegylated and pegylated interferon (0.49 vs 0.59 to ***[Academic-in-confidence]***), the incremental cost-effectiveness ratio for watchful waiting with pegylated interferon alfa-2a compared to the same strategy for non-pegylated interferon alfa becomes £2,849 and for early treatment with pegylated interferon alfa-2a compared to early treatment with non-pegylated interferon alfa is £7,007. The incremental cost-effectiveness ratios for the same comparisons with pegylated interferon alfa-2b are £1,477 (watchful waiting compared to the same strategy for non-pegylated interferon) and £4,760 (early treatment with pegylated interferon alfa-2a compared to early treatment with non-pegylated interferon). This contrasts to the situation where watchful waiting with both pegylated interferons was cost saving, if the SVR for non-pegylated interferon alfa was estimated at 0.33.

Table 43 also shows clearly that the QALY gain from early treatment is not derived from gains in life expectancy. While discounted life expectancy is greater for either treatment strategy than for best supportive care, for both non-pegylated and pegylated interferon early treatment provides only a small increase in life expectancy (0.02 to 0.05 discounted life years) compared to watchful waiting. The QALY gain under the early treatment strategy results from the expectation that an individual would spend a greater proportion of life expectancy in the SVR health state, on average, compared to watchful waiting (see Table 44 and Table 45).
Table 45 shows that the SVR health state is associated with higher quality of life than the mild CHC state. Therefore, treatment strategies that provide for a greater proportion of an individual's life expectancy in this health state will be associated with the greatest QALY gains, even where none of the strategies is associated with substantial increases in life expectancy.

The proportion of the cohort developing cirrhosis under the best supportive care strategy is 32%, while for non-pegylated interferon treatment the proportion of the population predicted to develop cirrhosis with watchful waiting is between 18% and 23% depending on SVR and between 16% and 22% for early treatment, depending on

Table 44 - Life expectancy by health state by treatment strategy (life years)

Treatment strategy	SVR	Mild CHC	Mod/ Severe	CC	DC	HCC	LT	Total

				CHC					
Best supportive care		0.00	18.96	6.25	2.14	0.42	0.08	0.08	27.94
IFN Alfa-2b (SVR = 0.33)	Watchful	2.95	18.96	4.45	1.44	0.28	0.05	0.06	28.18
	Early tx	9.22	12.94	4.21	1.44	0.28	0.05	0.06	28.20
IFN Alfa-2b (SVR = 0.49)	Watchful	4.42	18.96	3.54	1.08	0.21	0.04	0.04	28.30
	Early tx	13.84	9.92	3.19	1.09	0.21	0.04	0.04	28.34
Peg Alfa-2a	Watchful	5.28	18.96	3.01	0.88	0.17	0.03	0.04	28.38
	Early tx	16.53	8.16	2.60	0.89	0.17	0.03	0.03	28.41
Peg Alfa-2b	Watchful	6.45	18.96	2.30	0.60	0.12	0.02	0.02	28.47
	Early tx	20.20	5.76	1.78	0.61	0.12	0.02	0.02	28.52

SVR = sustained virologic response; CC = compensated cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant

Table 45 – QALYs by health state by treatment strategy

Treatment strategy		SVR	Mild CHC	Mod/ Severe CHC	CC	DC	HCC	LT	Total
Best supportive care		0.00	14.60	4.13	1.18	0.19	0.03	0.04	20.17
IFN Alfa-2b (SVR = 0.33)	Watchful	2.15	14.60	2.83	0.79	0.13	0.02	0.03	20.55
	Early tx	7.55	9.87	2.78	0.79	0.13	0.02	0.03	21.16
IFN Alfa-2b (SVR = 0.49)	Watchful	3.23	14.60	2.24	0.60	0.10	0.02	0.02	20.80
	Early tx	11.33	7.55	2.10	0.60	0.10	0.02	0.02	21.72
Peg Alfa-2a	Watchful	3.86	14.60	1.89	0.48	0.08	0.01	0.02	20.94
	Early tx	13.52	6.21	1.71	0.49	0.08	0.01	0.02	22.04
Peg Alfa-2b	Watchful	4.72	14.60	1.41	0.33	0.05	0.01	0.01	21.13
	Early tx	16.53	4.37	1.18	0.34	0.05	0.01	0.01	22.48

SVR = sustained virologic response; CC = compensated cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant

SVR. A similar pattern, where a smaller proportion of patients develop cirrhosis under the early treatment strategy is shown for pegylated interferon (between 11% and 15% for watchful waiting, depending on SVR, and between 9% and 13% for early treatment).

Table 43, Figure 2, Figure 3, Figure 4 and Figure 5 illustrate the incremental cost-effectiveness of early intervention and watchful waiting for patients with mild HCV treated with interferon alfa (non-pegylated and pegylated) dual therapy. The dashed line in Figure 2, Figure 3, Figure 4 and Figure 5 indicates the cost effectiveness frontier, joining together the optimal treatment strategies – those which provide a given output at minimum cost. Points above the cost-effectiveness frontier are excluded, since the same output can theoretically be provided at lower cost by a combination of strategies that are found on the frontier. (Key for Figures 2 to 5 – WW = watchful waiting; Imm = early treatment).

Where the SVR for non-pegylated interferon dual therapy is 33%, both forms of pegylated interferon dominate non-pegylated interferon for the watchful waiting strategy, providing better outcome at lower cost (see Figure 2 Figure 4). Early treatment with non-pegylated interferon is excluded as it does not lie on the frontier, where the SVR is at the low value of 33% (Figure 2 and Figure 4). Where the SVR is at the higher value of 49%, early treatment with non-pegylated interferon dual therapy

is not excluded from the optimal path when compared with pegylated interferon alfa-2a.

The results of estimating the cost-effectiveness of early versus delayed anti-viral treatment by genotype are presented in Table 46 and Table 47. Non-pegylated interferon dual therapy is estimated to provide only a small health gain for genotype 1 patients, due to the low SVR. Watchful waiting with non-pegylated interferon is associated with a high incremental cost-effectiveness ratio, whereas early treatment provides a greater QALY gain, offsetting some of the increased cost.

Table 46 - Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) and ribavirin for genotype 1 patients (48 weeks treatment)

Treatment Strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.18	£ 9,074	28.07	20.33	£ 19,022[a]
	Early treatment		£ 14,297	28.08	20.66	£ 15,954[b]
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.30	£ 8,641	28.16	20.51	£ 7,766[a]
	Early treatment		£ 13,640	28.18	21.06	£ 9,021[b]
Pegylated Interferon Alfa 2a	Watchful waiting	0.39	£ 9,293	28.23	20.65	£ 6,867[a]
	Early treatment		£ 16,799	28.25	21.38	£ 10,270[b]
Pegylated Interferon Alfa 2b	Watchful waiting	*	£ 9,143	28.33	20.84	£ 4,670[a]
	Early treatment		£ 17,273	28.36	21.82	£ 8,324[b]

Notes: [a] – comparing watchful waiting to best supportive care
[b] – comparing early treatment to watchful waiting with same agent

**** [Academic-in-confidence]***

Figure 2 - cost-effectiveness map: pegylated interferon alfa-2a – IFN SVR = 0.33

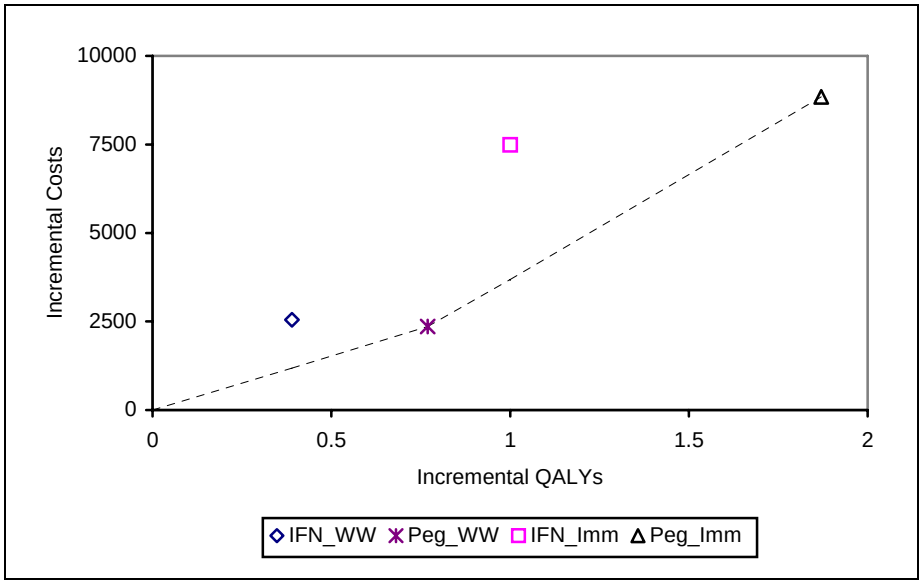


Figure 3 - cost-effectiveness map: pegylated interferon alfa-2a – IFN SVR = 0.49

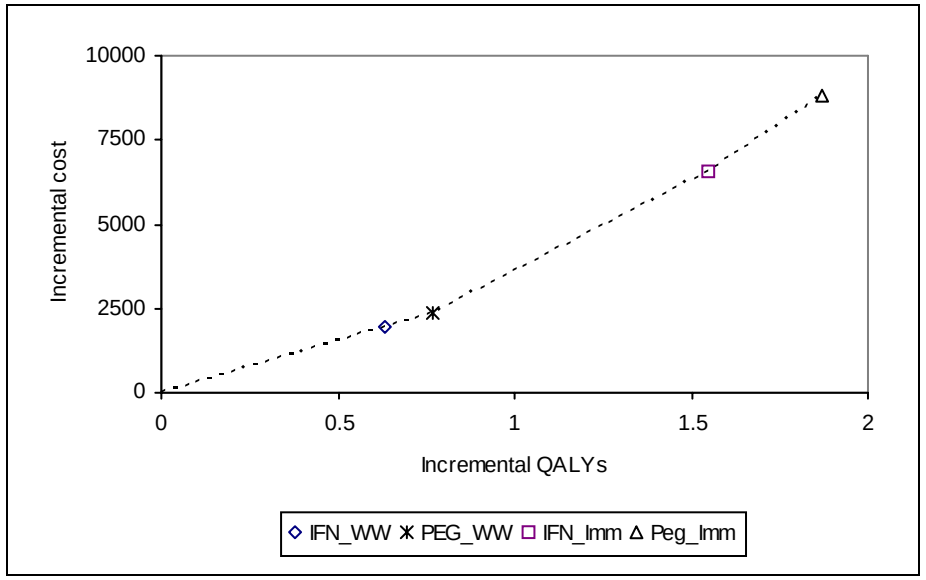


Figure 4 - cost-effectiveness map: pegylated interferon alfa-2b – IFN SVR = 0.33

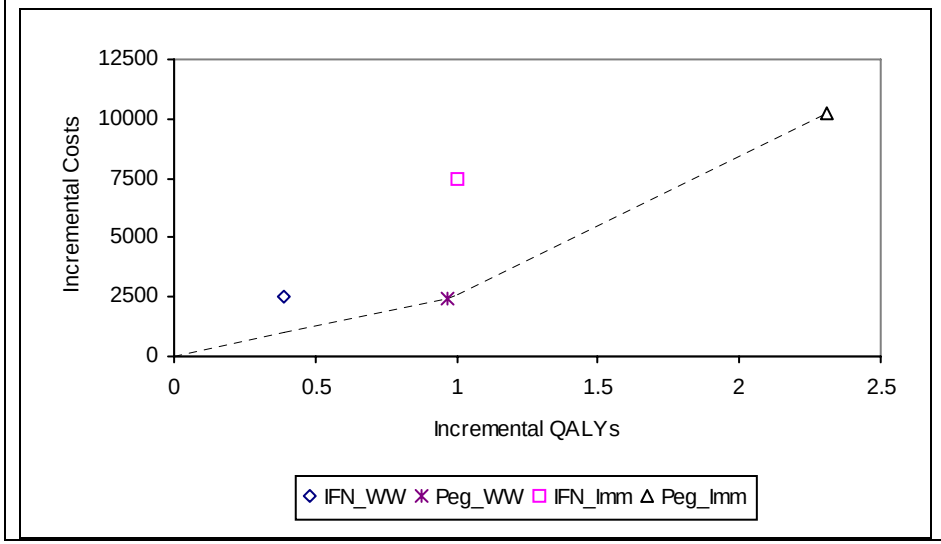
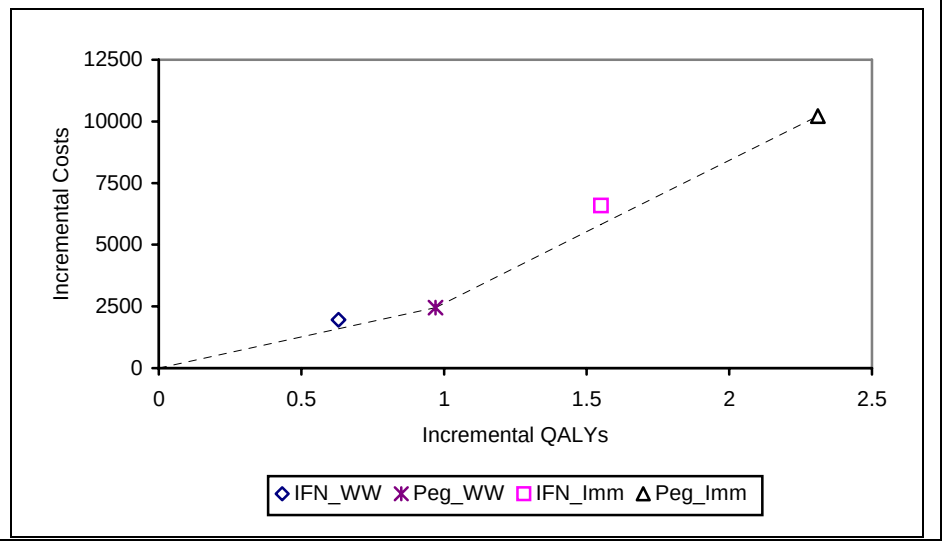


Figure 5 - cost-effectiveness map: pegylated interferon alfa-2b – IFN SVR = 0.49



For genotype 1, watchful waiting with pegylated interferon alfa-2a has an ICER of £4,668 when compared to watchful waiting with non-pegylated interferon. Comparing early treatment with pegylated interferon alfa-2a to early treatment with non-pegylated interferon has an ICER of £9,984. Due to the higher SVR reported for pegylated interferon alfa-2b the QALY gain is greater for both watchful waiting and early treatment. The ICER for watchful waiting compared to watchful waiting with non-pegylated interferon is £1,503 and for early treatment compared to early treatment is £4,803.

Table 47 - Base case cost-effectiveness for interferon alfa-2a (non-pegylated and pegylated) and ribavirin for genotype non-1 patients (48 weeks treatment)

Treatment Strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.49	£ 7,944	28.30	20.80	£ 3,105[a]
	Early treatment		£ 12,584	28.34	21.72	£ 5,050[b]
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.65	£ 7,351	28.43	21.04	£ 1,558[a]
	Early treatment		£ 11,687	28.47	22.27	£ 3,528[b]
Pegylated Interferon Alfa 2a	Watchful waiting	0.78	£ 7,399	28.52	21.23	£ 1,326[a]
	Early treatment		£ 12,868	28.57	22.70	£ 3,725[b]
Pegylated Interferon Alfa 2b	Watchful waiting	*	£ 7,733	28.62	21.42	£ 1,387[a]
	Early treatment		£ 15,138	28.68	23.14	£ 4,320[b]

Notes: [a] – comparing watchful waiting to best supportive care
[b] – comparing early treatment to watchful waiting with same agent

* ***[Academic-in-confidence]***

Given the higher SVRs for genotype non-1 patients, the health gains for each strategy are greater than for genotype 1. Watchful waiting with pegylated interferon alfa-2a is cost saving if the SVR for non-pegylated interferon is at the lower level of 49% and has an ICER of £252 when compared to watchful waiting with non-pegylated interferon if the SVR is 65%. Comparing early treatment with pegylated interferon alfa-2a to early treatment with non-pegylated interferon has an ICER of £2,755. Again, the reported SVR for pegylated interferon alfa-2b is higher than for pegylated interferon alfa-2a, resulting in a larger QALY gain for both watchful waiting and early treatment – the ICER for watchful waiting with pegylated interferon alfa-2b compared to watchful waiting with non-pegylated interferon is £996 and for early treatment compared to early treatment is £3,972.

5.5.1.2 Interferon alfa dual therapy - early stopping rules

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

Viral kinetic studies in clinical trial patients have shown that the majority of patients who achieve an SVR have responded to treatment by 12 weeks. There is a clinical consensus that patients who have not responded after 12 weeks of non-pegylated interferon should stop anti-viral therapy. An analysis of pooled data from two clinical trials identified 12 weeks was also the optimum stopping date for pegylated interferon in patients who had not responded to treatment[131]. This approach offers economic benefits, in terms of reduced drug costs, but will also avoid utility losses for patients

taking medication with significant adverse effect, from which they are unlikely to benefit.

In this analysis the early stopping rule applied at twelve weeks for all patients who failed to achieve an early virological response. This was defined as unquantifiable HCV RNA or a greater than or equal to a 2-log drop of HCV RNA from patient's baseline measurement. These data are not reported by genotype in the journal report from the UK Mild HCV trial[65], but are available in the full trial report to be published in the HTA monograph series. This reports that 26 out of 40 genotype 1 patients with quantitative virology had unquantifiable HCV RNA or 2-log drop at 12 weeks – representing a proportion with EVR of 65%. In the trial, all patients who achieved SVR also had an EVR. Therefore, stopping treatment according to EVR was predicted to have no impact on the SVR for non-pegylated interferon alfa, but would reduce the costs of treatment (by approximately 26% for average undiscounted drug costs).

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

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

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

Table 48 reports the cost-effectiveness estimates for interferon alfa dual therapy, after applying the early stopping rules. The application of early stopping rules has a substantial impact on estimated lifetime costs, with the effect being particularly marked for the early treatment strategy. Costs for the watchful waiting strategies typically reduce by around £700. However costs for early treatment fall by around £3,000. The effect on QALY outcomes is less dramatic. Treatment with interferon dual therapy was estimated to reduce the patient's health state utility by 0.11 while on treatment, due to side effects and adverse events. This reduction in utility was assumed to apply only when the patient was treated – therefore health state utility returned to the expected level for the health state when treatment ceased.

Table 48 - Base case cost-effectiveness estimates for interferon alfa and ribavirin, applying early stopping rules

Treatment Strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.33	£ 7,678	28.18	20.57	£ 4,153[a]
	Early treatment		£ 10,308	28.20	21.21	£ 4,135[b]
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.49	£ 7,087	28.30	20.82	£ 1,684[a]
	Early treatment		£ 9,413	28.34	21.76	£ 2,464[b]
Pegylated Interferon Alfa 2a	Watchful waiting	0.53	£ 7,546	28.34	20.87	£ 2,200[a]
	Early treatment		£ 11,447	28.37	21.88	£ 3,896[b]
Pegylated Interferon Alfa 2b	Watchful waiting	*	£ 7,503	28.43	21.06	£ 1,702[a]
	Early treatment		£ 12,258	28.47	22.29	£ 3,857[b]
Notes: [a] – comparing watchful waiting to best supportive care [b] – comparing early treatment to watchful waiting						

**** [Academic-in-confidence]***

Table 49 - Base case cost-effectiveness estimates for interferon alfa and ribavirin, applying early stopping rules. Genotype 1

Treatment Strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.18	£ 8,485	28.07	20.37	£ 12,443[a]
	Early treatment		£ 12,113	28.08	20.69	£ 11,104[b]
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.30	£ 8,052	28.16	20.55	£ 5,402[a]
	Early treatment		£ 11,457	28.18	21.10	£ 6,172[b]
Pegylated Interferon Alfa 2a	Watchful waiting	0.37	£ 8,821	28.22	20.65	£ 5,850[a]
	Early treatment		£ 14,925	28.24	21.36	£ 8,646[b]
Pegylated Interferon Alfa 2b	Watchful waiting	*	£ 8,685	28.31	20.84	£ 4,028[a]
	Early treatment		£ 15,411	28.34	21.78	£ 7,139[b]
Notes: [a] – comparing watchful waiting to best supportive care [b] – comparing early treatment to watchful waiting						

**** [Academic-in-confidence]***

The order of reduction in lifetime costs is slightly lower for genotype 1 patients than for the mixed cohort of genotype 1 and genotype non-1. Costs of watchful waiting reduce by around £500 and for early treatment the reduction in cost is around £2,000, Table 49.

Table 50 - Base case cost-effectiveness estimates for interferon alfa and ribavirin, applying early stopping rules. Genotype non-1

Treatment Strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.49	£ 6,824	28.30	20.80	£ 1,327[a]
	Early treatment		£ 8,432	28.34	21.77	£ 1,653[b]
Non-pegylated Interferon Alfa 2b	Watchful waiting	0.65	£ 6,232	28.43	21.04	£ 278[a]
	Early treatment		£ 7,534	28.47	22.32	£ 1,016[b]
Pegylated Interferon Alfa 2a	Watchful waiting	0.69	£ 6,352	28.45	21.10	£ 391[a]
	Early treatment		£ 8,271	28.50	22.39	£ 1,478[b]
Pegylated Interferon Alfa 2b	Watchful waiting	*	£ 6,321	28.55	21.28	£ 300[a]
	Early treatment		£ 9,105	28.60	22.80	£ 1,826[b]
Notes: [a] – comparing watchful waiting to best supportive care [b] – comparing early treatment to watchful waiting						

**** [Academic-in-confidence]***

The greatest reductions in cost are realised by applying a 24 week duration of treatment to genotype non-1 patients. Costs for watchful waiting reduce by approximately £1,000 and for early treatment by approximately £4,000. The effect of reducing treatment duration on health outcome is less marked, as shown in Table 50.

5.5.1.3 Interferon alfa monotherapy (48 weeks treatment)

Costs and outcomes modelled for non-pegylated and pegylated interferon alfa dual therapy for patients with mild hepatitis C are presented Table 51. The assumed treatment duration for all patients in the base case is 48 weeks, regardless of genotype. This table reports total costs (anti-viral treatment and supportive care), health outcomes (in terms of life years and QALYs for each treatment strategy) and the incremental cost per QALYs ratios for each intervention relative to their closest comparator. Costs are discounted at 6% and health outcomes discounted at 1.5%.

SVRs are lower than for interferon dual therapy, hence the estimated health gains are lower than for dual therapy. While each treatment strategy is estimated to increase life expectancy, as with dual therapy, early treatment is not expected to offer substantial increases in life expectancy over watchful waiting (0 to 0.03 increases in life expectancy). The health gain expected with early treatment rather than watchful waiting arises from gains in quality of life as the cohort will spend more life expectancy in the SVR health state, as reported for dual therapy (see Table 44).

Table 51 – Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) monotherapy – all patients (48 weeks treatment)

Treatment strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa-2b	Watchful waiting	0.17	£ 7,421	28.06	20.32	£ 9,395[a]
	Early treatment		£ 8,116	28.07	20.63	£ 2,203[b]
Pegylated Interferon Alfa-2a	Watchful waiting	0.41	£ 7,531	28.24	20.68	£ 3,019[a]
	Early treatment		£ 10,426	28.27	21.45	£ 3,765[b]
Pegylated Interferon Alfa-2b	Watchful waiting	0.31	£ 7,611	28.17	20.53	£ 4,487[a]
	Early treatment		£ 9,929	28.19	21.11	£ 3,998[b]

Notes: [a] – comparing watchful waiting to best supportive care
[b] – comparing early treatment to watchful waiting with same agent

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

Table 52 – Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) monotherapy – genotype 1 (48 weeks treatment)

Treatment strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa-2b	Watchful waiting	0.06	£ 7,819	27.98	20.15	Dominated
	Early treatment		£ 8,718	27.98	20.26	£ 8,390[b]
Pegylated Interferon Alfa-2a	Watchful waiting	0.31	£ 7,893	28.17	20.53	£ 5,265[a]
	Early treatment		£ 10,973	28.19	21.11	£ 5,313[b]
Pegylated Interferon Alfa-2b	Watchful waiting	0.14	£ 8,225	28.04	20.27	£ 20,773[a]
	Early treatment		£ 10,860	28.05	20.53	£ 10,196[b]
Notes: [a] – comparing watchful waiting to best supportive care [b] – comparing early treatment to watchful waiting with same agent						

Outcomes are better for genotype non-1 patients, given the higher SVRs reported for this group.

Table 53 – Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) monotherapy – Genotype non-1 (48 weeks treatment)

Treatment strategy		SVR	Cost	LY	QALY	ICER
Best Supportive Care		0.00	£ 5,989	27.94	20.17	
Non-pegylated Interferon Alfa-2b	Watchful waiting	0.28	£ 7,024	28.15	20.48	£ 3,268[a]
	Early treatment		£ 7,513	28.16	21.01	£ 936[b]
Pegylated Interferon Alfa-2a	Watchful waiting	0.50	£ 7,206	28.31	20.81	£ 1,886[a]
	Early treatment		£ 9,933	28.34	21.75	£ 2,904[b]
Pegylated Interferon Alfa-2b	Watchful waiting	0.47	£ 7,033	28.29	20.77	£ 1,739[b]
	Early treatment		£ 9,053	28.32	21.65	£ 2,290[b]
Notes: [a] – comparing watchful waiting to best supportive care [b] – comparing early treatment to watchful waiting with same agent						

5.5.2 Sensitivity analysis

5.5.2.1 Univariate sensitivity analysis

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

Table 54 reports the results of the sensitivity analysis for the overall cohort of patients. The table is divided to distinguish between analyses undertaken due to uncertainties in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values.

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

Previous economic evaluations (discussed in Section 5.2.2) and the industry models (discussed in Section 5.3 and Section **Error! Reference source not found.**) included the possibility of spontaneous remission of disease from the mild chronic hepatitis C health state. This is not included in our baseline model. When a spontaneous remission transition is included in the model it improves outcomes (in terms of life years and QALYs) under the best supportive care strategy, thus reducing the incremental effectiveness of the anti-viral treatment strategy that is compared with supportive care (non-pegylated interferon alfa-2a dual therapy in this case). Including a spontaneous remission transition also improves outcome under the early treatment strategies by increasing the proportion of the cohort achieving a SVR, since those who fail to respond to treatment, but remain in the mild chronic hepatitis C health state are eligible for spontaneous remission.

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

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

The parameter that would be expected to have the greatest influence on cost-effectiveness estimates for anti-viral treatment of chronic hepatitis C is the SVR associated with any treatment strategy. Clinical trials, reviewed in Section 4.1, have reported a wide range of estimates for the SVR for non-pegylated interferon alfa (from 33% to 54%) among trials using the same dosage and duration of treatment. In the absence of head-to-head comparisons of non-pegylated and pegylated interferon in patients with mild disease it is necessary to make indirect comparisons. However the variability in the SVR reported between trials makes such comparisons difficult.

Table 54 includes four entries to investigate the effect of reducing the differential between the SVR for non-pegylated and pegylated interferon, both at the lower value

observed in the UK Mild HCV trial and at the higher value observed in the trial reported by Manns and colleagues[17]. Grieve and colleagues[12] estimated odds ratios of SVR for pegylated interferon and ribavirin compared to non-pegylated interferon and ribavirin. These were based on the SVRs reported by Manns and colleagues[17]. The odds ratios were applied to the proportion of patients achieving SVR in the UK Mild HCV trial to infer an SVR for pegylated interferon alfa-2b and ribavirin in routine UK clinical practice. These values (odds ratio 1.43 for genotype 1 and 1.25 for genotype non-1, giving estimated SVRs for pegylated interferon alfa-2a of 24% and 55% respectively) were used in the first sensitivity analysis on SVR (scenario a in the table). The incremental cost per QALY gained for non-pegylated interferon alfa does not change, since the base case SVR of 33% is being used. The incremental cost-effectiveness ratios for watchful waiting and immediate treatment with pegylated interferon are much greater than under the base case. For watchful waiting with pegylated interferon dual therapy, lifetime costs are £1,200 higher than in the base case and quality adjusted life expectancy is 0.5 lower, while for immediate treatment lifetime costs are almost £2,000 higher than in the base case and quality adjusted life expectancy has reduced by 1.1. The incremental cost-effectiveness ratio for early treatment with pegylated interferon alfa-2a compared to non-pegylated interferon is £23,252 – this contrasts to a value of approximately £2,000 for the base case with the low SVR for non-pegylated interferon.

The second scenario to investigate the impact of the SVR involved increasing the differential between non-pegylated interferon and pegylated interferon alfa-2b while keeping the SVR for non-pegylated interferon at its lower level (scenario b in the table). This second estimate of the SVR for pegylated interferon alfa-2b used the same method of inference as described above. However, the odds ratio on which it was based uses SVRs reported by Manns and colleagues[17] for patients receiving >10.6 mg/kg of ribavirin – 10.6 mg/kg is at the lower end of what is currently considered the optimal dose range. The odds ratios calculated for pegylated interferon alfa-2b versus non-pegylated interferon are 1.77 for genotype 1 and 1.82 for genotype non-1 giving inferred SVRs of 28% and 64% respectively, and an overall SVR of 45%. By increasing the difference between the SVR for non-pegylated interferon and pegylated interferon alfa-2b this reduces the incremental cost effectiveness ratio for pegylated interferon alfa-2b dual therapy compared to best supportive care. The incremental cost-effectiveness ratio for watchful waiting with pegylated interferon compared to the same strategy with non-pegylated interferon is £4,789. The incremental cost-effectiveness ratio for early treatment with pegylated interferon compared to same strategy with non-pegylated interferon is £10,183.

The above analyses were repeated for the higher SVR for non-pegylated interferon observed in the trial reported by Manns and colleagues (scenario c in the table). This shows a similar but smaller increase in cost-effectiveness ratio compared to the base case. The incremental cost-effectiveness ratio for early treatment with pegylated interferon alfa-2a compared to non-pegylated interferon is £19,961 where the SVR for non-pegylated interferon is 49% and the SVR for pegylated interferon alfa-2b is 56%. These analyses are only reported for pegylated interferon alfa-2b since we only have estimates of SVR for non-pegylated interferon alfa-2b, and there are no studies showing the relative effectiveness of non-pegylated interferon alfa-2b and pegylated interferon alfa-2a.

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

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

Table 54 - Univariate sensitivity analysis results (all patients)

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

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

Notes: all cost per QALY ratios are calculated on the same basis as in Table 43 to Table 53. Watchful waiting strategies are compared to best supportive care and early treatment strategies are compared to watchful waiting with the same anti-viral agent

* ***[Academic-in-confidence]***

5.5.2.2 Probabilistic sensitivity analysis

The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis (see Table 43 for base case analysis). Table 55 reports the mean costs and outcomes from the probabilistic analysis, including the 2.5 and 97.5 percentiles to give an indication of the range of the simulated values, and the incremental cost-effectiveness ratios based on the values generated in the probabilistic analysis.

Table 55 - Costs and outcomes from probabilistic analysis (all patients)

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

Figure 6 shows the cost-effectiveness acceptability curves for the early treatment and watchful waiting strategies for non-pegylated interferon, pegylated interferon alfa-2a and best supportive care. The chart indicates the probability that a given intervention is optimal compared to the other illustrated interventions. This suggests that at lower willingness to pay thresholds watchful waiting with pegylated interferon may be an optimal strategy, although early treatment strategies appear to be optimal strategies from a threshold around £7,500 per QALY. Early treatment with pegylated interferon appears to be the optimal intervention over a wide range of values for willingness to pay (which reflects the difference in SVR with pegylated interferon alfa-2a against non-pegylated interferon in the data used in the evaluation), although there is a non-negligible probability that early treatment with non-pegylated interferon may be optimal.

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

Figure 6 - cost effectiveness acceptability curves for early treatment and watchful waiting with non-pegylated interferon and pegylated interferon alfa-2a for mild chronic hepatitis C (All patients)

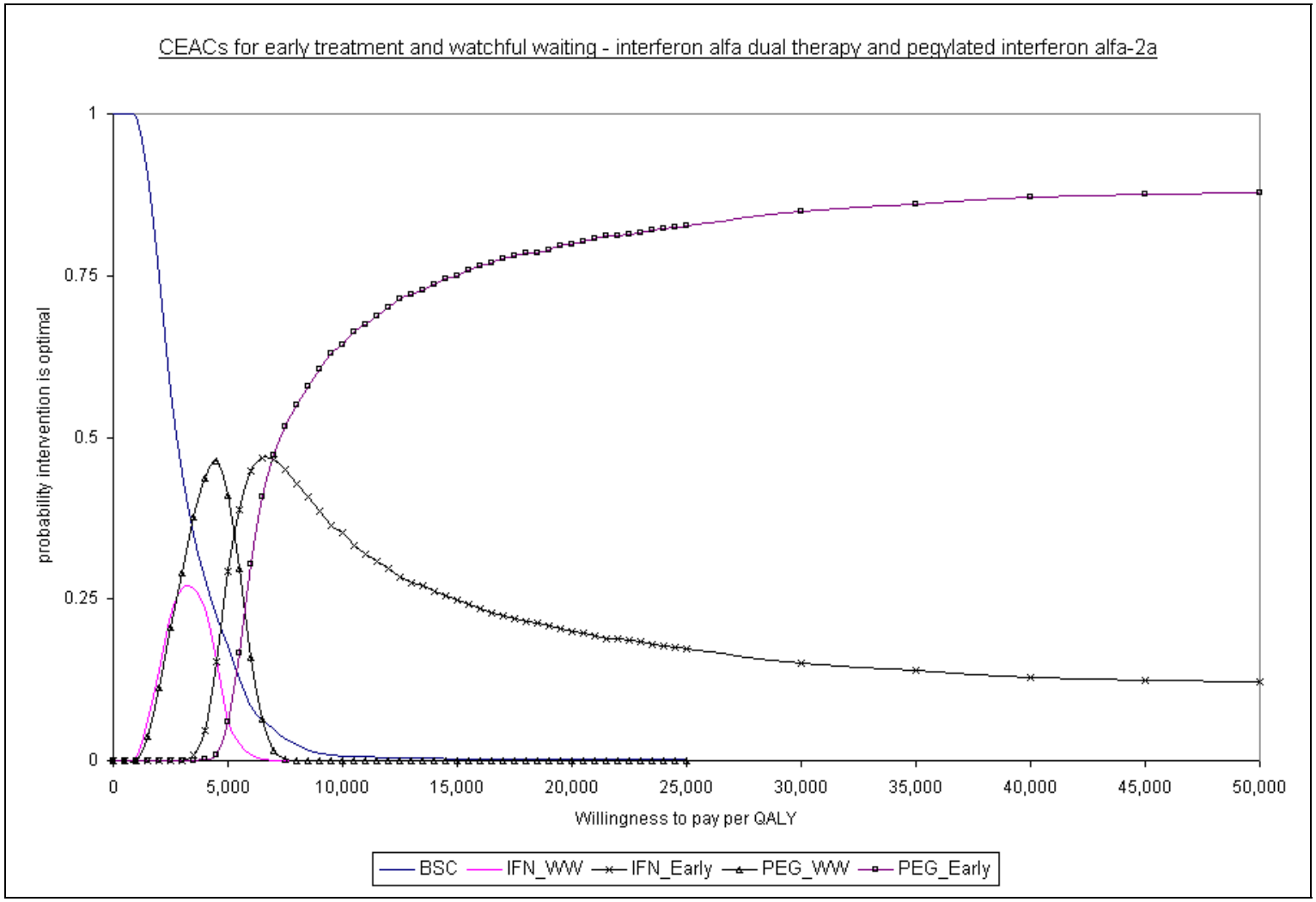
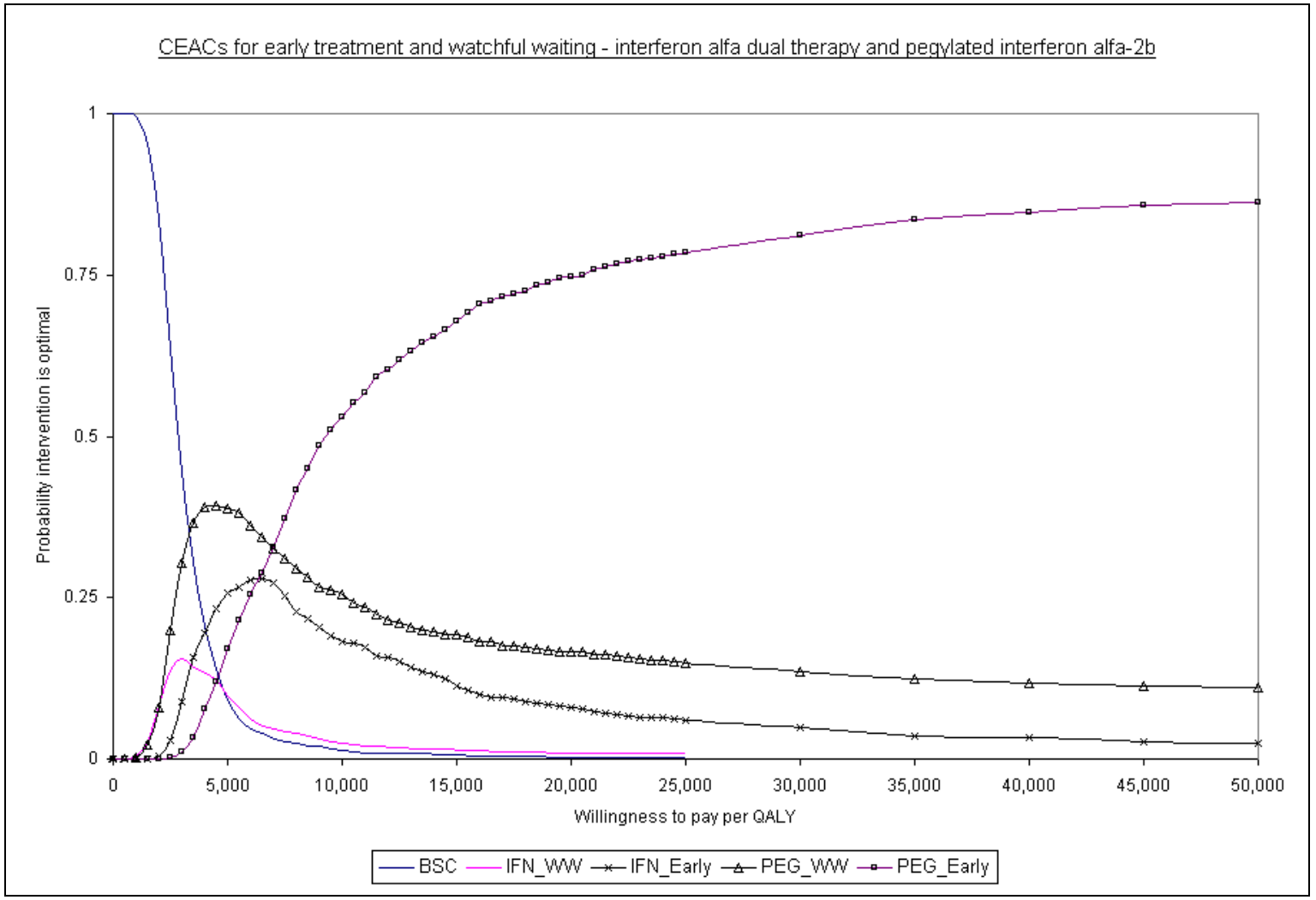


Figure 7 - cost effectiveness acceptability curves for early treatment and watchful waiting with non-pegylated interferon and pegylated interferon alfa-2b for mild chronic hepatitis C (All patients)



6 IMPLICATIONS FOR OTHER PARTIES

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

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

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

7 FACTORS RELEVANT TO NHS

7.1 Identifying infections

Existing NICE guidance on the use of both pegylated and non-pegylated interferon alfa in the treatment of HCV will have undoubtedly raised the profile of anti-viral treatment in the UK. Extension of this guidance to cover a wider group of patients will raise awareness further, potentially encouraging more people to present to health services for assessment and possible treatment. Guidance may help the Department of Health to fulfil its objective to increase awareness of HCV among the general public, as set out in the Hepatitis C Strategy (2002) and Hepatitis C Action Plan for England

(2004). However, concerted efforts are needed to identify a greater proportion of the currently undiagnosed pool of infection ('active case finding'). Linked to this is the need to ensure equitable access to hepatology services, particularly for those who may be socially and economically disadvantaged. This will include some IDUs, and some immigrants to the UK. Outreach services and specialist clinics, as used to target IDUs, may be appropriate. All new initiatives should be subjected to rigorous evaluation.

7.2 Referral and management

Efforts to identify anti-HCV infections need to be augmented by appropriate methods of referral to specialist care for further investigation and, if appropriate, anti-viral treatment. As discussed in Section 2.2.2, a study in the Trent region of England found that only just over 50% of people who tested positive were appropriately referred[57]. A high proportion of those who were not referred were never informed of their test result. The proportion of patients with confirmed referral who progressed through the stages of the care pathway steadily diminished so that only 10% actually received anti-viral treatment, with an estimated 5% achieving a sustained viral response. Reasons for patient drop-out included logistical problems (e.g. patients moving to different areas of the country), service failure (e.g. patients not being told of their result), and patient choice/drop-out (e.g. not attending specialist clinics).

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

7.3 Budget and resource impact

An increase in the number of patients eligible for anti-viral treatment will have obvious budget implications for Primary Care Trusts who commission hepatology services. A recommendation to extend anti-viral treatment to mild HCV may dramatically increase the number of eligible patients in some areas. As reported in Section 2.1.3, the proportion of histologically mild patients in one English clinic based cohort was 44%.

Adequate funding will need to be set aside to pay for an increased demand for drugs, although tailoring drug regimens according to patient characteristics (e.g. genotype) is likely to ensure more cost-effective use of resources. Although treatment is generally administered by specialist hepatology departments, commissioning and funding arrangements are complicated by the fact that a number of other agencies may be

involved in the prevention, investigation, referral and management and rehabilitation of patients. These include primary care, genito-urinary medicine/sexual health services, drug and alcohol services, prison health services, and specialist agencies dealing with the health needs of high risk ethnic groups. An integrated approach to commissioning is therefore desirable. The Foundation for Liver Research suggest the involvement of a nominated lead Primary Care Trust for liver disease, with involvement from Strategic Health Authorities and Regional Specialised Commissioning Groups.

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

7.4 Managed Clinical Hepatology Networks

Effective implementation of national guidance on anti-viral therapy may be facilitated by the National Plan for Liver Services[53] which recommends that all patients receive treatment and care that is uniformly of high standard, via Managed Clinical Hepatology Networks (MCHN). In particular, it is expected that MCHNs will show commitment in implementing NHS directed research on evidence based treatments. The plan also recommends accurate data collection to monitor clinical-effectiveness to enable planning and adoption of best clinical practice, and to enable comparison of patient outcomes across the country. It is envisaged that there will be 10 to 15 MCHNs in the UK, each responsible for between 1 and 5 million people. It is hoped that patients with liver diseases have equivalent access to specialist treatment as patients with renal or cardiac diseases.

7.5 Liver biopsy

The evidence from this report suggests that patients with histologically mild HCV can be treated effectively with anti-viral therapy. This is particularly so for particularly for patients with favourable genotypes 2 and 3 in whom the proportion successfully treated reached as high as 80%. Consequently, there is less of a necessity to gauge disease severity to decide if treatment is necessary. The emphasis is now on when to treat, rather than whether to treat. Not all patients with mild HCV will want to be treated, at least in the short term. Some, such as genotype 1 patients of whom only a relatively small proportion of respond to treatment, may wish to wait until newer, more effective treatments are available. They will therefore require monitoring and further investigation over time to assess the extent of fibrosis progression, and to initiate treatment if there is significant deterioration. One suggestion might be that panels of non-invasive biochemical tests and algorithms should be the first line, and only in cases of remaining doubt should liver biopsy be necessary. However, some clinicians still prefer to use biopsy as it provides additional useful information (as outlined in Section 2.1.2.1). Practice is therefore likely to reflect clinician / patient choice. Evaluation of alternatives to biopsy, such as biochemical tests is beyond the

scope of this review, and therefore might be an appropriate topic for a future technology appraisal (see Section 8.4).

7.6 Implementation

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

7.7 Clinical guidelines

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

8 DISCUSSION

8.1 Clinical-effectiveness

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

Of the eight RCTs in our primary analysis, only three evaluated pegylated interferon (all PEG-2a). One of these, by Zeuzem and colleagues[66], was originally designed to test the effectiveness of treating patients with persistently normal alanine aminotransferase (PNALT) levels. However, the majority of included patients showed evidence of mild fibrosis at baseline, enabling it to be included in this review. Around half of the patients enrolled achieved an SVR when treated for 48 weeks, substantially reducing their risk of long term liver disease. The SVR was even higher in another trial (Hadziyannis and colleagues, 2004)[69] at 63% for a comparable treatment regimen (although the SVR is based on all patients in the trial, rather than the sub-set with

histologically mild HCV). There were no RCTs of the other pegylated interferon alfa (2b) that met our inclusion criteria. However, the trial by Manns and colleagues[17] was one of the 11 RCTs which reported results for sub-groups of patients according to disease severity. The SVR for the sub-group of patients with no or minimal fibrosis at baseline was 57%, and this reached 61% for patients given a higher dose of ribavirin. These trials show that patients with mild HCV can be effectively treated with both pegylated interferon alfa 2a and 2b, in combination with ribavirin.

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

Interestingly in the UK mild HCV RCT[65], a trial designed specifically to evaluate treatment in this patient group, the SVR for non-pegylated interferon alfa and ribavirin (33%) was relatively lower than that achieved by the other trials. Differences in response might be explained by heterogeneity between the trials, although all were multi-centre RCTs comprising mostly middle-aged male patients, with generally comparable distributions of genotypes, and with similar inclusion criteria. The SVR in the UK trial is also lower than reported for the same regimen in earlier trials of patients with moderate to severe disease. In our systematic review of non-pegylated interferon alfa and ribavirin, published in 2000, the SVR for 48 weeks treatment was 41% (95% CI 36-45) (based on a pooled analysis of two large multi-centre RCTs of interferon alfa 2b)[85]. When the combination of non-pegylated interferon alfa and ribavirin was evaluated as a comparator in the later licensing RCTs of pegylated interferon alfa, SVRs were even higher, in the range 44% to 47%[11] (although it was recognised that these SVRs were unusually higher than previously reported). The other explanation is that the UK trial reflects a 'real world' scenario, whereby effectiveness is lower than often observed in large international multi-centre trials conducted to support licence applications. This had implications for the assessment of cost-effectiveness (see Section 8.3).

No direct comparisons between pegylated and non-pegylated interferon alfa in histologically mild HCV patients were identified. This is in contrast to the moderate to severe HCV group where a number of RCTs have compared the two. A direct comparison between the two interferons would have been helpful in this assessment. However, it is doubtful that such a trial would ever be commissioned. It is more likely that funds will be directed towards evaluating newer technologies for treating HCV (see Section 8.4).

No RCTs were identified that evaluated 'early' treatment of histologically mild HCV patients compared to watchful waiting. However, such a trial would take years to complete, and may not be ethical given the emerging evidence for the effectiveness of anti-viral treatment in mild patients. Two of the eight RCTs in the primary analysis reported viral response for sub-groups of patients with mild and moderate to severe HCV[63;69]. In both trials SVRs were higher for patients with low fibrosis, but only one of these reported statistical significance. A similar trend was observed in the 11 studies that reported sub-group analyses. However, few reported whether differences

were statistically significant, and many of the studies were likely to be underpowered. For the purposes of our cost-effectiveness model we assumed that treatment in patients with mild HCV as of similar effectiveness to treatment of patients with more advanced disease (see Section 8.3).

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

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

Some of the trials also reported virological response according to other patient characteristics. In two trials[63;65], SVRs tended to be higher in patients aged less than 40 years, although differences were not statistically significant. Similarly, there were no statistically significant differences in SVR according to gender (measured in two trials [63;65]). In one trial[63] baseline ALT levels (raised or normal) did not have a significant effect on SVR rates. There has been discussion about the potential benefit of individualised treatment strategies, taking into account patient characteristics such as ALT, age, and genotype. Alberti (2005) [61] proposes treatment algorithms based on such factors (see Section 2.2.5). A recently published RCT evaluated a range of individualised treatment strategies based on viral response at 6 weeks of treatment with pegylated interferon alfa-2a and ribavirin[135]. Patients were classed as having rapid, slow, flat or null viral response, and a treatment strategy was then prescribed accordingly. For example, some patients with a rapid viral response continued for only 24 weeks, whereas patients with null response continued with high dose pegylated interferon alfa. No additional benefit was observed for the individualised strategies compared to control group who received standard treatment.

The generalisability of the findings of the RCTs to patients co-infected or with co-morbidities is limited. Patients with concurrent infections such as HIV and HBV, and conditions such as haemophilia, diabetes, and psychiatric disease tend to be excluded from clinical trials making it difficult to assess what benefits these patients may derive. There is, however, a growing literature on the effectiveness of anti-viral treatment in patients with HIV. The study by Chung and colleagues[68], as described

earlier, found that nearly 30% of co-infected patients with mild HCV achieved an SVR when treated with pegylated interferon alfa-2a and ribavirin.

8.2 Cost effectiveness

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

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

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

In all cases anti-viral treatment was estimated to increase life expectancy over best supportive care. However, there was little difference in life expectancy between strategies using the same anti-viral agent. Discounted life expectancy for the cohort offered non-pegylated interferon alfa, and based on the SVR reported for the UK Mild HCV trial, was estimated to be 28.18 years for watchful waiting and 28.20 for early intervention. The QALY gain associated with early treatment was 0.6, which comes from the expectation that a greater proportion of life expectancy would be spent in the 'cured' SVR health state and less in the mild disease state. The proportion of the

cohort developing cirrhosis under best supportive care was 32%, whereas 18-23% where predicted to develop cirrhosis under watchful waiting and 16-22% under early treatment. Under the base case assumptions, pegylated interferon (both alfa-2a and alfa-2b) yielded superior QALY gains to non-pegylated interferon without a disproportionate increase in costs. This largely arose from the assumed large difference in SVR between non-pegylated and pegylated interferon. The incremental cost-effectiveness ratios were sensitive to changes in key model parameters, including:

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

8.3 Assumptions, limitations and uncertainties

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

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

Second, constructing a definition of mild HCV that could be used in the screening of eligible studies was problematic. Liver histology, via biopsy, appears to be the most accepted method of grading and staging the severity of HCV liver disease. As discussed in Section 2.1.2.2, a number of biopsy classification systems exist, but they vary in scoring methods. Expert opinion and published literature enabled us to judge the comparability of the different classification systems, and to develop a common threshold of histologically mild HCV. It was anticipated that very few clinical trials were likely to recruit exclusively mild patients. It was therefore necessary to define a threshold for the proportion of patients in a trial who were histologically mild. However, this is essentially an arbitrary decision. Yet, without setting a threshold there would have been very little evidence to include in this report. Further, it has to be accepted that the SVRs reported by the included studies reflects treatment outcome for up to 30% of patients with moderate to severe HCV. This may have the effect of under-estimating the effect, based on the notion that treatment effects are higher in patients with mild HCV. This has yet to be confirmed in a prospective head to head trial (and such a trial is unlikely to be commissioned).

The screening process was further hampered by poor reporting of the baseline histological profile of patients included in the potentially eligible studies. Just under half of the otherwise eligible reports retrieved for full screening were classified as unclear on this basis. Common problems were the failure to report baseline fibrosis scores (and in some cases any baseline histology at all), or not reporting which biopsy classification system was used. It is not possible to classify these studies without

obtaining further information from the corresponding authors. However, it is anticipated that few of these studies would have included a sufficient proportion of mild HCV patients to quality for our primary analysis (thus joining the RCTs presented in Section 4.1.1.1).

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

Fourth, the lack of head-to-head comparisons between pegylated and non-pegylated interferon alfa meant that the economic evaluation reported here made use of indirect comparisons, drawing information from a range of trials and selected sub-groups. In face of the variation in the SVRs observed for non-pegylated interferon alfa, the evaluation considered high and low estimates for the SVR. Estimates of the SVR for pegylated interferon alfa used data supplied by the manufacturers for patients with mild disease who were included in clinical trials of pegylated interferon and ribavirin. These SVRs are relatively high, especially in the context of the lower SVR for non-pegylated interferon observed in the UK Mild HCV trial. The effect of alternative assumptions for the SVR of pegylated interferon were explored in a sensitivity analysis and are reported in Section 5.5.2.

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

8.4 Research needs

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

- Research and development needs to be directed towards newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects. The National Horizon Scanning Centre recently reported that Thymalfasin (Zadaxin) is in phase III trials for treatment of HCV patients not responding to previous therapy. If licensed it would be used in combination with pegylated interferon alfa. An EU licence submission is expected in mid 2007.
- This assessment would have benefited from an RCT with economic evaluation comparing early (mild HCV) treatment versus delayed (moderate to severe HCV) treatment. However, this may not be practical given the length of time such a trial would take, and it would likely be unethical now to withhold treatment.
- Further research into the natural history of HCV is required to better estimate the rate of liver disease progression. Larger cohorts need to be followed up for longer periods, with repeat biopsies (or alternative non-invasive investigations) where possible.
- Further research is needed into the effectiveness of non-invasive biochemical markers of liver disease, as an alternative to liver biopsy. This might be a suitable topic for a NICE appraisal of clinical and cost effectiveness.

9 CONCLUSIONS

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

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

Results from economic modeling suggest that early treatment with pegylated interferon alfa and ribavirin generally results in cost-utility estimates within the range considered by NHS decision-makers to represent good value for money.

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Appendix 1 - Liver biopsy classification systems

Knodell (Histological Activity Index) 1981[22]

The Knodell score or histologic activity index (HAI) is also commonly used to stage liver disease. It a somewhat more complex process, but some experts believe that it is a better tool for defining the extent of liver inflammation and damage. It is composed of four individually assigned numbers that make up a single score.

1. Perioportal and/or bridging necrosis is scored 0-10.
2. Intralobular degeneration is scored 0-4
3. Portal inflammation is scored 0-4.
   - The combination of these three markers indicates the amount of inflammation in the liver:
     - 0 = no inflammation
     - 1-4 = minimal inflammation
     - 5-8 = mild inflammation
     - 9-12 = moderate inflammation
     - 13-18 = marked inflammation
4. The fourth component indicates the amount of scarring (fibrosis) in the liver and is scored from:
   - 0 (no scarring)
   - 1
   - 3
   - 4 (extensive scarring or cirrhosis).

The total possible HAI score is: 22

Ishak (Histological Activity Index), 1995[23]

This is a modified version of Knodell's system

Modified HAI grading: necroinflammatory scores	Score
A. Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around 60% of tracts or septa)	3
Severe (continuous around >50% of tracts or septa)	4
B. Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3

Zone 3 necrosis+occasional portal-central (P-C) bridging	4
Zone 3 necrosis+multiple P-C bridging	5
Panacinar or multiacinar necrosis	6
C. Focal (spotty) lytic necrosis, apoptosis and focal inflammation*	
Absent	0
One focus or less per 10xobjective	1
Two to four foci per l0xobjective	2
Five to ten foci per l0xobjective	3
More than ten foci per 10xobjective	4
D. Portal inflammation	
None	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4
Maximum score for grading	18

Modified staging: architectural changes, fibrosis and cirrhosis	
Change	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1 2
Fibrous expansion of most portal areas, with or without short fibrous septa	3
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	4
Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C))	5
Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	6
Cirrhosis, probable or definite	
Maximum possible score	**6**

Disease severity thresholds

Fibrosis:
≤ 2 Mild
3-5 Moderate
6 Severe (cirrhosis)

Necro-inflammatory score:
1-8 Mild
9-18 Moderate / Severe

(NB. If fibrosis = 6 then the patient is classified as having severe HCV, irrespective of the necro-inflammatory score)

Total Ishak HAI score = 24

METAVIR (1996)[24]

Specially designed for HCV

Necro-inflammation

A0 – No histological activity
A1 – Mild activity
A2 – Moderate activity
A3 – Severe activity

Fibrosis

F0 – no scarring
F1 – minimal scarring
F2 – scarring has occurred but extends outside the areas that the liver contains blood vessels
F3 – bridging fibrosis is spreading and connecting to other areas that contain fibrosis
F4 – cirrhosis or advanced scarring of the liver

Total METAVIR score = 7

Appendix 2 - Anti-viral drugs – licensed indications

Interferon alfa-2a / 2b

Interferon alfa has been used in the treatment of chronic hepatitis C for a number of years, primarily as a single agent, until the introduction of combination therapy with ribavirin in 1999. Interferons are naturally occurring proteins with complex effects on immunity and cell function, and there are at least 15 different molecular species. Interferon alfa was the first pure human protein found to be effective in the treatment of cancer and has been used to treat chronic myelogenous leukaemia and other myeloproliferative disorders, renal carcinoma and infections such as chronic hepatitis B.

Three preparations are available:

- interferon alfa-2a ("Roferon A", Roche)
- interferon alfa-2b ("Intron A", Schering-Plough)
- interferon alfa-2b ("Viraferon, Schering-Plough)

Pegylated interferon alfa-2a / 2b

A newer 'pegylated' derivative of interferon alfa has superseded the use of 'conventional' non-pegylated interferon. Pegylation involves the attachment of an inert polyethylene glycol polymer to the interferon molecule to produce a larger molecule with a prolonged half life. Pegylation prolongs the biological effect necessitating fewer injections and therefore is more convenient for patients. There are differences between the two pegylated interferons, such as the size and structure of their polyethylene glycol molecule, and the bond between the PEG molecule and the interferon.

The pegylated interferons are licensed in Europe for the treatment of chronic hepatitis C in combination with ribavirin (or as monotherapy in those for whom ribavirin is contra-indicated) (Pegylated interferon alfa-2a is also licensed in the EU for the treatment of chronic hepatitis B). Treatment is indicated in both previously untreated patients, and for those who have previously been treated with, and responded to, interferon alfa but who have subsequently relapsed.

Three preparations are available:

- 40 kD Pegylated interferon alfa-2a ("Pegasys"; Roche). Currently indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis. A licence variation was announced in 2003 to remove the phrase "histologically proven" for patients with genotypes 2 and 3. Further, the European Medicines Agency (EMEA) announced in November 2004 that it had approved Pegasys for the treatment of chronic hepatitis C patients with persistently normal liver enzymes (it had previously been indicated in patients with elevated ALT levels).
  - Dose: 180 µg/week via subcutaneous injection.
- 12 kD Pegylated interferon alfa-2b ("PegIntron", Schering-Plough). Currently indicated for the treatment of adult patients who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

  - Dose: 1.5 µg/kg/week via subcutaneous injection.
- 12 kD Pegylated interferon alfa-2b ("ViraferonPeg"; Schering-Plough). (licensed indication – as for PegIntron).

Ribavirin

Ribavirin is a synthetic nucleoside analogue with a broad spectrum of antiviral activity against DNA and RNA viruses. It is indicated in combination with pegylated interferon alfa or interferon alfa for patients with chronic hepatitis C not previously treated, without liver decompensation and who have fibrosis or high inflammatory activity or for relapse following previous response to interferon alfa.

Two preparations are available for use in chronic hepatitis C:

- "Rebetol", Schering-Plough.
  - Dose: body-weight < 65 kg, 400 mg twice daily; body-weight 65–85 kg, 400 mg in the morning and 600 mg in the evening; body-weight over 85 kg, 600 mg twice daily.
- "Copegus", Roche.
  - Dose: body-weight < 75 kg, 400 mg in the morning and 600 mg in the evening; body-weight 75 kg and over, 600 mg twice daily. For patients with genotypes 2 or 3 the dose of Copegus is lower (800mg), usually administered as 400mg twice daily.

Appendix 3 –Clinical-effectiveness search strategy (Medline, via Ovid)

1 (hepatitis c or HCV).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Hepatitis C/
3 Hepatitis C, Chronic/
4 Hepacivirus/
5 1 or 2 or 3 or 4
6 (peginterferon$ or peg-ifn or peg-interferon$ or (pegylat$ adj3 interferon$) or peg$ or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or Pegasys).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 limit 7 to (english language and yr=2003-2005)
9 exp interferon type i, recombinant/ or exp interferon-alpha/ or exp interferon alfa-2a/ or exp interferon alfa-2b/ or exp interferon alfa-2c/
10 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab.
11 9 or 10
12 11 and 5
13 limit 12 to (english language and yr=2000-2005)
14 13 not 8
15 meta-analysis/
16 (meta analysis or metaanalysis).ab,pt,ti.
17 (systematic$ adj2 (review$ or overview$)).ti,ab,pt.
18 or/15-17
19 (letter or editorial or comment).pt.
20 18 not 19
21 randomized controlled trial.pt.
22 controlled clinical trial.pt.
23 randomized controlled trials/
24 random allocation/
25 double-blind method/
26 single-blind method/
27 exp evaluation studies/
28 exp clinical trials/
29 clinical trial.pt.
30 (clin$ adj5 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
33 exp placebos/
34 placebo$.tw.
35 random$.tw.
36 exp research design/
37 32 or 33 or 34 or 35 or 36
38 31 or 37
39 8 and 20
40 8 and 38
41 14 and 20
42 14 and 38

The clinical effectiveness search strategy was combined with a systematic review and randomised controlled trials filter where possible to locate high quality evidence.

The above strategy was translated to run in the following electronic databases: Medline (Ovid); PreMedline (Ovid); Embase (Ovid); Cochrane Library including Cochrane Database of Systematic Reviews; Cochrane CENTRAL Register of Controlled Trials; Centre for Reviews and Dissemination (University of York) databases: DARE (Database of Abstracts of Reviews of Effects) HTA (Health Technology Assessment Database); ISI Web of Science, Science Citation Index, ISI Proceedings; Biosis Previews (Edina); National Research Register; Current Controlled Trials; Clinical Trials.

Appendix 4 – Costs and cost-effectiveness search strategy

The cost effectiveness searches were run in Medline (Ovid); Embase (Ovid); CRD NHS EED (Economic Evaluations Database); and EconLit.

Medline, via Ovid

1 (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3 or/1-2
4 exp "costs and cost analysis"/
5 Cost-Benefit Analysis/
6 exp Health Care Costs/
7 4 or 5 or 6
8 7 and 3
9 limit 8 to (english language and yr=2000 - 2005)

Embase, via Ovid

1 (hepatitis C or hcv).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
2 exp Hepatitis C/ or exp Hepatitis C virus/
3 or/1-2
4 (peginterferon$ or peg-ifn or peg-interferon$ or (peg$ adj3 interferon$) or (polyethylene glycol adj3 interferon$) or Pegasys or pegintron or viraferonpeg).mp.
5 peginterferon/ or peginterferon alpha2a/ or peginterferon alpha2b/
6 4 or 5
7 3 and 6
8 limit 7 to (english language and yr=2003-2005)
9 interferon/ or alpha2a interferon/ or alpha2b interferon/ or alpha interferon/
10 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab.
11 9 or 10
12 3 and 11
13 12 not 7 (
14 limit 13 to (english language and yr=2000-2005)
15 (cost$ adj2 effective$).ti,ab.
16 (cost$ adj2 benefit$).ti,ab.
17 cost effectiveness analysis/
18 cost benefit analysis/
19 budget$.ti,ab.
20 cost$.ti.
21 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
22 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti.
23 (price$ or pricing$).ti,ab.
24 (financial or finance or finances or financed).ti,ab.
25 (fee or fees).ti,ab.
26 cost/
27 cost minimization analysis/

28 cost of illness/
29 cost utility analysis/
30 drug cost/
31 health care cost/
32 health economics/
33 economic evaluation/
34 economics/
35 pharmacoeconomics/
36 budget/
37 economic burden.ti,ab.
38 "resource use".ti,ab.
39 or/15-38
40 (editorial or letter).pt.
41 39 not 40
42 41 and 3
43 41 and 8
44 41 and 14

Appendix 5 – Health related quality of life search strategy

The health related quality of life search strategy was translated and applied to Medline (Ovid); PreMedline (Ovid) and Embase (Ovid).

Medline, via Ovid

1 value of life/
2 quality adjusted life year/
3 quality adjusted life.ti,ab.
4 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
5 disability adjusted life.ti,ab.
6 daly$.ti,ab.
7 health status indicators/
8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.
13 (euroqol or euro qol or eq5d or eq 5d).ti,ab.
14 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
15 (hye or hyes).ti,ab.
16 health$ year$ equivalent$.ti,ab.
17 health utilit$.ab.
18 (hui or hui1 or hui2 or hui3).ti,ab.
19 disutil$.ti,ab.
20 rosser.ti,ab.
21 quality of well being.ti,ab.
22 quality of wellbeing.ti,ab.
23 qwb.ti,ab.
24 willingness to pay.ti,ab.
25 standard gamble$.ti,ab.
26 time trade off.ti,ab.
27 time tradeoff.ti,ab.
28 tto.ti,ab.
29 (index adj2 well being).mp.
30 (quality adj2 well being).mp.
31 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33 quality adjusted life year$.mp.

34 (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
35 (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
36 rating scale$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
37 linear scal$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38 linear analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 visual analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41 or/1-40 (
42 (letter or editorial or comment).pt.
43 41 not 42
44 (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
46 44 or 45
47 46 and 43
48 limit 47 to (english language and yr=2000 - 2005)

Appendix 6 – Epidemiology search strategies (Medline, via Ovid)

The epidemiology/ natural history searches were run in Medline, PreMedline and Embase (Ovid) databases.

1 (hepatitis C or hcv).mp.
2 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3 or/1-2
4 incidence.ti.
5 prevalence.ti.
6 epidemiol$.ti.
7 ((natural$ or disease$ or fibrosis or cirrhosis or hepatocellular carcinoma) adj4 (progress$ or course$ or histor$ or survival)).ti,ab.
8 Alanine Transaminase/bl
9 (normal adj4 (aminotransferase or transaminase)).mp.
10 or/4-9
11 3 and 10
12 limit 11 to (english language and yr=2003 - 2005)

Appendix 7 - Inclusion worksheet for clinical effectiveness studies

Trial Name or Number:				
Patients with **mild chronic Hepatitis C***? Mild HCV defined by liver biopsy fibrosis threshold scores • Ishak ≤ 2/6 • Knodell ≤ 1/4 • Metavir ≤ 1/5 • Scheur ≤ 1/4 • or other scoring/staging systems • Proportion of patients below the threshold in trial at baseline, if reported, should be no less than 70% • Mean/median score (if reported) should be lower than the 70% threshold • However, trial can be included if SVR is reported for sub-group of mild patients	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Type: EXCLUDE1 (not HCV or mild HCV)
Design: RCT or systematic review***	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	EXCLUDE2 (not the right study design)
Intervention** 1. Pegylated interferon + ribavirin 2. Pegylated interferon monotherapy 3. Interferon (non-pegylated) + ribavirin	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	EXCLUDE3 (not the right intervention)
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	EXCLUDE4 (not the right outcome measures)
Final Decision	**INCLUDE**	**UNCLEAR (Discuss)**	**EXCLUDE**	**Results of Discussion:**

*NB. It is unlikely that many studies will report disease severity in title and abstract so advice is to be over-inclusive at this stage and include any relevant study that includes patients with HCV. Obvious exceptions include where the patients have cirrhosis, decompensated liver disease, hepatocellular carcinoma or are undergoing liver transplant. These patients, by definition, have moderate to severe disease.

**Likely comparators (can include, but not restricted to):

1) PEG + RBV vs:
- PEG + RBV (different dose/regimen or in different patient sub-group)
- No treatment
- IFN + RBV
- PEG monotherapy
- IFN monotherapy

2) PEG monotherapy vs:
- PEG monotherapy (different dose/regimen or in different patient sub-group)
- No treatment
- IFN monotherapy

3) IFN + RBV vs:
- IFN + RBV (different dose/regimen or in different patient sub-group)
- No treatment
- IFN monotherapy

*** Systematic review normally defined by reporting of search strategy and inclusion criteria. Not all systematic reviews report an explicit assessment of quality but if reported this is an additional indicator that the review has been conducted according to 'systematic' methods.

Appendix 8 – Cheng and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Cheng et al, 2002[67] **Trial design**: Double blind RCT **Country**: Taiwan **Sponsor**: Schering-Plough AB and National Cheng-Kung University Hospital, Taiwan	**Intervention 1:** n = 26 IFN α-2b (s.c.) Dose: 6 MU 3 times per week Duration: 24 weeks RBV (oral) Dose: twice daily at a total dose of 1000mg for patients ≤75kg, 1200mg for patients >75kg Duration: 24 weeks **Intervention 2:** n = 26 IFN α-2b (s.c.) Dose: 6 MU 3 times per week Duration: 24 weeks Placebo Dose: twice daily Duration: 24 weeks	**Total numbers involved**: 72 screened, 52 randomised and analysed **Eligibility**: adult CHC patients who had previously responded to IFN-α but who had then relapsed, positive HCV antibody, HCV RNA positive, using effective contraception **Recruitment**: patients from the National Cheng-Kung Hospital, Taiwan, between Jan 1999 and July 2000 **Exclusion criteria**: patients <18 yrs or >65 yrs, decompensated liver disease, other causes of chronic liver disease (hepatitis B, Epstein-Barr virus, cytomegalovirus, autoimmune hepatitis and metabolic liver diseases), haemoglobin <13 mg/dl for males or <12 mg/dl for females, white blood cell count <4,000/mm^3, neutrophil count <2,000/mm^3, platelet count <100,000/mm^3, chronic alcoholism, HIV infection, pregnancy, previous organ transplant, severe psychiatric conditions, seizure disorders, renal failure, evidence of ischaemic heart disease, retinal abnormalities, poorly controlled diabetes mellitus, haemoglobinopathy, haemophilia. **Baseline measurements**: **Viral load,** mean HCV RNA (±SD), MEq/ml: 6.7 (±9.9) Gp 1, 8.2 (±12.7) Gp 2 **Serum ALT**, mean (±SD), U/l **:** 206.2 (±175.0) Gp 1, 229.0 (±195.6) Gp 2 **Histology**: Classification system used: Knodell Fibrosis score, mean (±SD): 0.5 (±1.0) Gp 1, 0.2 (±0.4) Gp 2 Necroinflammatory score, mean (±SD): 2.1 (±1.3) Gp 1, 2.2 (±1.8) Gp 2 Timing of liver biopsy: performed before and at the end of treatment **Genotypes, no. (%)**: 1b: 22 (42%) 2a+c: 22 (42%) 2b: 2 (4%) 1a+2: 3 (6%) 2 (not subtyped): 3 (6%)	**Primary outcomes**: SVR (loss of detectable serum HCV RNA at end of follow-up) **Secondary outcomes**: • end of treatment virological response • biochemical response (normalisation of ALT[a]) • change in liver histology • adverse events **Length of follow up**: 24 weeks after stopping treatment

		Gender, no. (%): 41 m (79%), 11 f (21%) **Age (yrs), mean (±SD)**: 43.4 (±10.3) Gp 1; 45.1 (±8.5) Gp 2 **Ethnic groups, no. (%)**: not reported **Mode of infection, no. (%)**: not reported **Losses to follow up**: 0 **Compliance**: 2 patients did not complete the study: 1 withdrew due to adverse effects, 1 was withdrawn due to decreased neutrophil count.		
Outcome % (No.)		**IFN α-2b (6 MU) + RBV (1000-1200mg)**	**IFN α-2b (6 MU) + placebo**	***p*-value (between group comparison)**
Viral Response End of treatment SVR at follow-up		 92% (24/26) 69% (18/26)	 81% (21/26) 23% (6/26)	 ns <0.001
SVR by genotype 1 non-1		 50% (7/14) 92% (11/12)¶	 27% (3/11) 20% (3/15)	 <0.005
SVR by viral load ≤3 MEq/ml >3 MEq/ml		 92% (12/13)‡ 46% (6/13)	 50% (6/12)* 0 (0/14)	 <0.05 <0.005
Biochemical Response End of treatment End of follow-up		 92% (24/26) 65% (17/26)	 81% (21/26) 19% (5/26)	 ns <0.001
Histological improvement (n=48) Inflammation, mean decrease Fibrosis, mean decrease		 1.3 ± 0.5 0.8 ± 3.3	 1.3 ± 0.5 0.0 ± 2.1	 0.27
Adverse Events,[b] No. (%) dose discontinuation for adverse event other[c] dose reduction for anaemia other[d] Specific adverse events malaise fever headache rigors anorexia diarrhoea insomnia depressed mood alopecia palpitation cough		 1 (4) 1 (4) 6 (23) 6 (23) 22 (84) 20 (76) 19 (73) 14 (53) 23 (88) 10 (38) 18 (69) 4 (15) 19 (73) 4 (15) 4 (15)	 0 (0) 0(0) 0 (0) 8 (31) 20 (76) 19 (73) 18 (69) 12 (46) 17 (65) 7 (26) 10 (38) 3 (11) 19 (73) 2 (7) 3 (11)	 <0.05 <0.05

[a]Normal range of ALT values is within 5-55 U/l. *p<0.005 for comparison with HCV RNA level >3 MEq/ml; ‡p<0.05 for comparison with HCV RNA level >3 MEq/ml; ¶p<0.05 for comparison with genotype 1.[b]Only adverse events that occurred >5% were included, [c]decreased neutrophil count, [d]leukopenia or neutropenia.

Additional Results:

Histological response:

- In non-responders, a decrease in the inflammation score (1.00 ±2.04), but not a decrease in the fibrosis score (-0.29 ±1.27), was observed.

Predictive values of response:

- In week 4, the IFN + placebo group reached 83% sensitivity, 45% specificity, 31% PPV and 90% NPV. In comparison, the IFN + RBV group reached 90% sensitivity, 100% specificity, 90% PPV and 100% NPV (see definitions below).

Safety:

- Haemoglobin values were significantly lower in the IFN/RBV group than in the IFN/placebo group after the second week of treatment. However, haemoglobin values returned to baseline values within 4 weeks after completion of treatment.

Methodological comments:

Allocation to treatment groups: patients were randomly assigned to one of two treatment arms by the random permuted block method. Does not state whether this is computer generated or manual.
Allocation concealment: random permuted block method – reference cited.
Blinding of outcome assessors: study described as double-blind. Patients received RBV or a matched placebo. All biochemical and haematological tests were performed by autoanalysers – no further details. An experienced pathologist who was unaware of treatment aims and results analysed liver biopsy samples.
Analysis by intention to treat: reports that data were analysed by ITT. Results were reported for all 52 randomised pts.
Comparability of treatment groups at pre-treatment: groups appear comparable at baseline for demographic, biochemical, haematological and histological characteristics. Statistical values not presented.
Method of data analysis: Statistical methods used to analyse the data included Chi-square test, Fisher exact test and Student t-test with a type I error of 0.05, two-tailed as appropriate.
Power analysis: to detect a 35% difference in the rate of primary endpoint between IFN and IFN/RBV treatments, with a power of 80% and a two-tailed type I error of 0.05, 19 pts on each treatment were needed.
Attrition/drop-out: Two pts in the IFN/RBV group (2/26, 8%) did not complete the study. One patient withdrew due to insomnia, palpitation and dizziness at wk 3 of treatment; the other was withdrawn at wk 8 of treatment due to decreased neutrophil count. Pre- and post-treatment liver biopsies were collected from 48 of 52 pts – 2 pts refused biopsy, in 2 pts only pre-treatment biopsy specimens were collected due to withdrawal from study.

General comments

Generalisability: Patients with mild chronic HCV without other co-morbidities – mean fibrosis is very low (≤0.5). The authors report that patients represented a reasonable genotypic cross-section of the contemporary Taiwanese population.
Conflict of interests: Study supported in part by a grant from Schering-Plough AB.
Other: The paper states that the decreased fibrosis score for the IFN/RBV group was 0.8 ± 3.3. However, baseline mean fibrosis score for this group was 0.5 ± 1.0. Therefore, it is assumed that this is 0.8 of 0.5 = 0.4.
Definitions: Sensitivity - fraction of all SVR patients identified by undetectable HCV RNA; Specificity - fraction of all non-SVR patients identified by detectable HCV RNA; PPV, positive predictive value - chance of SVR if HCV RNA is undetectable; NPV, negative predictive value – chance of non-SVR if HCV RNA is detectable; Knodell histological activity index inflammation score ranged from 0-18; histological improvement was defined as a decrease in the inflammation score of at least two points or a decrease in the fibrosis score of at least one point relative to the pre-treatment biopsy.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Partial
2. Was the treatment allocation concealed?	Inadequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Inadequate
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 9 – Chung and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Chung et al, 2004[68] **Trial design**: Multicentre RCT **Country**: USA **Sponsor**: National Institutes of Health	**Intervention 1:** n = 66 Peg IFN α-2a (s.c.) Dose: 180µg once weekly Duration: 48 weeks RBV (oral) Dose: 600mg daily Duration: 4 weeks Dose: 800mg daily Duration: 4 weeks Dose: 1,000mg daily Duration: 40 weeks **Intervention 2:** n = 67 IFN α-2a (s.c.) Dose: 6 million IU three times per wk Duration: 12 weeks Dose: 3 million IU three times per wk Duration: 36 weeks RBV (oral) Dose: 600mg daily Duration: 4 weeks Dose: 800mg daily Duration: 4 weeks Dose: 1,000mg daily Duration: 40 weeks	**Total numbers involved**: 133 randomised and analysed **Eligibility**: HIV infected patients, ≥18 yrs, confirmed diagnosis of chronic hep C (>600 IU/ml HCV RNA level), biopsy findings consistent with the presence of chronic hep C, not previously treated with IFN-α, normal or elevated ALT levels, cirrhosis acceptable provided there was no evidence of hepatic decompensation (i.e. ascites, encephalopathy, jaundice, hypoalbuminemia or coagulopathy) **Recruitment**: 21 centres in the USA between Dec 2000 and June 2001 **Exclusion criteria**: clinically significant anemia, neutropenia or thrombocytopenia; renal disease; positive tests for hep B surface antigen; uncontrolled cardiopulmonary disease; poorly controlled psychiatric disease; active HIV-related opportunistic infection **Baseline measurements**: **Viral Load,** HCV RNA level $x10^{-6}$ IU/ml Mean (±SD): 6.2 (±0.4) Gp 1, 6.2 (±0.3) Gp 2 > $1x10^{6}$ IU/ml, %: 83% Gp 1, 82% Gp 2 **ALT,** abnormal level, %: 66% Gp 1, 68% Gp2 **Histology**: Classification system used: Ishak Fibrosis score, median: 2.0 Gp 1, 2.0 Gp 2 Cirrhosis, %: 11% Gp 1, 9% Gp 2 Hepatitis activity index score, median: 5.0 Gp 1, 5.0 Gp 2 Timing of liver biopsy: within 48 weeks before study entry **Genotype 1,** %: 77% Gp 1, 78% Gp 1 **Gender, no. (%)**: 109 m (82%), 24 f (18%) **Age, mean**: 45yrs Gp 1, 44 yrs Gp 2 **Ethnic groups, no. (%)**: White: 64 (48%) Black: 44 (33%) Hispanic: 18 (14%) Other: 7 (5%)	**Primary outcomes**: virologic response at wk 24 of treatment **Secondary outcomes**: • SVR • end of treatment virologic response • early virologic response • histologic response • adverse events **Length of follow up**: 24 weeks after completion of therapy

		Mode of infection, no. (%): not reported **Losses to follow up**: 8 subjects in each group (12%) were prematurely withdrawn from treatment because of abnormalities in lab values or adverse events. **Compliance**: 0		
Outcome, No. (%)		**Peg IFN α-2a + RBV**	**IFN α-2a + RBV**	***p*-value (between group comparison)**
Viral Response				
24 wks		29/66 (44%)	10/67 (15%)	<0.001
End of treatment (48 wks)		27/66 (41%)	8/67 (12%)	<0.001
SVR at follow-up		18/66 (27%)	8/67 (12%)	0.03
SVR by genotype				
1		7/51 (14%)	3/52 (6%)	
non-1		11/15 (73%)[†]	5/15 (33%)[†]	0.07
Histology				
No virologic response at wk 24		(n=37)	(n=57)	
histologic response		9/26[a] (35%)	16/45[a] (36%)	
Virologic response at wk 24		(n=39)		
histologic improvement		14/27[b] (52%)		
no change		11/27[b] (41%)		
worsening disease		2/27[b] (7%)		
Adverse events at weeks 0-24, no. of subjects[c]		(n=66) Grade 2/3/4[d]	(n=67) Grade 2/3/4[d]	
Signs & symptoms		26/15/ 0	20/19/1	
Influenza-like symptoms		19/12/ 0	20/13/0	
Depression		5/2/0	6/2/0	
Abnormal laboratory values		18/22/15	26/21/4	
Anaemia		0/0/2	1/0/0	
Neutropenia		13/18/5	10/7/3	
Thrombocytopenia		10/2/1	2/0/0	
Glucose high or low		12/3/4	14/2/0	
ALT high		18/2/0	12/7/0	
Lipase high		5/4/0	6/3/0	
Lactate high		0/0/0	0/1/0	
Adverse events at weeks 25-72, no. of subjects[c]		(n=35) Grade 2/3/4[d]	(n=26)[e] Grade 2/3/4[d]	
Signs & symptoms		10/4/0	7/3/0	
Influenza-like symptoms		5/3/0	4/1/0	
Depression		1/1/0	0/0/0	
Abnormal laboratory values		13/10/7	8/4/1	
Anaemia		0/0/1	0/0/0	
Neutropenia		7/6/4	1/2/0	
Thrombocytopenia		3/0/0	0/0/0	
Glucose high or low		5/4/1	4/1/0	
ALT high		5/2/0	1/0/1	
Lipase high		3/1/0	2/1/0	
Lactate high		0/0/0	0/0/0	
Dose discontinuation		8	8	

[†]$p<0.001$ for comparison with genotype 1; [a]26 of 37 subjects underwent liver biopsy, [a]45 of 57 subjects underwent liver biopsy, [b]27 of 39 subjects underwent liver biopsy at wk 48; [c]subjects could have >1 adverse event; [d]grade 2 indicates a moderate adverse event, grade 3 a severe adverse event, grade 4 a potentially life-threatening adverse event; [e]included 3 subjects who continued treatment beyond wk 24 while awaiting liver biopsy.

Additional Results:

- *Virologic response*:
  - In genotype 1 subjects at wk 24, the virologic response was 33% (17/51) and 8% (4/52) for Peg IFN and IFN respectively (p=0.001); in genotype non-1 (predominantly genotypes 2 and 3), the virologic response was 80% (12/15) and 40% (6/15) for Peg IFN and IFN respectively.
  - In genotype 1 subjects at the end of treatment, the virologic response was 29% (15/51) and 6% (3/52) for Peg IFN and IFN respectively; in genotype non-1, the virologic response was 80% (12/15) and 33% (5/15) for Peg IFN and IFN respectively ($p<0.001$ for genotype non-1 vs genotype 1 for the Peg group).
  - Receipt of Peg IFN + RBV, genotype non-1, absence of prior injection drug use, a detectable level of HIV-1 RNA at entry, and a Karnofsky score of 100 were predictive of an SVR in univariate analysis. In multivariate analysis, all these variables except the Karnofsky score independently predicted an SVR.
  - Of the 106 subjects in whom HCV RNA levels were measured at wk 12, 43 (41%) had an early virologic response. 22 of these 43 subjects (51%) had an SVR. In contrast, none of the 63 subjects who did not have an early virologic response had an SVR (negative predictive value, 100%).
- *Safety*:
  - The rate of premature withdrawal (12%) was similar to that in similar studies of subjects with HCV monoinfection. Also, see *attrition/drop-out* below.
  - 2 subjects in the Peg gp discontinued therapy because of grade 4 neutropenia (<500 neutrophils/mm^3). In 6 others (3 Peg, 3 IFN) grade 4 neutropenia was successfully managed with a dose reduction, with or without hematopoietic growth factor.
  - There was one hospitalisation due to clinically significant pancreatitis, and treatment was discontinued at wk 16. The subject was also receiving didanosine. Of 18 subjects with lipase elevations of grade 2 or higher, 4 were taking didanosine.

Methodological comments:
Allocation to treatment groups: randomisation was stratified according to HCV genotype (1 vs non-1) and antiretroviral therapy status (current vs none). No details reported on actual randomisation method.
Allocation concealment: not reported.
Blinding of outcome assessors: a central pathologist assessed histologic response; no further details reported.
Analysis by intention to treat: reports that data were assessed using ITT analysis. Results were reported for all 133 randomised patients.
Comparability of treatment groups at pre-treatment: there were no statistically significant differences between groups at baseline for demographics, histology, biochemical or HIV-related characteristics.
Method of data analysis: Associations between dichotomous variables were evaluated with Fisher's exact test. Associations involving ordered categorical data or continuous data were evaluated with a Wilcoxon test adjusted for ties. Univariate- and multicovariate-adjusted P values for the association of the virologic response at wk 24 with covariates were evaluated with logistic regression stratified according to the HCV genotype and HIV treatment history. All P values were 2-sided. Univariate analyses of SVR were performed with log-rank tests, and multicovariate analyses with proportional hazards regression. Because of the limited sample size and because SVR was not a primary outcome, these tests were not stratified according to the group or the HCV genotype. The proportion of subjects who continued to have SVR was estimated with the use of the life-table method.
Power analysis: the study was designed to have a statistical power of 80% (with a 2-sided alpha value of 0.05) to detect an absolute difference in the rate of virologic response between groups of 30%. The target sample size of 132 was adjusted for a group-sequential design.
Attrition/drop-out: 8 subjects in each gp (12%) were prematurely withdrawn from treatment because of abnormalities in lab values or other adverse events. Of the 16 subjects, 3 declined further participation and 1 died of unrelated causes. The remaining 12 were withdrawn because of neuropsychiatric issues (primarily depression) or the need to manage multiple signs and symptoms and abnormal lab values.

General comments
Generalisability: subjects were co-infected with HIV
Conflict of interests: six authors reported having received consulting fees or grant support from a range of pharmaceutical companies; 3 of these authors received fees/support from Roche and Schering-Plough.
Other: study design - treatment duration was 48 wks. However, an efficacy and safety assessment was performed at wk 24 to determine whether subjects could continue. Subjects who had a virologic response continued treatment until wk 48 at

which time they had a liver biopsy. Subjects with no virologic response at wk 24 underwent a liver biopsy at that time. Those with a histologic response continued treatment until wk 48; those with no histologic response or who did not undergo biopsy stopped taking the study drug.
Definitions: SVR, sustained virologic response - HCV RNA level <60 IU/ml 24 wks after completion of therapy, allowing a 6-wk window for the sample; end of treatment response - HCV RNA level <60 IU/ml at the completion of therapy; early virologic response – the clearance of HCV RNA or a reduction in HCV RNA levels by more than 2 log (on a base-10 scale) IU/ml at 12 wks of treatment; histologic response – an improvement in the total hepatic activity index of at least two points as judged by a pathologist.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	N/a as trial was open label
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 10 – Hadziyannis and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Hadziyannis *et al*, 2004[69] **Trial design**: Multicentre, double-blind RCT **Country**: International **Sponsor**: Roche	**Intervention 1: 24-LD** n = 207 Peg IFN α-2a Dose: 180µg / week Duration: 24 weeks RBV Dose: 800mg / d Duration: 24 weeks **Intervention 2: 24-SD** n = 280 Peg IFN α-2a Dose: 180µg / week Duration: 24 weeks RBV Dose: 1000mg/d for patients <75kg, 1200mg/d for patients ≥75kg Duration: 24 weeks **Intervention 3: 48-LD** n = 361 Peg IFN α-2a Dose: 180µg / week Duration: 48 weeks RBV Dose: 800mg / d Duration: 48 weeks **Intervention 4: 48-SD** n = 436 Peg IFN α-2a Dose: 180µg / week Duration: 48 weeks RBV Dose: 1000mg/d for patients <75kg, 1200mg/d for patients ≥75kg Duration: 48 weeks	**Total numbers involved**: 1736 screened, 1311 randomised, 1284 analysed **Eligibility**: treatment naïve adult patients, serum HCV RNA >2000 copies/mL, elevated serum ALT (documented on ≥2 occasions ≥14 days apart within previous 6 mths), compensated liver disease, biopsy consistent with CHC (obtained in previous 15 mths) **Recruitment**: 99 centres in Europe, N. and S. America, Australia, New Zealand and Taiwan, between Nov 1999 and Jan 2002 **Exclusion criteria**: neutropenia (neutrophil count <1.5 x10^9 cells/L), thrombocytopenia (platelet count <90 x10^9 cells/L), anaemia (haemoglobin level <120 g/L in women and <130 g/L in men) or a medical condition that would be clinically significantly worsened by anaemia, serum creatinine level >1.5 times the upper limit of normal, co-infection with hepatitis A or B virus or HIV, history of bleeding from oesophageal varices or other conditions consistent with decompensated liver disease, organ transplant, severe or poorly controlled psychiatric disease (especially depression), malignant neoplastic disease, severe cardiac or chronic pulmonary disease, immunologically mediated disease (except controlled thyroid disease), seizure disorder, severe retinopathy, alcohol or drug dependence within 1 yr of study entry, clinically significant co-morbid medical conditions, pregnancy, unwillingness to practice contraception **Baseline measurements**: **Viral Load,** mean HCV RNA level x10^3 copies/mL (±SD): 5047 (±5358) 24-LD 5513 (±7002) 24-SD 7156 (±8223) 48-LD 6059 (±6847) 48-SD **Mean ALT, U/L[a]:** 88.3 (±62.5) 24-LD 91.1 (±67.5) 24-SD 81.3 (±52.6) 48-LD 87.0 (±60.9) 48-SD **Histology**: Classification system used: Knodell	**Primary outcomes**: SVR **Secondary outcomes**: • end of treatment virological response • adverse events **Length of follow up**: 24 weeks after completion of treatment

		Fibrosis score, no. (%): Non-cirrhosis (F0, F1): 963 (75%) Bridging cirrhosis (F3): 231 (18%) Cirrhosis (F4): 90 (7%) Timing of liver biopsy: obtained within previous 15 mths **Genotypes, no. (%)**: 1: 740 (58%) non-1: 544 (42%) 2: 204 (16%) 3: 288 (22%) **Gender, no. (%)**: 838 (65%) m, 446 (35%) f **Age (yrs), mean (±SD)**: 41.2 (±8.9) 24-LD 42.0 (±9.2) 24-SD 42.6 (±10.4) 48-LD 43.0 (±10.1) 48-SD **Ethnic groups, no. (%)**: White: 1146 (89%) Black: 38 (3%) Asian: 87 (7%) Other: 13 (1%) **Mode of infection, no. (%)**[b]: Injection drug use: 457 (36%) Transfusion: 231 (18%) Unknown or other: 427 (33%) **Losses to follow up**: 270 pts discontinued treatment (of which18 pts were lost to follow-up). 1014 pts completed their allocated treatment, which is 77% of those initially randomised (n=1311) or 79% of those who received ≥1 dose of study medication (n=1284). Similarly, 1022 pts completed 24 wks of follow-up, which is 78% or 80% respectively (see methodology section for further explanation). **Compliance**: 27 pts were randomised but not treated.			

Outcome % with response (n)*	**24-LD**	**24-SD**	**48-LD**	**48-SD**
Viral Response				
End of treatment				
genotype 1	68% (69/101)	78% (92/118)	60% (150/250)	69% (187/271)
genotype 2 or 3	94% (90/96)	90% (130/144)	82% (81/99)	85% (130/153)
SVR by genotype and baseline viral load				
Genotype 1	29% (29/101)	42% (50/118)	41% (103/250)	52% (141/271)
low viral load[c]	41% (21/51)	52% (37/71)	55% (33/60)	65% (55/85)
high viral load[d]	16% (8/50)	26% (12/47)	36% (68/190)	47% (88/186)
Genotype 2 or 3	84% (81/96)	81% (117/144)	79% (78/99)	80% (122/153)
low viral load[c]	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)
high viral load[d]	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)

SVR by genotype and baseline fibrosis[e]				
F3 or F4 fibrosis + genotype 1	26% (6/23)	26% (7/27)	28% (19/67)	41% (32/78)
F3 or F4 fibrosis + genotype 2 or 3	75% (15/20)	74% (29/39)	70% (14/20)	73% (24/33)
F0 or F1 fibrosis + genotype 1	29% (23/78)	46% (42/91)	45% (83/183)	57% (110/193)
F0 or F1 fibrosis + genotype 2 or 3	87% (66/76)	84% (88/105)	81% (64/79)	83% (100/120)

Treatment effects by genotype and baseline viral load	**Odds Ratio (95% CI)**	***p*-value**	**Difference in SVR Rate (95% CI), %**
48 vs 24 wks of treatment (48-LD and 48-SD vs 24-LD and 24-SD)			
Genotype 1 (n=740)	2.19 (1.52 to 3.16)[†]	<0.0001	11.2 (3.6 to 18.9)
high viral load[d] (n=473)	2.90 (1.66 to 5.07)[†]	0.0001	20.9 (11.4 to 30.3)
low viral load[c] (n=267)	1.71 (1.05 to 2.80)[‡]	0.034	13.2 (1.2 to 25.1)
Genotype 2 or 3 (n=492)	0.89 (0.56 to 1.42)[‡]	>0.2	-2.7 (-9.6 to 4.2)
Standard vs low RBV dose (24-SD and 48-SD vs 24-LD and 48-LD)			
Genotype 1 (n=740)	1.55 (1.14 to 2.10)[§]	0.005	11.9 (4.7 to 18.9)
high viral load[d] (n=473)	1.56 (1.06 to 2.29)[¶]	0.025	10.4 (1.7 to 19.1)
low viral load[c] (n=267)	1.53 (0.93 to 2.52)[¶]	0.101	10.4 (-1.8 to 22.4)
Genotype 2 or 3 (n=492)	1.00 (0.63 to 1.61)[§]	>0.2	-0.7 (-7.8 to 6.3)

Incidence of adverse events, n (%)	**24-LD (n=207)**	**24-SD (n=280)**	**48-LD (n=361)**	**48-SD (n=436)**
Severe adverse events	46 (22)	63 (23)	116 (32)	141 (32)
Serious adverse events	7 (3)	19 (7)	33 (9)	44 (10)
Treatment-related serious adverse events[f]	3 (1)	8 (3)	15 (4)	14 (3)
Deaths				
Premature withdrawal	0	1 (<1)	1 (<1)	2 (<1)
for adverse events/lab abnormalities				
for insufficient responses[g]	10 (5)	13 (5)	59 (16)	67 (15)
for any reason				
Reduction or omission of ≥1 doses for	0 (<1)	0 (<1)	31 (9)	24 (6)
adverse events/lab abnormalities	14 (7)	22 (8)	117 (32)	117 (27)
Peg IFN α-2a				
RBV				
	63 (30)	73 (26)	120 (33)	159 (36)
Specific adverse events[h]	39 (19)	76 (27)	101 (28)	166 (38)
headache				
fatigue				
myalgia	102 (49)	136 (49)	187 (52)	239 (55)
pyrexia	98 (47)	135 (48)	182 (50)	211 (48)
insomnia	91 (44)	120 (43)	154 (43)	163 (37)
nausea	81 (39)	114 (41)	156 (43)	173 (40)
rigors	69 (33)	99 (35)	146 (40)	146 (33)
irritability	64 (31)	91 (33)	107 (30)	151 (35)
alopecia	64 (31)	87 (31)	87 (24)	119 (27)
arthralgia	59 (29)	76 (27)	96 (27)	112 (26)
pruritus	53 (26)	74 (26)	106 (29)	92 (21)
depression	50 (24)	70 (25)	106 (29)	105 (24)
diarrhoea	56 (27)	60 (21)	81 (22)	111 (25)
dermatitis	43 (21)	42 (15)	79 (22)	104 (24)
decreased appetite	44 (21)	46 (16)	65 (18)	96 (22)
	34 (16)	49 (18)	69 (19)	86 (20)
	30 (14)	41 (15)	66 (18)	91 (21)

[a]ALT level divided by the upper limit of normal for the local laboratory value; [b]reports numbers do not add up to 100% because of rounding, but total only adds up to 87%; *percentages given in bar chart, numbers calculated by reviewer; [c]low viral load, ≤2 x10^6 copies/mL; [d]high viral load, >2 x10^6 copies/mL; [†]adjusted for the effect of RBV dose, viral load and

study region; [‡]adjusted for the effect of RBV dose and study region; [§]adjusted for the effect of treatment duration, viral load and study region; [¶]adjusted for the effect of treatment duration and study region; [e]F3 - bridging fibrosis, F4 - cirrhosis, F0 or F1 - mild fibrosis; [f]as judged by investigator; [g]pts in gps 48-LD and 48-SD who did no achieve either undetectable HCV RNA or normalisation of ALT levels at wk 24 were considered non-responders and discontinued further treatment; [h]adverse events related to treatment, as judged by investigators, that occurred in ≥ 20% of pts who received ≥1 dose of study medication and had ≥1 post-baseline safety assessment.

Additional Results:

Virological response

- Pts treated for 48 wks were more likely to achieve an SVR than pts treated for 24 wks (48-LD or 48-SD vs 24-LD or 24-SD; odds ratio 1.53 (95% CI 1.17 to 2.01), *p*=0.002). Similarly, pts receiving a standard weight-based dose of RBV were more likely to achieve an SVR than pts receiving a low dose of RBV (24-SD or 48-SD vs 24-LD or 48-LD; odds ratio 1.41 (95% CI 1.10 to 1.81), *p*=0.01).
- Peg IFN α-2a and standard RBV for 48 wks produced an overall SVR rate of 63% (95% CI 59% to 68%).
- In multiple logistic regression analysis, HCV genotype was the predominant predictor of response (odds ratio for genotype non-1 vs genotype 1 5.4 (95% CI 4.1 to 7.1), *p*<0.001). In addition, the interaction between treatment duration and genotype was highly significant (odds ratio 0.42 (95% CI 0.24 to 0.75), *p*=0.003).
- The subgroup of pts with/without bridging fibrosis/cirrhosis is too small to draw definitive conclusions.
- 36 pts with genotype 4 were included in the study. At the end of follow-up, SVR rates were obtained in 0% (0/5), 67% (8/12), 63% (5/8) and 82% (9/11) of those randomly assigned to groups 24-LD, 24-SD, 48-LD and 48-SD respectively.

Safety

- Most adverse events were mild to moderate in severity and all were typical of those previously reported for IFN and RBV.

Methodological comments:

Allocation to treatment groups: randomisation was centralised, blocked and stratified by geographic region. Pts were randomised unequally to 1 of 4 treatment gps based on genotype and baseline viral load in order to reduce the number of pts with more difficult-to-treat characteristics (genotype 1 and high viral load) who would receive 24 wks of treatment. After 3 mths, it became apparent that the number of pts with genotype non-1 and low viral load could not be recruited within an acceptable time frame, and thus the randomisation procedure was revised. Pts with genotype 1 and low viral load were initially randomised to gps 24-LD, 24-SD, 48-LD and 48-SD in a 1:2:1:2 ratio, subsequently changed to 1:1:1:1; pts with genotype 1 and high viral load were initially randomised in a 1:1:3:3 ratio, subsequently changed to 1:1:5:5.

Allocation concealment: centralised computer generated randomisation list. Randomisation numbers were allocated sequentially in the order in which pts were enrolled.

Blinding of outcome assessors: study described as double-blind. Investigators and pts were blinded to RBV dose and treatment duration until wk 24. A matching placebo tablet identical to the RBV tablets and packaged in identical bottles was provided through a central distribution process to maintain blinding. All pts received the same number of tablets per day (RBV or placebo). Serum HCV RNA and HCV genotyping were determined in a central laboratory.

Analysis by intention to treat: does not specifically state that it was ITT analysis but all pts who received ≥1 dose of study medication were included in the efficacy analysis (n=1284). Pts without follow-up data were considered not to have achieved an SVR. Pts in gps 48-LD and 48-SD with detectable HCV RNA and elevated ALT levels at wk 24 were classified as non-responders and discontinued further treatment.

Comparability of treatment groups at pre-treatment: baseline demographics and disease characteristics were generally comparable across treatment gps, with the exception of genotype and viral load (the 48-wk gps had a greater proportion of genotype 1 pts and higher viral load). This reflects the unequal stratified randomisation procedure. The differences in baseline HCV RNA levels between strata were reported to be minimal and not clinically meaningful.

Method of data analysis: the results for end of treatment virological response, SVR by genotype and viral load and SVR by genotype and fibrosis stage were presented in bar charts, specifying the virological response rate numerically at the top of each bar with 95% CI shown as vertical bars. The Cochran-Mantel-Haenszel test, stratified by a combination of geographic region, HCV genotype (1 vs non-1), baseline viral load ($\leq 2 \times 10^6$ vs $>2 \times 10^6$ copies/mL) and RBV dose (800 and 1000-1200mg/d), was used to compare treatment duration. This test was also used to compare RBV dose, stratified by a combination of region, genotype, viral load and treatment duration. The Breslow-Day test assessed the homogeneity of the odds ratios over the strata formed by the combination of geographic region, genotype, baseline viral load and RBV dose. Because of the large number of strata (64 strata for the comparisons of treatment duration), the absence of heterogeneity across the strata (lack of treatment group by strata interaction could have resulted form insufficient statistical power. For this reason, an alternative test for homogeneity suggested by Breslow and Day was used. Several logistic regression models were conducted to further explore the effect of intervention variables (treatment duration and RBV dose) and several pre-treatment factors on the likelihood of achieving an SVR. The following covariates were considered: age, weight, pre-treatment ALT quotient, pre-treatment HCV RNA levels, gender, race, genotype and fibrosis stage. 9 interaction terms with

duration were tested in this model.
Power analysis: assumed that SVRs after 24 wks of treatment with Peg IFN α-2a + RBV, 1000 or 1200mg/d, would be 70% in pts with genotype non-1 regardless of viral titre, 40% in pts with genotype 1 and low viral titre, and 10% in pts with genotype 1 and high viral titre. An improvement of 10-12% in SVR was required to justify extending the treatment duration to 48 wks in these sub-groups. The study had 80% power to detect an improvement in SVR from 70- 80% in pts with genotype non-1, 40-52% in pts with genotype 1 and low viral load, and 10-30% in pts with genotype 1 and high viral load, between the 24- and 48-wk treatment groups.
Attrition/drop-out: 1311 pts were initially randomised, 1284 received ≥1 dose of study medication, 1014 completed their allocated treatment, 1022 completed 24 wks follow-up. The number discontinuing treatment (n=270) was reported, with reasons. Pts who withdrew from treatment after 12 wks or more and had –ve HCV RNA levels were encouraged to return for follow-up. For this reason, the number of pts who completed follow-up is higher than the number of pts who completed treatment in 2/4 gps (48-LD and 48-SD).

General comments
Generalisability: pts appear representative of pts with mild chronic HCV without other co-morbidities.
Conflict of interests: the study was supported by Roche, Basel, Switzerland. A large number of the authors had potential conflicts of interest in terms of employment, consultancies, honoraria, grants received or grants pending with Roche and/or Schering-Plough.
Definitions: 24-LD, 24 wks of therapy with a low dose of RBV; 24-SD, 24 wks of therapy with a standard weight-based dose of RBV; 48-LD, 48 wks of therapy with a low dose of RBV; 48-SD, 48 wks of therapy with a standard weight-based dose of RBV; severe psychiatric disease – treatment with an anti-depressant medication or major tranquiliser for major depression or psychosis respectively, for ≥3 mths at any time or a history of a suicide attempt, hospitalisation, or period of disability due to psychiatric disease; SVR, sustained virological response – undetectable serum HCV RNA level at the end of treatment and during the 12-24 week follow-up;

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 11 – Mangia and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Mangia *et al*, 2001 [63] **Trial design**: Multicentre RCT **Country**: Italy **Sponsor**: Not reported but ribavirin provided by Schering-Plough	**Intervention 1:** n = 96 IFN α-2b (s.c.) Dose: 5 MU 3 times per wk Duration: 12 months **Intervention 2:** n = 96 IFN α-2b (s.c.) Dose: 5 MU 3 times per wk Duration: 12 months RBV (oral) Dose: twice daily at a total dose of 1000mg for patients <75kg, 1200mg for patients >75kg Duration: 12 months	**Total numbers involved**: 192 randomised and analysed **Eligibility**: treatment naïve patients, raised ALT for at least 6 mths, HCV RNA positive, histopathological evidence of chronic hepatitis (liver biopsy taken with previous 6 mths of enrolment into study) **Recruitment**: 9 community hospitals in Italy, between April 1997 and June 1998 **Exclusion criteria**: patients with decompensated cirrhosis (i.e. ascites, bleeding varices, encephalopathy, serum albumin <35 g/l, platelet count <100,000 mm^3 and white cell count <3,500 mm^3), anaemia (haemoglobin conc <12 g/dl in women and <13 g/dl in men), psychiatric conditions, diabetes, autoimmune diseases, concurrent hepatitis B or HIV infection, high alcohol intake, current i.v. drug use, previous treatment with IFN, pregnancy or concomitant significant medical illness **Baseline measurements**: **Viral Load,** mean serum HCV RNA (±SD): No. equivalent genomes/ml ($x10^6$): 6.2 (±8.3) Gp 1; 6.8 (±12.2) Gp 2 >200,000 equivalent genomes/ml, no. (%): 58 (60%) Gp 1; 60 (63%) Gp 2 **Serum ALT:** not reported **Histology**: Classification system used: Scheuer Fibrosis stage, no. (%): 0, 1: 148 (77%) > 1: 44 (23%) Necro-inflammation, no. (%): 1, 2: 176 (92%) 3: 16 (8%) Timing of liver biopsy: within the previous 6 mths of enrolment into study **Genotypes, no. (%)**: 1b: 91 (47%) 2a: 66 (34%) 3: 26 (14%) Others: 9 (5%)	**Primary outcomes**: SVR **Secondary outcomes**: • normalisation of ALT values • adverse events **Length of follow up**: 6 months post-treatment

		Gender, no. (%): 128 m (67%), 64 f (33%) **Age (yrs), mean (±SD)**: 49 (±21) Gp 1; 46 (±24) Gp 2 **Ethnic groups, no. (%)**: not reported **Mode of infection, no. (%)**: Injecting drug use: 40 (21%) Transfusion: 11 (6%) Community acquired: 141 (73%) **Losses to follow up**: 0 **Compliance**: 174/192 (91%) completed therapy. 18 patients (9%) (10 treated with combination therapy and 8 with IFN alone) stopped treatment for non-compliance (n=6) or severe side-effects (n=12)		

Outcome No. with response (%, 95% CI)	**IFN α-2b (5 MU)**	**IFN α-2b (5 MU) + RBV (1000-1200mg)**	***p*-value**
Viral Response			
12 wk	42/96 (43.4%)	64/96 (66.7%)	0.001
End of treatment	33/96 (34.4%; 25-44)	57/96 (59.4%; 50-70)	0.0007
SVR at follow-up	20/96 (20.8%;13-29)	52/96 (54.2%; 44-64)	0.0001
Biochemical Response (ALT normalisation)			
End of treatment	38/96 (39.6%; 30-49)	66/96 (68.8%; 60-70)	0.0001
End of follow-up	22/96 (22.9%; 15-31)	55/96 (57.3%; 48-67)	0.0001

Outcome variable No. (%, 95% CI)	**IFN α-2b (5 MU)**	***p*-value[a]**	**IFN α-2b (5 MU) + RBV (1000-1200mg)**	***p*-value[a]**
SVR by genotype				
1, 4 or 5	7/55 (13%; 4-21)	0.005	17/45 (38%; 23-51)	0.002
2 or 3	15/41 (36%; 21-51)		35/51 (69%; 56-81)	
SVR by HCV RNA level				
Low[b]	10/38 (26%; 13-40)	0.52	18/37 (49%; 32-64)	0.39
High[b]	12/58 (21%; 10-31)		34/59 (58%; 45-70)	
SVR by age				
≤40 yrs	5/33 (15%; 20-27)	0.19	20/33 (61%; 44-77)	0.35
≥40 yrs	17/63 (27%; 16-37)		32/63 (51%; 38-63)	
SVR by gender				
female	8/37 (22%; 8-35)	0.54	14/27 (52%; 33-71)	0.77
male	14/59 (24%; 13-34)		38/69 (55%; 43-66)	
SVR by fibrosis staging				
0 or 1	15/77 (19%; 10-28)	0.10	45/71 (63%; 52-74)	0.004
> 1	7/19 (37%; 15-58)		7/25 (28%; 10-45)	
SVR by necro-inflammation grading		0.52		0.14
1 or 2	48/90 (53%; 43-63)		17/86 (20%; 11-28)	
3	4/6 (67%; 28-104)		4/10 (40%; 19-80)	
SVR by combination of virologic factors Genotype				

2,3 + low viremia[b] 2,3 + high viremia[b] Genotype 1,4,5 + low viremia[b] 1,4,5 + high viremia[b]	4/15 (27%; 4-49) 11/27 (41%; 22-59) 4/24 (17%; 17-31) 2/30 (7%; 0-9)	0.36 0.22	12/17 (71%; 48-92) 25/34 (74%; 59-88) 7/22 (32%; 12-51) 8/23 (35%; 15-54)	0.82 0.83
Outcome	**IFN α-2b (5 MU)**	**IFN α-2b (5 MU) + RBV (1000-1200mg)**	***p*-value**	
Histology (proportion with improvement)	not measured	not measured		
Adverse Events Mild neuropsychiatric effects IFN dose discontinuation for any adverse event anaemia	13/96 (13.5%) 8 0	4/96 (4.2%) 10 0		

[a]Favourable vs unfavourable baseline features in each treatment group; [b]low viremia: ≤200,000 equivalent genomes/ml, high viremia: ≥ 200,000 equivalent genomes/ml

Additional Results:

- *Virologic and biochemical response*:
  - The virologic relapse rate after monotherapy and combination therapy occurred in 13/33 (39.4%; 95% CI 23-56) and 5/57 (9%; 95% CI 1-16) of end-of-therapy responders respectively (p=0.0007).
  - The combined rate of sustained biochemical and virologic response was 22.7% (95% CI 14-31) and 60.5% (95% CI 50-71) with IFN monotherapy and combination therapy respectively (p<0.0001).
  - At the end of follow-up, normalisation of ALT values was associated with undetectable levels of serum HCV RNA in 98.6% of patients who had an SVR: apart from a single patient in the combination therapy gp, 71 patients who had an SVR had persistently normal serum ALT concentrations. Serum HCV RNA levels remained detectable after treatment, despite persistently normal ALT concentration, in 5/77 (6.5%) patients, two cases in monotherapy and three in combination therapy.
- *Combination of baseline characteristics with response*:
  - Patients treated with combination therapy were more likely to have a sustained virologic response regardless of their baseline characteristics. Patients with baseline features known to negatively influence the response to IFN monotherapy, such as genotype 1, high viremia levels, male gender, liver fibrosis, and age >40 yrs, when treated with combination therapy had a significantly higher chance of responding than those receiving IFN monotherapy (p<0.005 for each single feature).
  - Using univariate analysis, genotype appeared to influence the rate of sustained response in each of the two treatment gps (p=0.005), whereas baseline viremia, age, gender, presumed source or duration of infection and grading did not (p>0.05). The histological staging affected the response in the combination therapy gp (p=0.004).
  - Logistic regression analysis indicated that treatment with IFN+RBV was the strongest predictor of response (X^2=21.3: p=0.0001). In addition to treatment regimen, only genotype had an independent effect on a sustained response (X^2=19.8; p=0.0001).
- *Predictive values of response:*
  - Examination of the month 3 HCV RNA status in patients with a sustained response showed that the positive predictive value (PPV, the probability that HCV RNA would still be +ve at month 6 of follow-up if the HCV RNA was +ve at treatment month 3) was 82% (95% CI 67-98) for combination therapy patients and 98% (95% CI 94-100) for monotherapy patients.
  - Viral persistence at mth 3 of therapy was a better predictor of non-response to monotherapy (1/50 experienced a late viral clearance) than to combination therapy (4/23 experienced a late viral clearance).
  - In IFN monotherapy, normal ALT levels during therapy were unhelpful in predicting a response (NPV <40%), whereas increased ALT concentrations were highly predictive of non-response (PPV = 97% at treatment mth 3). In combination therapy patients, ALT levels at treatment mth 3 were of better prediction than corresponding values at treatment mth 1: normal ALT levels at treatment mth 3 predicted a response in 50/69 patients (NPV = 72%), whereas abnormal ALT levels were predictive of a non-response in 15/17 patients (PPV = 88%). Evaluating these levels at treatment mth 6 increased these rates in combination therapy patients.
- *Safety*:
  - A RBV dose reduction to 600-800mg was necessary in 12/96 (12.5%) of combination therapy patients when

haemoglobin concentrations decreased to 10 g/dl. This did not affect long-term response.
- Flu-like symptoms occurred early in the majority of patients at an equal rate in the two treatments.
- 44/192 (23%) patients had to switch from recombinant IFN α-2b to natural leukocyte IFN due to hard to tolerate side effects: 26 could continue the trial with the new IFN, whereas 18 (10 combination, 8 monotherapy) discontinued therapy by mth 6 due to no compliance (n=6), major psychiatric symptoms (n=5), infections (n=4), malaise (n=3). Response rates were not influenced by the change in IFN.

Methodological comments:
- *Allocation to treatment groups:* no details reported on randomisation method. Patients were randomised 1:1.
- *Allocation concealment*: not reported.
- *Blinding of outcome assessors*: Testing for HCV RNA was carried out in a single lab for all patients. No further details. A single liver pathologist who was unaware of the patient's treatment and response to therapy scored the pre-therapy liver biopsies for hepatic inflammation and fibrosis.
- *Analysis by intention to treat:* reports that data were assessed using ITT analysis. Results were reported for all 192 randomised patients.
- *Comparability of treatment groups at pre-treatment:* groups appear comparable at baseline for demographics, duration and source of HCV infection, and liver histology. There were some differences in the distribution of genotypes: there were less (42% vs 53%) genotype 1b patients, and twice the number of genotype 3 patients (18% vs 9%), in the combination therapy gp compared with monotherapy, although the authors report that the distribution of HCV genotypes was similar in the two groups. No *p* values were presented.
- *Method of data analysis:* Baseline demographics and clinical features of the disease were compared with the X^2 test for discrete variables, and Wilcoxon's rank-sum test for continuous variables. Pre-therapy features were evaluated by logistic regression analysis without variable selection in order to determine their relatedness with sustained response. All statistical tests were two-tailed.
- *Power analysis:* A sample size of 164 patients was estimated on an α type of error of 0.05, and a β error of 0.10 for a primary two-sided test, on the assumption of 40% response in the combination group and 22% response in the monotherapy group. Expecting a drop-out rate of 10%, 192 patients were included and treated.
- *Attrition/drop-out:* Of 192 patients, 174 completed therapy: 18 patients stopped treatment for non-compliance or severe side effects. No patient was lost to follow-up.

General comments
Generalisability: patients would appear to be representative of patients with mild chronic HCV without other co-morbidities.
Conflict of interests: The Schering-Plough Co. of Italy provided a generous supply of ribavirin.
Definitions: SVR: sustained virologic response defined as the disappearance of HCV RNA at 6 mths post- therapy cessation; ALT: aminotransferase; PPV: patients with positive serum HCV RNA or elevated ALT who do not achieve a response (prediction of non-response); NPV: patients with negative serum HCV RNA or normal ALT who achieve response (prediction of response)

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	N/a as open label trial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 12 – Reichard and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Reichard *et al*, 1998[70] **Trial design**: Multicentre, double-blind RCT **Country**: Sweden **Sponsor**: Schering-Plough	**Intervention 1:** n = 50 IFN α-2b (s.c.) Dose: 3 MU 3 times per week Duration: 24 weeks RBV (oral) Dose: twice daily at a total dose of 1000mg for patients ≤75kg, 1200mg for patients >75kg Duration: 24 weeks **Intervention 2:** n = 50 IFN α-2b (s.c.) Dose: 3 MU 3 times per week Duration: 24 weeks Placebo Dose: twice daily Duration: 24 weeks	**Total numbers involved**: 100 randomised and analysed **Eligibility**: persistently raised aminotransferases for at least 6 mths, serum antibodies to HCV, detectable HCV RNA, biopsy findings (taken in preceding 12 mths) consistent with a diagnosis of chronic hepatitis **Recruitment**: 5 university hospitals in Sweden between March 1995 and June 1995 **Exclusion criteria**: age <18yrs or >70yrs, previous treatment with IFN α-2b or RBV, history of alcohol abuse or haemolytic disease, decompensated cirrhosis, autoimmune hepatitis, chronic hepatitis-B infection, HIV infection, current i.v. drug use, drug-related liver disease, pregnancy **Baseline measurements**: **Viral Load,** geometric mean HCV RNA x10^6 (±SD), Eq/mL: 4.06 Gp 1, 3.20 Gp 2 **Alanine aminotransferase,** mean (±SD), IU/L: 156 (±114) Gp 1, 138 (±90) Gp 2 **Histology**: Classification system used: Batts & Ludwig/ Sciot & Desmet Fibrosis score, mean (±SD): 1.6 (±0.7) Gp 1, 1.4 (±0.7) Gp 2 Cirrhosis: 13 (13%) Necroinflammatory score, mean (±SD): 1.4 (±0.5) Gp 1, 1.3 (±0.5) Gp 2 Timing of liver biopsy: obtained in the preceding 12 mths and at wk 24 **Genotypes, no. (%)**: 1a: 17 (17%) 1b: 19 (19%) 1 (not sub-typed): 3 (3%) 1a+b: 5 (5%) 2a: 1 (1%) 2b: 17 (17%) 2a+b: 1 (1%) 3a: 33 (33%) 4 (not sub-typed): 2 (2%) 4c+d: 1 (1%) 5a: 1 (1%)	**Primary outcomes**: SVR **Secondary outcomes**: • biochemical response • histological response • adverse effects **Length of follow up**: 24 weeks after completion of therapy

		Gender, no. (%): 62 (62%) m, 38 (38%) f **Age (yrs), mean (±SD):** 39.6 (±9.6) Gp 1, 39.4 (±7.5) Gp 2 **Ethnic groups, no. (%)**: not reported **Mode of infection, no. (%)**: Injection drug use: 51 (51%) Transfusion: 16 (16%) Unknown: 33 (33%) **Losses to follow up**: 90/100 pts (90%) completed 24wks treatment. 3 pts (3%) were lost to follow-up. Liver biopsies were available from 99 pts before treatment, and from 90 pts at the end of treatment. **Compliance**: 1 pt (1%) discontinued treatment due to i.v. drug use. 7 pts refused a second biopsy.		
Outcome % with response (n)		**IFN α-2b (3MU) + RBV (1000-1200mg)**	**IFN α-2b (3MU) + placebo**	***p*-value (between group comparison)**
Viral Response End of treatment SVR at follow-up		 52% (26/50) 36% (18/50)	 52% (26/50) 18% (9/50)	 1.00 0.047
SVR by genotype 1a 1b 1 not sub-typed/1a+b 2 3a		 36% (4/11) 13% (1/8) 0/3 43% (3/7) 53% (10/19)	 17% (1/6) 9% (1/11) 0/5 25% (3/12) 21% (3/14)	 0.60 1.00 0.62 0.09
SVR by baseline viral load (Eq/mL)[a] <1 x10^6 1-2.99 x10^6 3-7.99 x10^6 8-19.99 x10^6 ≥20 x10^6		 45% (5/11) 10% (1/10) 10% (1/10) 62% (8/13) 50% (3/6)	 45% (5/11) 23% (3/13) 0/13 13% (1/8) 0/5	 1.00 0.60 1.00 0.07 0.18
Biochemical Response End of treatment End of follow-up		 66% (33/50) 44% (22/50)	 56% (28/50) 24% (12/50)	 0.41 0.057
Histology, mean (±SD) Inflammation (grade score) before treatment end of treatment Fibrosis (stage score)		 1.4 (±0.5) 0.9 (±0.5) no change	 1.3 (±0.5) 0.8 (±0.7) no change	 <0.001
Adverse Events, % (no. of pts) dose discontinuation for any adverse event other[b] dose reduction for any adverse event		 8% (4/50) 6% (3/50) 14% (7/50)	 6% (3/50) 0	

anaemia	2% (1/50)	0	
neutropenia	2% (1/50)	6% (3/50)	
dose reduction or discontinuation	32% (16/50)	12% (6/50)	0.03
Specific adverse events, % (no. of pts)			
fatigue	90% (45/50)	78% (39/50)	0.11
nausea	34% (17/50)	12% (6/50)	0.02

[a]bDNA assay; [b]lost to follow-up.

Additional Results:

Virological and biochemical response

- Neither eradication of viraemia, nor geometric mean HCV RNA concs differed significantly between the groups during the treatment period, but did differ sig by wk 48 ($p<0.05$).
- 4 pts with biochemical sustained responses were classified as virological non-responders although HCV RNA was -ve at follow-up. 2 pts in the IFN + RBV group were HCV RNA -ve at wk 12, +ve in very low concs at wk 24, and –ve at wk 48; 2 pts (1 in each group), who had declining +ve HCV RNA concs at wk 12 and wk 24 became HCV RNA –ve at wk 48. One year after treatment stopped, all 4 pts had no detectable HCV RNA and normal serum aminotransaminase concs, which suggests that they had a virological sustained response. If these pts are included, the SVR rate in the IFN + RBV group is 42% (21/50) vs 20% (10/50) in the IFN + placebo group ($p=0.03$).
- In the IFN + RBV group, baseline HCV RNA concs were sig lower in the SVR group than in those who did not achieve an SVR (geometric mean 0.95 $x10^6$ vs 4.17 $x10^6$ Eq/mL, $p=0.008$); whereas HCV genotype, liver histology score, sex and age did not affect the SVR rate.
- In the IFN + placebo group, no baseline factor predicted an SVR.
- The SVR was sig greater in pts with a baseline viral load >3 $x10^6$ Eq/mL who received IFN + RBV compared to those who received IFN + placebo, 41% (12/29) vs 4% (1/26), $p=0.009$.

Histological response

- No difference in histological improvement between the groups was found.
- The greatest reduction in mean grade score was seen in the pts with a sustained response but was also sig in pts with non-sustained or no response to treatment.

Safety

- Other side effects were experienced by pts, but did not differ between treatment groups and the data is not shown. They include: headache, myalgia, arthralgia, fever, vertigo, abdominal pain, anorexia, depression, irritability, insomnia, alopecia, pruritus, coughing, hypothyroidism and hyperthyroidism.

Methodological comments:

Allocation to treatment groups: randomly generated numbers were placed in individually sealed envelopes that were distributed by a central pharmacy to the individual centres in blocks of ten (5 RBV and 5 placebo). Does not report how the numbers were randomly generated.

Allocation concealment: central randomisation procedure. The randomisation code was not broken until all pts had completed the follow-up period.

Blinding of outcome assessors: study described as double-blind. Pts received RBV or a matched placebo. Liver biopsies were scored by a single blinded pathologist. No details are reported re the outcome assessors for the virological assays.

Analysis by intention to treat: reports that data were analysed by ITT. Results were reported for all 100 randomised pts. Pts who discontinued treatment or were lost to follow-up were classified as non-responders.

Comparability of treatment groups at pre-treatment: groups were not significantly different at baseline for demographic, biochemical and histological characteristics (*p*-values presented).

Method of data analysis: baseline characteristics were compared by Student's *t*-test. Quantitative variables were tested by the Mann-Whitney *U* test, the paired *t*-test and the two-sample Wilcoxon signed-rank test where appropriate. Fisher's exact two-tail test was used to compare categorical variables.

Power analysis: with a power of 80% at the 5% significance level, a sample size of 100 pts was needed to show a difference between treatment groups and to allow for a 20% drop-out rate.

Attrition/drop-out: 90 pts (90%) completed 24 wks treatment. 7 pts (7%) discontinued treatment (reasons given) and 3 pts (3%) were lost to follow-up. Biopsy samples were available for 99 pts pre-treatment and 90 pts at the end of treatment. 7 pts refused a second biopsy; 1 pre-treatment and 3 post-treatment biopsy samples were too small to allow a valid evaluation.

General comments

Generalisability: pts seem representative of pts with mild chronic HCV without other co-morbidities.

Conflict of interests: the study was supported by grants from Schering Plough AB, Sweden and Schering Plough International

Definitions: SVR, sustained virological response – the absence of HCV RNA on PCR at both wk 24 and wk 48; biochemical response – serum aminotransferase concentrations within the normal range;

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Partial
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 13 – Verbaan and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Verbaan et al. 2002 201 **Trial design**: RCT **Country**: Sweden **Sponsor:** Schering-Plough AB, Sweden	**Intervention 1:** n = 57 IFN α-2b Dose: 3 million units three times per week s.c. Duration: 52 weeks Ribavirin (oral) Dose: 1000mg per day for patients ≤75kg, 1200mg per day for patients >75kg Duration: 52 weeks **Intervention 2:** n = 59 IFN α -2b Dose: 3 million units three times per week s.c. Duration: 52 weeks Placebo Dose: twice daily Duration: 52 weeks	**Total numbers involved**: 128 randomised. 116 started treatment and analysed. **Eligibility**: • Previously untreated adults aged 18-60 years, with histologically mild chronic HCV infection. • HCV RNA positive in serum or plasma, liver biopsy within the previous 12 months showing a mild histological picture, and raised ALT for at least 6 months. • Knodell activity score between ≥1 and ≤6 with periportal piecemeal necrosis ± bridging necrosis ≤3; interlobular degeneration and focal necrosis ≤3 and portal inflammation ≤4. • Only patients with a fibrosis stage of ≤1 could be included. **Recruitment**: 15 centres for gastroenterology or infectious diseases in Sweden. Between February 1997 and July 1998. **Exclusion criteria**: • Persistently normal ALT. • Clinical or serological evidence of: - active hepatitis B infection or HIV infection, - metabolic or autoimmune liver diseases, - immunologically mediated diseases, - chronic pulmonary disease, - heart disease, - serious mental disease or a seizure disorder, - inadequate levels of haemoglobin (<115 g/l for females, <130 g/l for males), - platelet count <100 x 10^9 /l, - white blood count <3 x 10^9 /l - granulocyte count <1.5 x 10^9 /l, - pregnancy or breast feeding, - malignancy. • History of intravenous drug abuse within the previous 12 months or ongoing alcohol abuse (>50 g of alcohol per day) **Baseline measurements**: **Viral Load**: Geometric HCV RNA bDNA version 3, copies/ml: Gp 1: 2.34 x 10^6 Gp 2: 9.16 x 10^5 **Histology**: Knodell score Mean grade (range) Gp 1: 4.3 (1-6); Gp 2: 3.9 (1-6)	**Primary outcomes**: • HCV RNA negativity by PCR in both serum and in liver tissue 26 weeks post-treatment. **Secondary outcomes**: • Haematological and biochemical parameters • Clinical signs and side effects • Liver histology **Length of follow up**: 26 weeks after treatment was discontinued

		Mean stage Gp 1: 0.4; Gp 2: 0.3 Timing of liver biopsy: not reported **Genotypes (proportions)**: 1a: Gp 1 35%, Gp 2 35% 1b: Gp1 12%, Gp 2 16% 2b: Gp 1 17%, Gp 2 14% 3A: Gp 1 30%, Gp 2 33% 4: Gp 1 2% 1b+3a: Gp 1 2% Unknown: 2% **Gender (% male)**: Gp 1 64%, Gp 2 58% **Age (mean & range)**: Gp 1 38 years (20-55), Gp 2 36 years (23-49) **Ethnic groups**: not reported **Mode of infection (%):** Intravenous drug use: Gp 1 65%, Gp 2 56% Transfusion: Gp 1 7%, Gp 2 10% Other: Gp 1 5%, Gp 2 9% Unknown: Gp 1 23%, Gp 2 25%. **Losses to follow up**: Seven patients dropped out before starting treatment. 5 were excluded because of incorrect inclusion. Week 52: sera from 6 patients missing. Week 78: sera from 17 patients missing. HCV RNA in liver tissue analysed in 17 cases. Liver biopsy week 78 performed on 81 patients, 13 lost to follow-up. **Compliance**: not reported	

Outcome	**Intervention 1**	**Intervention 2**	**Significance**
Number HCV RNA negative end of treatment (week 52) (n=94)*	28	19	
Number with a viral breakthrough	4 (weeks 27-52)	9	
SVR in plasma at follow-up (week 78) (n=99)**	54.4% (31/57)	20.3% (12/59)	P<0.001
Relapse during follow-up	3	5	
SVR by genotype at follow-up			
1	8 (28%)	1 (4%)	P=0.014
Non-1	22 (81%)	10 (36%)	P=0.003
Not included	1	1	
Viral load at baseline			
Sustained responders:			
Genotype 1	1.9×10^5	3.3×10^5	
Genotype non-1	6.4×10^5	5.3×10^5	

All	4.6 x 10^5	5.9 x 10^5	
Non- responders:			
Genotype 1	2.5 x 10^6	2.9 x 10^6	
Genotype non-1	8.2 x 10^5	4.1 x 10^6	
All	2.0 x 10^6	2.4 x 10^6	
*Authors report that at 52 weeks, 94 patients were tested for HCV RNA (groups not specified). ** At follow-up HCV RNA was tested in 99 patients while sera from 17 patients were missing, all being classified as HCV RNA positive.			
Histology (n=81), mean grade			
Sustained responders	(n=30)	(n=9)	
At entry	4.3	4.1	
At follow-up	1.3	1.3	
P value (entry vs follow-up)	p<0.00	P=0.018	
Non-responders	(n=15)	(n=27)	
At entry	3.4	4.4	
At follow-up	3.5	4.9	
P value (entry vs follow-up)	P=ns	P=ns	
Adverse Events			
dose discontinuation for:			
Serious adverse events	3 (1 related to study treatment – visual defect in right eye due to hypertension)	0	
Depression	1	0	
Headache	0	1	
Myalgia	0	1	
Cough	1	0	
Fatigue	1	1	
dose reduction for			
anaemia	4	0	
psychiatric side-effects	3	1	
neutrophil count <1.5 x 10^9/l	1	0	
diarrhoea	1	0	
myalgia	1	0	
fatigue	1	0	
hypothyroidism	1	0	
dizziness	1	0	
vomiting	1	0	
alopecia	0	1	
Discontinuation of treatment: HCV RNA positive at week 26 (in accordance with protocol)	18	24	
Other reasons for discontinuation of treatment:			
Non-compliance with protocol (iv drug or alcohol abuse)	1	2	
By patient without specific reason	1	4	
Myoma op	0	1	

Additional Results

- Liver tissue analysed in 74 cases. All but one with SVR were HCV RNA negative in both plasma and liver tissue. All patients with detectable HCV RNA in plasma were also HCV RNA positive in liver tissue.
- All except 12 patients reported at least one adverse event, the majority being classified as mild to moderate even where patients discontinued treatment. A flu-life syndrome with fever, fatigue, headache and myalgia was the most common, followed by alopecia, anorexia and depression, which did not differ between treatment groups.
- Histology: The low fibrosis stage did not change in either group, irrespective of treatment results (data not shown).

Methodological comments:

- *Allocation to treatment groups:* Patients were randomly assigned to one of two treatment arms in blocks of two, according to a computed generated list.
- *Allocation concealment*: Computer generated list set up by a central pharmacy.
- *Blinding of outcome assessors*: Study described as double blind. Liver histology was assessed by the same pathologist who was unaware of the patients' assignment or treatment response. No further details.
- *Analysis by intention to treat:* yes, for patients who started treatment (n=116) (but not all those randomised (n=128).
- *Comparability of treatment groups at pre-treatment:* No difference in sex, age, HCV genotypes, geometric mean HCV RNA level or histological grade and stage.
- *Method of data analysis:* Chi-squared or Fisher's exact test was used to determine the two-tailed statistical significance of differences between proportions in 2 x 2 tables. Student's t test used for normally distributed continuous variables and Mann-Whitney U test used when skewed. P value less than 0.05 taken to be indicative of statistical significance.
- *Power analysis:* Sample size was calculated assuming a complete, sustained response to IFN monotherapy of 25%, compared with a 50% response for combination therapy with IFN/ribavirin. With a power of 80% at the 5% significance level a sample size of 65 patients in each group would be required to allow for a 25% dropout rate.
- *Attrition/drop-out:* Study protocol stated that treatment was to be stopped if serum HCV RNA was still detectable after 6 months of therapy, however all patients were to be monitored for the planned follow-up.
- 6 months post-treatment, 13 patients lost to follow-up: 6 discontinued treatment before week 26 and the remaining refused a second liver biopsy.

General comments

Generalisability: Patients with mild HCV infection without comorbidities or clinical signs of liver disease.
Conflict of interests: Grants were received from Schering-Plough AB, Sweden.
Definitions:

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 14 – Wright and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Wright *et al*, 2005 [65] **Trial design**: Multicentre, unblinded, RCT **Country**: UK **Sponsor:** HTA Programme	**Intervention 1:** n = 98 IFN α-2b (s.c.) Dose: 3 MU 3 times per week Duration: 48 weeks RBV (oral) Dose: 1000mg daily for patients <75kg, 1200mg daily for patients >75kg Duration: 48 weeks Both drugs were commenced at the same time **Intervention 2:** n = 98 no treatment	**Total numbers involved**: 286 screened, 204 randomised, 196 analysed (attended baseline visit) **Eligibility**: treatment naïve, adult patients with mild chronic hepatitis C (Ishak necroinflammatory score ≤3, fibrosis score ≤2), serum positive for HCV, normal or raised ALT **Recruitment**: 13 centres in the UK, between Jan 1999 and Jan 2002 **Exclusion criteria**: liver disease of other aetiology, HIV coinfection, ongoing psychiatric morbidity, i.v. drug use, excessive alcohol intake (>28 units for men, >21 units for women), cardiovascular disease, uncontrolled diabetes mellitus, haemophilia, organ transplant, autoimmune disease, unwillingness to practice contraception **Baseline measurements**: **Viral Load, IU/mL***: <4×10^5: 56/98 (57%) treated patients >4×10^5: 42/98 (43%) treated patients Not reported for control patients **ALT**: Normal: 35/91 (38%) treated patients Raised: 56/91 (62%) treated patients Not reported for control patients **Histology**: Classification system used: Ishak Fibrosis score, mean (±SD): 1.01 (±0.77) treated patients 1.18 (±0.79) control patients Necroinflammatory score, mean (±SD): 1.96 (±1.06) treated patients 2.2 (±0.99) control patients Timing of liver biopsy: within 1 year prior to screening visit **Genotypes (proportions)**: 1: 101 (52%) non-1: 95 (48%) **Gender**: 119 m (61%), 77 f (39%)	**Primary outcomes**: SVR (HCV RNA) **Secondary outcomes**: • adverse events • quality of life **Length of follow up**: 24 weeks post-intervention

		Age, mean (±SD): 40.68 (±8.82) treated patients 40.71 (±8.29) control patients **Ethnic groups**: White: 177 (90%) Non-white: 14 (7%) Not recorded: 5 (3%) **Mode of infection**: Injection drug use: 104 (53%) Blood products: 31 (16%) Unknown: 61 (31%) **Losses to follow up**: EOT data available for 97/98 treated patients and 87/98 control patients; 24 wk follow-up period completed for 91/98 treated patients and 87/98 control patients (N.B. on ITT analysis). **Compliance**: The length of time on therapy was variable and not all patients were able to complete the full treatment protocol.		

Outcome	**IFN α-2b (3 MU) + RBV (1000-1200mg)**	**No treatment**	***p*-value (subgroups of treatment arm)**
Viral Response			
4 weeks	-	-	-
12 weeks	-	-	-
End of treatment	44% (43/98)	0	-
SVR at follow-up	33% (32/98)	0/98	≤0.00001
SVR by genotype			
1	18% (9/51)	0/50	0.02
non-1	49% (23/47)	0/48	
SVR by gender			
male	39% (23/59)	0/56	0.47
female	28% (9/32)	0/42	
SVR by age			
>40 yrs	32% (14/44)	0/47	0.65
<40 yrs	38% (18/47)	0/51	
SVR by ALT			
normal	34% (12/35)	0/42	0.92
raised	36% (20/56)	0/56	
SVR by viral load*			
<4 x 10^5	34% (19/56)	ND	0.82
>4 x 10^5	31% (13/42)		
Histology (proportion with improvement)	not measured	not measured	
Adverse Events†			
flu-like symptoms	41	9	
depression/low mood	48	14	
sensitive skin	51	16	
blood abnormality	31	0	

insomnia	20	21	
total events	770	257	
dose discontinuation for any adverse event	10	0	
dose reduction for any adverse event	46	0	
hospitalisations	4	0	

*1 IU is equivalent to approximately five RNA copies; †5 most common adverse events listed

Additional Results:

- Logistic regression analysis of all treated patients showed that only viral genotype was an independent predictor for SVR (p=0.002).
- Quantitative virology was performed on 75 patients (51 treated, 17 control patients) (those who attended 5/6 initial early visits and for whom there was a follow-up sample at 24 wks post-therapy). Patients had a 57% PPV of achieving an SVR if there was a 2-log viral load drop at 12 weeks (n=54); no patient who failed to achieve a 2-log drop (n=21) went on to SVR.
- Quality of life (SF-36): data were available for 24/32 (75%) of the SVRs, 44/68 (65%) of the non-SVRs, and 58/98 (56%) of the control group. Data were unavailable for those patients who had failed to attend their post week 24 visits, and for those who had not filled in the questionnaires correctly. At 24 wks after EOT, there was a mean improvement in 7/8 of the SF-36 scales in SVRs (significant for bodily pain, general health and vitality, p=0.01 c.f. controls), in 5/8 scales in non-SVRs, and in 0/8 scales in control group, where substantial reductions were seen.
  - 67% (16/24) of SVRs, 61% (27/44) of non-SVRs and 41% (24/58) of controls reported an improvement in the physical component summary score (PCS) (p<0.05 for SVRs and non-SVRs c.f controls).
  - There was an overall deterioration in the role function emotional scale in the SVRs, which was significantly different to the improvement seen in the non-SVRs (p<0.05).
  - There were no statistical differences in the mental component summary score (MCS).
  - There were significant inverse correlations between baseline PCS and the change in PCS in both the SVRs (R= -0.46, p=0.02) and non-SVRs (R= -0.45, p=0.002) but not the controls. This suggests that individuals with low well-being scores prior to treatment saw a sustained improvement 24 weeks after therapy, regardless of virological outcome. In contrast, patients with preserved baseline well-being scores experienced no long-term improvement.

Methodological comments:

- *Allocation to treatment groups:* randomisation was stratified within centres according to viral genotype (1 vs non- 1). No details reported on actual randomisation method.
- *Allocation concealment*: central randomisation procedure.
- *Blinding of outcome assessors*: qualitative and quantitative virological assays were performed centrally (blinding not specifically mentioned).
- *Analysis by intention to treat:* yes, for all patients who received at least one dose of study medication (n=98 in each arm). At the end of the trial, 13 treated patients and 24 control patients failed to attend their final visit – all were recorded as being PCR positive in line with the ITT principle.
- *Comparability of treatment groups at pre-treatment:* no statistically significant demographic, histological, haematological or biochemical differences at baseline (p-values presented).
- *Method of data analysis:* Treatment responses were compared using the chi-squared test. Relationships between pre-treatment variables and outcomes were assessed using step-wise logistic regression. Viral load was plotted as a log-scale against time for each individual patient. Sensitivity and specificity for presence or absence of a 2-log viral load drop and prediction of SVR were calculated and tabulated for each time point; the optimal time point was determined by receiver-operating characteristic (ROC) curves. SF-36 scales: ANOVA used for continuous parametric data, and Kruskall-Wallis test used when data was not normally distributed; pair-wise comparisons made using a Student's t-test or Mann-Whitney U-test as appropriate.
- *Power analysis:* to achieve a power of 80% to detect an SVR, expected to be 38%, with a precision of ±5% required 115 patients per group.
- *Attrition/drop-out:* 11/98 control patients declined to participate further after learning of their randomisation to no treatment. Patients who dropped out prior to the final follow-up visit were classified as having failed to respond; patients with no data were classified as 'no clearance'.

General comments

- *Generalisability:* patients would appear to be representative of those with mild chronic HCV without other co-morbidities.

- *Conflict of interests:* Ribavirin was provided as a gift by Schering Plough.
- *Other*: the paper states that '13 treated patients and 28 control patients failed to attend the final post-week 24 visit.' However, these numbers don't tally with the patient flow chart presented on p.60.
- *Definitions:* mild chronic hep C: Ishak necroinflammatory score ≤3, fibrosis score ≤2; SVR: sustained viral response defined as the absence of serum HCV RNA at 24 weeks post-treatment cessation; EOTR: end-of-treatment response; non-SVR patients: treatment failures, including non-responders and relapsed patients.; PPV: positive predictive value is the chance of achieving an SVR.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	N/a as trial was open-label
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 15 – Zeuzem and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Zeuzem *et al*, 2004 [66] **Trial design**: Open-label, multicentre, RCT **Country**: International **Sponsor**: Roche	**Intervention 1:** n = 212 PEG IFN α-2a, 40 kilodaltons (s.c.) Dose: 180µg once weekly Duration: 24 weeks RBV (oral) Dose: 400mg twice daily Duration: 24 weeks **Intervention 2:** n = 210 PEG IFN α-2a, 40 kilodaltons (s.c.) Dose: 180µg once weekly Duration: 48 weeks RBV (oral) Dose: 400mg twice daily Duration: 48 weeks **Intervention 3:** n = 69 no treatment Randomised in a 3:3:1 ratio	**Total numbers involved**: 514 randomised, 491 analysed **Eligibility**: treatment naïve patients, ≥18 yrs, positive antibody to HCV antibody test, detectable serum HCV RNA, biopsy findings consistent with a diagnosis of chronic hep C, persistently normal ALT levels **Recruitment**: 70 centres in Australia, Europe, New Zealand, N. America and S. America **Exclusion criteria**: no histologic evidence of liver disease, ≥1 elevated ALT values (i.e. > ULN) within previous 18 mths, patients with transition to cirrhosis or cirrhosis on biopsy, history of bleeding from oesophageal varices, other conditions consistent with decompensated liver disease, neutropenia (absolute neutrophil count <1500 cells/mm^3), thrombocytopaenia (<90,000 platelets/mm^3), anaemia (HB conc <12 g/dL in women and <13 g/dL in men), serologic evidence of infection with HIV or hepatitis A or B, serum creatinine level >1.5 times the ULN, organ transplant recipients, severe cardiac disease, history of severe psychiatric disease (esp. depression), evidence of drug abuse (incl excessive alcohol intake) within preceding year, other serious systemic disease. **Baseline measurements**: **Viral Load,** mean HCV RNA level x 10^3 IU/mL (±SD): 1222 (±1452) Gp 1 1055 (±1287) Gp 2 1303 (±1302) Gp 3 **ALT,** maximum mean value,* IU/L (±SD): 23.7 (±6.7) Gp 1 24.5 (±6.4) Gp 2 23.9 (±4.9) Gp 3 **Histology**: Classification system used: Ishak Fibrosis score, no. (%): 0-1: 338 (69%) 2: 98 (20%) 3-4: 49 (10%) >4: 1 (<1%) Missing values: 5 (<1%)	**Primary outcomes**: SVR (at the end of the 24 week untreated follow up for Gps 1 & 2) **Secondary outcomes**: adverse events **Length of follow up**: 72 weeks, representing 48 wks follow-up after 24 wks therapy (Gp 1), 24 wks follow-up after 48 wks therapy (Gp 2), or 72 wks of untreated follow-up (Gp 3)

		Mean fibrosis score (±SD): 1.2 (±1.02) Gp 1 1.2 (±1.0) Gp 2 1.0 (±0.85) Gp 3 Total mean fibrosis score = 1.4 Necroinflammation score, mean (±SD): 3.7 (±1.87) Gp 1 3.5 (±1.80) Gp 2 3.3 (±1.56) Gp 3 Timing of liver biopsy: obtained within 36 months before study onset **Genotypes, no (%)**: Type 1: 332 (68%) 1a: 191 (39%) 1b: 139 (28%) Other: 2 (<1%) Type non-1: 159 (32%) 2: 92 (19%) 3: 44 (9%) 4: 19 (4%) 5: 1 (<1%) 6: 3 (<1%) **Gender**: 198 m (40%), 293 f (60%) **Age (yrs), mean (±SD)**: 43.8 (±10.0) Gp 1 43.9 (±9.7) Gp 2 41.0 (±10.2) Gp 3 **Ethnic groups, no. (%)**: White: 420 (86%) Black: 40 (8%) Asian: 12 (2%) Other: 19 (4%) **Mode of infection, no. (%)**: Injecting drug use: 151 (31%) Transfusion: 114 (23%) Other: 67 (14%) Unknown: 159 (32%) **Losses to follow up**: In total, 370/514 (72%) patients initially randomised completed the study. **Compliance**: 19 patients were randomised but not treated; 78 patients withdrew prematurely.	

Outcome	**Group 1 (24 wks)**	**Group 2 (48 wks)**	**Risk difference (95% CI)**	**RR, 48wk vs 24wk (95% CI)**
Viral Response (%) End of treatment SVR at follow-up	- 63/212 (30%; 23.6-35.9)†	- 109/210 (52%; 45.1-58.7)†	- 22 (13-31)	- 1.7 (1.4-2.2), p<0.001
SVR as a function of genotype and baseline viral load‡ Genotype 1 (%)	19/144 (13%; 7.7-18.7)†	57/141 (40%; 32.3-48.5)†	27 (17-37)	3.1 (1.9-4.9), p<0.001

Low viral load	14/87 (16)	42/89 (47)		
High viral load	5/55 (9)	14/51 (27)		
Non-1 genotypes (%)	44/68 (65)	52/69 (75)		
Low viral load	25/36 (69)	30/38 (79)		
High viral load	19/32 (59)	22/31 (71)		
Genotypes 2 or 3 (%)	42/58 (72%; 60.9-83.9)[†]	46/59 (78%; 67.4-88.5)[†]	6 (-10 to 21)	1.1 (0.9-1.3), *p*=0.452
Low viral load	24/30 (80)	25/31 (81)		
High viral load	18/28 (64)	21/28 (75)		
Genotype 4 (%)	1/8 (13)	5/9 (56)		
Low viral load	1/6 (17)	4/6 (67)		
High viral load	0/2 (0)	1/3 (33)		

Outcome	**Group 1 (24 wks, n=212)**	**Group 2 (48 wks, n=210)**	**Group 3 (control, n=69)**
Histology (proportion with improvement)	Not measured	Not measured	Not measured
Adverse Events (%)			
Any adverse event	209 (99)	207 (99)	53 (77)
Severe adverse events	56 (26)	70 (33)	10 (14)
Life-threatening adverse events	3 (1)	8 (4)	2 (3)
Treatment-related adverse events	204 (96)	206 (98)	n/a
Serious adverse events	18 (8)	34 (16)	4 (6)
Treatment-related serious adverse events	6 (3)	20 (10)	n/a
Deaths	0	0	1
Premature withdrawal for adverse events or lab abnormalities	15 (7)	38 (18)	n/a
Dose modification for adverse events			
PEG IFN α-2a	23 (11)	40 (19)	n/a
RBV	42 (20)	62 (30)	n/a
Dose modification for lab abnormalities			
PEG IFN α-2a			
RBV	33 (16)	47 (22)	n/a
Specific adverse events[§]	19 (9)	45 (21)	n/a
headache			
fatigue	93 (44)	117 (56)	5 (7)
myalgia	109 (51)	107 (51)	12 (17)
pyrexia	81 (38)	93 (44)	5 (7)
insomnia	64 (30)	90 (43)	2 (3)
nausea	74 (35)	76 (36)	5 (7)
arthralgia	68 (32)	84 (40)	1 (1)
	68 (32)	62 (30)	3 (4)

[*]Maximum of the 3 measurements that qualified a patient for the trial. [†]Ranges are 95% CI. [‡]Low, ≤800,000 IU/mL; high, >800,000 IU/mL. Viral response - baseline measurements were missing for 3 patients with genotype 1. [§]Adverse events for which the incidence was >20% in at least one study group (7 most common listed).

Additional Results:

- No patient in the untreated control group (Group 3) cleared HCV.
- Prognostic factors for SVR:
  - In genotype 1 patients, treatment duration (24 vs 48wks: OR 4.39, 95% CI 2.42-7.98) and baseline viral load (>$8x10^5$ vs ≤$8x10^5$ IU/mL: OR 2.21, 95% CI 1.20-4.09) significantly and independently affected SVR rates.
  - In genotype 1 patients with a baseline HCV RNA concentration ≤$8x10^5$ IU/mL, the unadjusted probability of achieving an SVR was 77% higher than in patients with a viral load >$8x10^5$ IU/mL (unadjusted RR 1.77, 95%

CI 1.12-2.82).
    - For non-1 genotype patients, age was the only independent variable that was significantly associated with SVR rates (≤40yrs vs >40yrs: OR 2.31, 95% CI 1.02-5.24). Patients aged ≤40yrs had a 26% higher probability of achieving an SVR compared with patients >40yrs (RR 1.26, 95% CI 1.02-1.55).
- Adverse events were generally mild in severity, and no new adverse events were identified.
- Transient elevations in ALT activity were detected in treated and control patients during the study. The majority of moderate elevations coincided with virologic relapses in treated patients. Median ALT activity remained stable in untreated control patients but decreased up to 10 IU/L in treated patients and remained low in sustained responders.

Methodological comments:
- *Allocation to treatment groups:* randomisation was centralised and stratified by geographic region and HCV genotype (1 vs non-1). Patient identification numbers were allocated sequentially according to the order of enrolment. Patients were randomised in a 3:3:1 ratio (Gp 1: Gp 2: Gp 3) to maximise the number of patients receiving treatment.
- *Allocation concealment*: central randomisation procedure – prepared and managed by ICTI (Lambertville, NJ).*Blinding of outcome assessors*: HCV genotyping and HCV RNA qualitative and quantitative analyses were performed by the Nichols Institute (San Juan Capistrano, California) (blinding not specifically mentioned).
- *Analysis by intention to treat:* does not specifically state it is ITT analysis, but the analyses were carried out on all patients who received at least one dose of study medication and all untreated control patients with at least one post-baseline assessment. Patients without follow-up data were considered not to have achieved an SVR.
- *Comparability of treatment groups at pre-treatment:* baseline characteristics were similar across the 3 groups. Statistical values were not presented.
- *Method of data analysis:* Pair-wise comparisons among the 3 treatment gps were made using the Cochran-Mantel-Haenszel test stratified by geographic region and pre-treatment HCV genotype. For the analysis of prognostic factors for SVR rates in treated patients, the SVR rates were based on a single HCV RNA determination during follow-up. Logistic regression and analysis of co-variance were used to analyse categorical and continuous variables respectively.
- *Power analysis:* the study was designed to have 80% power to detect an increase in the SVR rate from 5% in the untreated control gp to 22-25% in either of the treated gps at a 2-sided significance level of 0.05. Numbers of patients required were not reported.
- *Attrition/drop-out:* 19 patients were randomised but not treated (reasons given); 78 patients withdrew prematurely from treatment (reasons given). One patient randomised to control gp was treated by mistake for 24wks, and so was included in Gp 1 for efficacy and safety analysis. In gp 1: 191/219 (87%) completed 24wks treatment, 190/219 (87%) completed 24wks follow-up, and 161/219 (74%) completed 48wks follow-up; in Gp 2: 181/221 (82%) completed 24wks treatment, 152/221 (69%) completed 48wks treatment, and 148/221 (67%) completed 24wks follow-up; in Gp 3: 69/74 (93%) completed 24wks of observation, 69/74 (93%) completed 48wks of observation, and 61/74 (82%) completed 72wks of observation.

General comments:
- *Generalisability:* patients would appear to be representative of patients with mild chronic HCV without other co-morbidities.
- *Conflict of interests:* Roche sponsored the study and was responsible for the collection and statistical analysis of the data.
- *Definitions:* Persistently normal serum ALT: ALT activity ≤ the upper limit of normal (ULN) documented on at least 3 occasions, a min of 4 wks apart, with at least one value obtained during the 42-day screening period and at least one value obtained 6-18 mths before screening; SVR: undetectable serum HCV RNA by qualitative PCR at the end of the 24-wk untreated follow-up period (in groups 1 & 2); RR: relative risk. OR: odds ratio.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	N/a as trial was open-label
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 16 – Lindsay and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Lindsay *et al*, 2001[73] **Trial design**: Multicentre, double-blind RCT **Country**: International **Sponsor**: Schering Plough Research Institute and University of Southern California	**Intervention 1:** n = 315 Peg IFN α2b (s.c.) Dose: 0.5 µg/kg once weekly Duration: 48 weeks **Intervention 2:** n = 297 Peg IFN α2b (s.c.) Dose: 1.0 µg/kg once weekly Duration: 48 weeks **Intervention 3:** n = 304 Peg IFN α2b (s.c.) Dose: 1.5 µg/kg once weekly Duration: 48 weeks **Intervention 4:** n = 303 IFN α2b (s.c.) Dose: 3 MIU 3 times per week Duration: 48 weeks	**Total numbers involved**: 1224 randomised, 1219 analysed **Eligibility**: adult CHC patients not previously treated with IFN, detectable serum HCV RNA, biopsy findings (in preceding 1yr) consistent with a diagnosis of chronic hepatitis, abnormal ALT values at entry and at least once during the 6 mths before screening, using effective contraception. In addition: haemoglobin ≥12 g/dL for females and ≥13 g/dL for males, WBC ≥4,000/mm^3, neutrophil count ≥1,800/ mm^3, platelets ≥130,000/ mm^3, alpha fetoprotein within normal limits or ≤50 ng/mL and ultrasound negative for evidence of hepatocellular carcinoma within 3 mths before screening. **Recruitment**: 53 centres in the USA, Europe and Australia, between Aug 1997 and Aug 1999 **Exclusion criteria**: any other cause for liver disease (hep B infection, haemochromatosis, alpha-1 anti-trypsin deficiency, Wilson disease, autoimmune hepatitis, alcohol-, drug- or obesity-induced liver disease), HIV infection, haemophilia, hemoglobinopathies, active substance abuse, any known pre-existing medical condition that could interfere with participation, pregnant or breastfeeding. **Baseline measurements**: **Viral Load,** serum HCV RNA: Geometric mean copies (x10^6/ml): 3.4 Gp 1, 3.3 Gp 2, 3.0 Gp 3, 3.7 Gp 4 >2 million copies/mL serum, no. (%): 231 (73%) Gp 1 225 (76%) Gp 2 220 (72%) Gp 3 227 (75%) Gp 4 **Serum ALT,**[a] median (range), xULN: 2.3 (0.6-15.9) Gp 1 2.2 (1.0-11.4) Gp 2 2.3 (0.5-9.7) Gp 3 2.3 (0.7-10.9) Gp 4 **Histology**: Classification system used: Knodell Fibrosis score, no. (%): F3 (bridging): 164 (13%) F4 (cirrhosis): 43 (4%)	**Primary outcomes**: SVR **Secondary outcomes**: • normalisation of ALT • improvement in liver histology **Length of follow up**: 24 weeks after completion of therapy

		Mean Knodell score: I + II + III (inflammation): 6.9 IV (fibrosis): 1.4 Timing of liver biopsy: performed within the preceding year (or if not, performed at baseline) **Genotypes, no. (%)**: 1: 851 (70%) 2: 125 (10% 3: 200 (16%) Other: 43 (4%) **Gender, no. (%)**: 770 (63%) m, 449 (37%) f **Age (yrs), mean (range)**: 43.1 (18-73) **Ethnic groups, no. (%)**: Caucasian: 1109 (91%) **Mode of infection, no. (%)**: Transfusion: 261 (21.4%) Parenteral: 588 (48.2%) Sporadic/other: 370 (30.4%) **Losses to follow up**: Of 1219 treated pts, 943 (77%) competed the 72-wk study. Pre- and post-treatment liver biopsies were analysed in 744 (61%) pts. **Compliance**: 5 pts were randomised but not treated; 106 pts (9%) discontinued treatment	

Outcome % with response (n)	**Peg IFN □2b 0.5 µg/kg**	**Peg IFN □2b 1.0 µg/kg**	**Peg IFN □2b 1.5 µg/kg**	**IFN □2b 3 MIU**
Virologic Response				
End of treatment	33% (105/315)*	41% (121/297)†	49% (149/304)†	24% (73/303)
SVR at follow-up[b]	18% (57/315)**	25% (73/297)†	23% (71/304)†	12% (37/303)
Combined Virologic and Biochemical Response				
End of treatment	25% (79/315)	31% (92/297)‡	33% (100/304)†	20% (61/303)
SVR at follow-up[c]	17% (52/315)	24% (70/297)†	23% (69/304)†	12% (37/303)
SVR by genotype and baseline viral load				
Genotype 1 (all tx groups)	10% (12/211)	14% (28/199)	14% (31/223)	6% (14/217)
≤2 million copies	27% (14/52)	38% (16/42)	34% (19/56)	21% (10/48)
>2 million copies	5% (8/159)	8% (12/157)	7% (12/167)	2% (4/169)
Genotype 2 or 3 (all tx groups)	35% (31/88)	47% (39/83)	49% (36/73)	28% (23/81)
≤2 million copies	58% (14/24)	62% (13/21)	68% (15/22)	36% (9/25)
>2 million copies	27% (17/64)	42% (26/62)	41% (21/51)	25% (14/56)
Genotype 4, 5, or 6 (all tx groups)	20% (2/10)	31% (4/13)	60% (3/5)	0/4
≤2 million copies	33% (2/6)	50% (4/8)	75% (3/4)	0/2
>2 million copies	0/4	0/5	0/1	0/2

Histology (proportion with improvement)				
Inflammation (%)	49% (97/198)	50% (89/178)	48% (85/177)	47% (90/191)
mean change	-1.5	-1.8	-1.5	-1.2
Fibrosis (%)	20% (40/198)	19% (34/178)	15% (27/177)	13% (25/191)
mean change	-0.1	0	0.1	0.1
Adverse Events, %				
dose discontinuation for				
any adverse event	9	11	9	6
dose reduction for				
any adverse event	9	14	19	6
thrombocytopenia	2 - 3	2 - 3	2 - 3	0.3
neutropenia	2 - 3	2 - 3	5	2 - 3
Specific adverse events, %				
headache	61	64	64	58
fatigue	43	51	45	50
chills	34	40	44	33
fever	31	45	44	30
myalgia	48	54	61	53
musculoskeletal pain	19	28	20	22
nausea	21	26	25	20
anorexia	10	20	25	17
irritability	19	18	17	24
insomnia	17	23	20	23
alopecia	20	22	34	22
injection site inflammation	44	42	40	16

[a]5 subjects had normal ALT levels at baseline, all had at least 1 abnormal ALT level before baseline; [b]95% CI for the difference in response rate: Peg 1.5 vs IFN (-0.172, -0.051), Peg 1.0 vs IFN (-0.185, -0.062), Peg 0.5 vs IFN (-0.115, -0.002); [C]95% CI for the difference in response rate: Peg 1.5 vs IFN (-0.174, 0.036), Peg 1.0 vs IFN (-0.183, -0.044), Peg 0.5 vs IFN (-0.106, 0.020); *p=0.01, **p=0.04, [†]p<0.001, [‡]p=0.002 for comparison with IFN.

Additional Results:

Virologic and biochemical response

- The higher EOTR rate in pts treated with Peg 1.5 vs Peg 1.0 (49% vs 41%, *p*=0.049) was largely the result of a significantly higher response rate in HCV genotype 1 infected pts (87/223, 39% vs 50/199, 25% respectively, *p*=0.002).
- Unlike the EOTR, there was not a dose response between the Peg 1.0 and Peg 1.5 groups for SVR, 25% and 23% respectively). This was related to a significantly higher relapse rate in the HCV genotype 1 pts treated with Peg 1.5 compared with Peg 1.0, 66% (57/87) and 46% (23/50) respectively (*p*=0.025), whereas the relapse rate among pts infected with genotypes 2 or 3 was similar, 36% (20/56) and 38% (24/63) respectively.
- Logistic regression analysis identified only 2 covariates associated with SVR: HCV genotype other than 1 and baseline HCV RNA levels of ≤2 million copies/mL serum, *p*< 0.001.
- In each treatment group, the likelihood of an SVR occurring was highest in pts whose first negative HCV RNA occurred at treatment wk 4 (77%-86%), compared with those in whom HCV RNA was first negative at treatment wk 12 (32% - 52%), and those whose HCV RNA was first negative at treatment wk 24 (13% -20%). Nearly all pts who eventually became sustained responders had developed undetectable serum HCV RNA by treatment wk 24 (93% - 100%).
- Negative predictive values for treatment wk 4 were 85% and 77% respectively for pts treated with Peg 1.0 and 1.5.
- Positive predictive value at treatment wk 4 was 84% and 90%, respectively for Peg 1.0 and 1.5.
- Sustained normal ALT values were a poor predictor of sustained HCV RNA loss. Among subjects with normal ALT values after 24 wks follow-up, SVRs occurred in 67%, 68%, 80% and 82% of pts treated with IFN, Peg 0.5, Peg 1.0 and Peg 1.5 respectively.

Histological response

- The proportions of subjects who showed an improvement in hepatic inflammation and fibrosis scores were higher among subjects who had a sustained response than among those who either relapsed or did not respond.

Safety

- No new or unexpected adverse events specific to Peg IFN □2b were reported.

- In all cases, the characteristics of the injection-site reaction were similar for both IFN and Peg IFN: the event was generally mild, not treatment-limiting, and characterised by localised erythema.

Methodological comments:
Allocation to treatment groups: pts were randomly assigned to 1 of 4 treatment groups. No further details.
Allocation concealment: not reported.
Blinding of outcome assessors: study double-blinded for all PEG doses. Assays performed by a central laboratory. Liver biopsies scored by a single blinded pathologist.
Analysis by intention to treat: does not specifically state that it was ITT analysis but efficacy assessments were obtained in all pts who were randomised and received at least 1 dose of study drug (n=1219).
Comparability of treatment groups at pre-treatment: baseline demographics and disease characteristics were generally comparable across all treatment groups. However, there was a higher proportion of pts with genotype 1 in the Peg 1.5 group (73%) than in the Peg 1.0 and 0.5 groups (67% in each, $p = 0.09$).
Method of data analysis: all statistical tests were 2-sided with a 0.05 level of significance. The SVR for Peg v IFN calculated by χ^2 test. Baseline characteristics were compared using Kruskal-Wallis test. Relation of baseline characteristics and treatment response evaluated by logistic regression.
Power analysis: not reported.
Attrition/drop-out: efficacy results were based on all pts receiving at least one dose. The number discontinuing treatment was reported, but not reasons. Overall, 23% of pts not completing the study was relatively high; the report states that discontinuation rates were comparable across all treatment groups.

General comments
Generalisability: patients seem representative of European pt populations with a high percentage of genotype 1 and high baseline HCV RNA levels.
Conflict of interests: supported in part by a research contract from Schering Plough Research Institute, Kenilworth, NJ.
Definitions: SVR, sustained virological response – loss of detectable serum HCV RNA (<100 copies/mL serum) 24 wks after completion of therapy; biochemical response – normalisation of ALT values, expressed in relationship to the upper limit of normal (ULN); an 'improved' inflammatory score was defined as a decrease of ≥2 units relative to pre-treatment; an 'improved' fibrosis score was defined as a decrease of ≥1 unit relative to pre-treatment; EOTR, end of treatment virologic response; negative predictive value - the likelihood that an SVR would occur if HCV RNA was not detected; positive predictive value - the likelihood that an SVR would not occur if HCV RNA was detected.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 17 – Reddy and colleagues: data extraction and critical appraisal

Reference and Design	Intervention	Participants	Outcome measures
Reddy et al, 2001[72] **Trial design**: Multicentre RCT (3 cohorts, open-label) **Country**: USA **Sponsor**: Hoffman-La Roche, Ltd., Switzerland	**Intervention 1:** n = 33 IFN α2a (s.c.) Dose: 3 MIU 3 times per week Duration: 48 weeks **Intervention 2:** n's = 20, 20, 45, 41 Peg IFN α2a (40 kd) (s.c.) Dose: 45, 90, 180, or 270 µg once weekly Duration: 48 weeks Randomised in a 4:1 ratio.	**Total numbers involved**: 159 patients randomised and analysed **Eligibility**: treatment naïve patients with CHC without bridging fibrosis or cirrhosis, i.e. Ishak fibrosis score 3 or 4 (15 patients with bridging fibrosis inadvertently included), persistently abnormal serum ALT activity (2 occasions ≥ 14 days apart), a positive anti-HCV antibody, pre-treatment liver biopsy consistent with chronic hep C, detectable pre-treatment HCV RNA **Recruitment**: multicentre, 3 successive cohorts with ascending doses of Peg IFN α2a were recruited (45 or 90 µg of Peg v IFN then 180 µg of Peg v IFN then 270 µg of Peg v IFN). Conducted between Feb 1997 and March 1999 **Exclusion criteria**: liver disease from causes other than CHC, white blood cell count <1,500/mm^3, platelet count <90,000/mm^3, serum creatinine >1.5 times the upper limit of normal, history of pre-existing medical conditions such as severe psychiatric illness, retinopathy, neoplasm (active or likely to recur), seizure disorder, unstable thyroid dysfunction, and cardiac or renal disease, currently pregnant or breastfeeding, alcohol/drug dependence within previous 12 mths, therapy with systemic antineoplastic or immunomodulatory agents within the past 6 mths, administration of antiviral or investigational compounds within the past 3 mths. **Baseline measurements**: **Viral Load, mean HCV RNA (±SD), x10^6 copies/ml:** 3.1 (± 3.1) IFN 1.7 (± 1.6) Peg 45 1.2 (± 1.5) Peg 90 2.3 (± 2.0) Peg 180 2.8 (± 3.2) Peg 270 **ALT, mean (±SD), U/L:** 95 (± 47) IFN 111 (± 102) Peg 45 80 (± 27) Peg 90 98 (± 50) Peg 180 97 (± 35) Peg 270 **Histology**: Classification system used: Ishak	**Primary outcomes**: SVR **Secondary outcomes**: • Sustained biochemical response at wk 72 • virological and biochemical responses at end of treatment (wk 48) • histological response **Length of follow up**: 24 weeks post-treatment

		Fibrosis score, no. (%): Non-cirrhosis (≤ F2): 144 (91%) Bridging fibrosis (F3): 15 (9%) HAI score, mean: 10.8 IFN, 11.7 Peg 45, 10.6 Peg 90, 10.7 Peg 180, 10.0 Peg 270 Timing of liver biopsy: obtained within 12 mths before study treatment **Genotypes, no. (%):** 1: 73.6% non-1: 23.9% missing: 2.5% **Gender, no. (%):** 125 m (79%), 34 f (21%) **Age (yrs), mean (±SD)**: 41.8 (± 5.9) IFN 41.9 (± 4.8) Peg 45 43.1 (± 6.7) Peg 90 42.0 (± 6.4) Peg 180 41.6 (± 5.7) Peg 270 **Ethnic groups, no. (%)**: White: 139 (87%) Black: 14 (9%) Oriental: 2 (1%) Other: 4 (3%) **Mode of infection, no. (%)**: not reported **Losses to follow up**: 122 completed 48 wk of treatment. 23 were withdrawn due to adverse events. **Compliance**: not reported	

Outcome % with response (n)	**IFN □2a 3 MIU**	**PEG IFN □2a, 45 µg**	**PEG IFN □2a, 90 µg**	**PEG IFN □2a, 180 µg**	**PEG IFN □2a, 270 µg**
Viological Response					
End of treatment	12% (4/33)	30% (6/20)	45% (9/20)†	60% (27/45)§	56% (23/41)§
SVR at follow-up	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)
Biochemical Response					
End of treatment	15% (5/33)	20% (4/20)	20% (4/20)	38% (17/45)*	27% (11/41)
End of follow-up	9% (3/33)	10% (2/20)	25% (5/20)	38% (17/45)‡	27% (11/41)
Histology (in patients with paired pre- and post-treatment biopsies)	(n=23)	(n=15)	(n=17)	(n=30)	(n=29)
Change from baseline mean total HAI score (± SEM)	-2.0 ± 0.6	-0.9 ± 0.8	-2.6 ± 1.0	-2.8 ± 0.6	-2.5 ± 0.7
Change from baseline median total HAI score	-2.0	-1.0	-2.0	-3.0	-2.0
Proportion of histological					

responders, % (no.)	57% (13/23)	47% (7/15)	59% (10/17)	63% (19/30)	66% (19/29)
Adverse Events					
Severe adverse events	10%	7%	2%	10%	7%
Withdrawn for adverse events or laboratory abnormalities	9%	10%	0%	22%	20%
Dose reduction for any adverse event					49% (20/41)
Specific adverse events, No. (%)[a]					
fatigue	21 (70%)	14 (70%)	17 (85%)	30 (67%)	28 (70%)
headache	18 (60%)	8 (40%)	7 (35%)	26 (58%)	19 (48%)
myalgia	19 (63%)	8 (40%)	13 (65%)	14 (31%)	19 (48%)
rigors	14 (47%)	1 (5%)	4 (20%)	21 (47%)	20 (50%)
nausea	14 (47%)	9 (45%)	3 (15%)	20 (44%)	12 (30%)
depression	3 (10%)	6 (30%)	7 (35%)	12 (27%)	15 (38%)
diarrhoea	6 (20%)	5 (25%)	5 (25%)	14 (31%)	13 (33%)
irritability	4 (13%)	7 (35%)	4 (20%)	13 (29%)	13 (33%)
injection-site inflammation	6 (20%)	7 (35%)	6 (30%)	11 (24%)	10 (25%)
insomnia	7 (23%)	5 (25%)	1 (5%)	15 (33%)	12 (30%)
arthralgia	7 (23%)	4 (20%)	8 (40%)	8 (18%)	12 (30%)
pyrexia	9 (30%)	3 (15%)	2 (10%)	11 (24%)	11 (28%)
alopecia	6 (20%)	1 (5%)	6 (30%)	10 (22%)	10 (25%)
upper abdominal pain	5 (17%)	6 (30%)	2 (10%)	8 (18%)	11 (28%)

*p<0.05, †p≤0.01, ‡p<0.005, §p<0.001; [a]events observed in at least 10% of patients; adverse events which occurred in ≥30% of pts in at least one study gp are listed.

Additional Results:

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

Methodological comments:

Allocation to treatment groups: randomised within 3 cohorts in which patients were assigned to 45 or 90 µg PEG or IFN (cohort 1), 180 µg PEG or IFN (cohort 2), 270 µg PEG or IFN (cohort 3). Initial safety data (8 weeks) were reviewed by an independent safety review board for each cohort before successive cohorts were randomised to higher doses of PEG. Open-label trial.

Allocation concealment: not reported

Blinding of outcome assessors: Open-label. Virological and biochemical assays were performed at a central laboratory. Histological response evaluated by a central pathologist in a coded, blinded fashion.

Analysis by 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 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: This is an ascending-dose trial to establish the most appropriate dose of Peg IFN for subsequent, larger trials.
Definitions: SVR, sustained virological response – proportion of pts with <100 copies/mL HCV RNA) at wk 72; biochemical response – normalisation of serum ALT activity; histological response – a ≥ 2-point decrease in the total histological activity index (HAI) between biopsies obtained at baseline and wk 72 as determined by a pathologist.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	N/a as open-label trial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an intention to treat analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 18 – Bennett and colleagues: economic evaluation data extraction and critical appraisal

Reference

Bennett and colleagues, 1997[88]

Study Characteristics

Research question

What are the stated objectives of the evaluation?

To estimate the cost-effectiveness of interferon-alpha2b in mild chronic hepatitis C. More specifically, to determine whether treatment of histologically mild chronic hepatitis C with a single 6-month course of interferon-alpha2b would affect life expectancy and lifelong costs.

Study population

What definition was used for mild chronic hepatitis C?

No specific definition of mild chronic hepatitis C was provided. The paper states however that hepatitis C virus chronically infects 3.9 million persons in the United States and is the most common cause of chronic liver disease.

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

Age	One 35 year old patient
Sex	Unknown
Race (if appropriate)	Unknown
Genotype	Unknown
Other characteristics	Presenting with histologically mild chronic hepatitis C

Interventions and comparators

What number of interventions/ strategies were included?

The model assumed a single 6-month course of recombinant interferon-alpha2b.

Was a no treatment/ supportive care strategy included?

There was not a no treatment/supportive care strategy included.

Describe interventions/ strategies

Intervention/ strategy 1: The five clinical trials included were selected because they all used the same treatment regimen (recombinant interferon-alpha2b at a fixed dose of 3 million U administered three times weekly for 6 months), had systematic follow-up after treatment, and had liver biopsy slides and study databases available for review. All patients were positive for antibody to HCV and had no evidence of coexisting liver diseases.

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

A managed care perspective was used, as well as variable cost estimates (the amount spent by the hospital to care for one additional patient with the illness) based on individual variable cost estimates for actual patients with hepatitis C-related hospitalizations, including hospital and physician costs of the University of Florida.

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

Cost-effectiveness analysis

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

Hospital setting

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

Results were primarily developed from US and European studies. Costs are expressed in $US. Results may not therefore be generalisable to East Asia, Africa, the Middle East, and Australia, where HCV disease progression and response to interferon-alpha2b may differ. The publication does not provide information on the base year to which the costs relate.

Data Sources

Effectiveness
Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single study		
a review/ synthesis or combination of previous studies	√	Data was taken from five prospective trials and cost-effectiveness analyses. References for these studies are provided.
expert opinion		

Give the definition of treatment effect used in the evaluation

Treatment responses were determined according to baseline histologic findings by reanalysis of the pooled data from five clinical trials involving 287 patients with chronic hepatitis. Traditional definitions of response were used. Persons with no response had ALT levels that did not return to normal by the end of treatment, persons with an end-of-treatment response had an unsustained normalization of the serum ALT level, and persons with a sustained response had a persistently normal serum ALT level for at least 6 months after completion of therapy.

Give the size of treatment effect used in the evaluation

An end-of-treatment response occurred in 64% of patients with mild or moderate chronic hepatitis without fibrosis, 42% of those with chronic hepatitis with fibrosis, and 28% of those with cirrhosis. A sustained response occurred in 31% of those with mild or moderate hepatitis, 11% of those with chronic hepatitis with fibrosis, and 9% of those with cirrhosis.

include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)

Intervention Costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	Data was taken from five prospective trials and cost-effectiveness analyses. References for these studies are provided.
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

No indirect costs were included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion	√	No patient surveys were available. Therefore, a panel of hepatologists were asked to use linear scaling and time trade-off methods to estimate the quality of life or utility for each health state on a scale of 0 (death) to 10 (perfect health).

List the utility values used in the evaluation

Refer to table 3: Quality-of-life Adjustments

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation)

A decision analytic model using a Markov simulation was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

This was a newly developed model. Because data on the natural history of hepatitis C are recent and somewhat uncertain, the validity of the analysis was tested by comparing model predictions with findings from published studies.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

Given the lack of controlled clinical trials on the effect of interferon therapy in patients with mild chronic hepatitis C, the modest long-term response rate to interferon, and the many years usually required before disease complications arise, a decision analytic model was developed.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

Hypothetical cohorts of identical patients with histologically mild chronic hepatitis move through states of health defined by clinical and histologic descriptors. Time is represented by annual cycles during which patients may remain in the same histologic or clinical state; progress or regress to another histologic or clinical state; die of liver disease; or die of other causes as a function of sex, race, and attained age. The simulation was carried out in each cohort until all patients died of liver-related or other causes. Certain assumptions of the modelled were described. These are as follows: 1. Assumed that patients with relapse are not re-treated, and that their subsequent prognosis is identical to that of patients with no response 2. Assumed that patients who lose HCV either spontaneously or as a result of treatment will not develop progressive liver disease 3. Because data on the effect of extrahepatic complications of HCV infection on disease progression, morbidity, mortality, and response to treatment are insufficient, the impact of these data could not be modelled. 4. The authors could not determine with accuracy the age-dependent rate of liver disease progression from published studies. Thus, age was excluded from the model. 5. The authors did not consider serial liver biopsies. Because it was assumed that no re-treatment would be given, biopsy would not affect treatment and would only add cost and morbidity. Thus, although the model contains other histologic states, these states remain unobserved clinically until patients develop decompensated liver disease. 6. Although the model permits liver transplantation for cirrhosis, it does not consider liver transplantation for hepatocellular carcinoma. After patients undergo liver transplantation, the authors did not consider decreased survival from recurrent hepatitis C or hepatocellular carcinoma because of inadequate data. This is a bias against interferon-alpha2b. 7. Viral factors could not be considered, such as genotype, pre-treatment level of viremia, or presumed source of infection, in this model.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

Refer to Table 2: Annual Rates of Probability of Disease Progression in Patients with Chronic Hepatitis C

What is the model time horizon?

Annual cycles

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

Costs, wholesale prices, or charges adjusted by a cost-to-charge ratio were used for all calculations.

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Increase in life expectancy

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

In 27% of patients with mild chronic hepatitis C treated with interferon-alpha2b for 6 months, serum alanine aminotransferase levels permanently returned to normal and viral status remained negative. The model estimated that interferon-alpha2b treatment in this population should increase life expectancy by 3.1 years if given at 20 years of age, by 1.5 years at 35 years of age, and by 22 days at 70 years of age.

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

The cost of a 6-month course of interferon-alpha2b at 3 million U three times weekly was $2150; this cost increased to $2511 after the addition of drug-induced costs of counselling patients, additional follow-up laboratory evaluations, and visits. However, for patients who were unresponsive to interferon-alpha2b and had treatment discontinued after 3 months, the cost was reduced to $1253.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

The costs and outcomes are reported together. Discounted marginal cost-effectiveness ratios were $500 per year of life gained for patients treated at 20 years of age, $1900 at 35 years of age, and $62,000 for 70 years of age.

Give results of any statistical analysis of the results of the evaluation.

No further statistical analysis reported.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Sensitivity analysis was performed due to the variation in published data and expert estimates. The paper examined the effect of varying all the values over a wide range to assess their effect on the results. The range used was identified using the 95% CI's, halved and doubled cost and data estimates, or the range from the literature (whichever was greatest). Wherever possible, estimates that biased against interferon-alpha2b therapy were used.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

Each model variable was varied over a wide range of possible values. These were: annual probability of mild hepatitis becoming moderate; moderate hepatitis becoming cirrhosis; probability of durable viral-negative response to interferon-α2b and cost of interferon-α2b. Only four variables (cost of interferon-alpha2b, response to interferon-alpha2b, rate of transition from mild chronic hepatitis to moderate chronic hepatitis, and rate of transition from moderate chronic hepatitis to cirrhosis) changed the results significantly.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

Varying the long-term response rates and progression rates for mild and moderate chronic hepatitis to near zero in sensitivity analyses substantially affected the results. Ratios ranged from $31,000 for a 20 year old patient to $640,000 for a 70 year old patient. The base-case analysis biased against interferon-α2b by excluding quality of life adjustments and using conservative discounted variable costs. When both quality of life adjustments and DRG reimbursements were used, interferon-α2b was cost saving for 20-and 35-year old patients and had a discounted marginal cost-effectiveness ratio less than $5000 for all patients 45 to 70 years of age.

Conclusions/ Implications

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

On the basis of the estimations in this mathematical model of the natural history of chronic hepatitis C, treating mild chronic hepatitis with interferon-alpha2b should prolong life expectancy at a reasonable marginal cost per year of life gained, particularly in younger patients.

What are the implications of the evaluation for practice?

In the absence of a long-term clinical trial, the analysis suggests that a single 6-month course of interferon-alpha2b for mild chronic hepatitis should increase life expectancy at an economically reasonable cost that falls below that of many well-accepted health care interventions, particularly for younger patients.

Appendix 19 – Davis and colleagues: economic evaluation data extraction and critical appraisal

Reference

Davis and colleagues, 1998[90]

Study Characteristics

Research question

What are the stated objectives of the evaluation?

To utilize a previously reported and validated mathematical model and results of published clinical trials to determine whether the longer duration of IFN treatment, currently recommended for patients with chronic hepatitis C, results in an incremental gain in life expectancy and cost-effectiveness, as compared to either a 6-month course of IFN or no treatment, in patients with histologically mild chronic hepatitis C.

Study population

What definition was used for mild chronic hepatitis C?

The diagnosis of mild chronic hepatitis was defined as a Knodell periportal inflammation score of 0 or 1 without fibrosis or cirrhosis.

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

Age	35-year old patient
Sex	Unknown
Race (if appropriate)	Unknown
Genotype	Unknown
Other characteristics	Histologically mild hepatitis C

Interventions and comparators

What number of interventions/ strategies were included?

Two interventions were included

Was a no treatment/ supportive care strategy included?

There was no 'no treatment' strategy included.

Describe interventions/ strategies

Intervention/ strategy 1: Interferon-α2b given for 6 months Intervention/ strategy 2: Interferon-α2b given for 18-24 months

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

A managed-care perspective was utilised.

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

Cost-effectiveness analysis

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

Hospital setting

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

All costs were normalised to 1995 US$.

Data Sources

Effectiveness
Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single study		
a review/ synthesis or combination of previous studies	√	Treatment outcomes were taken from two large multi-centre trials of IFN-α2b given for 6 months or 18-24 months.
expert opinion		

Give the definition of treatment effect used in the evaluation

Responses were defined according to traditional definitions (Davis et al. 1989). A sustained response was defined as a persistently normal serum ALT level at the end of treatment and for at least 6 months after discontinuation of therapy.

Give the size of treatment effect used in the evaluation

Based on analysis of the pooled database from the two clinical studies, end-of-treatment response was obtained in 61.5% and 50.0% of patients with mild chronic hepatitis without fibrosis treated for 18-24 months or 6 months respectively.

include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)

Intervention Costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study	√	The wholesale cost of out-patient medications was based upon the 1995 Red Book.
a review/ synthesis or combination of previous studies		
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

The cost of a 6-month course of IFN-α2b at 3MU thrice weekly was $2150 and for an 18-month course, $6450. After including the drug induced costs for counselling patients, additional follow-up laboratory tests and visits, the total cost for a course was increased by $364 for each 6 months of therapy.

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	QOL adjustments were used as described by Bennett et al (1997)
expert opinion		

List the utility values used in the evaluation

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation)

A decision-analysis Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

A slight modification of the decision-analysis model developed by Bennett and colleagues was employed (Bennett et al. 1997: *Estimated cost-effectiveness of a single course of interferon-alpha2b in patients with histologically mild chronic hepatitis C*)

What was the purpose of the model (i.e. why was a model required in this evaluation)?

The model simulates disease progression and allows comparison of cohorts managed by observation alone or by IFN treatment.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

Hypothetical cohorts of identical patients with histologically mild chronic hepatitis move through health states defined by clinical and histological descriptors, e.g. mild hepatitis, compensated cirrhosis, death etc. The rates of progression between these states were derived from the medical literature with interpretation and clarification by an expert panel of hepatologists.
The assumptions of the decision analysis are those utilised by Bennett et al. (1997). These included the following:

1. For purposes of assessing the effect of long-term treatment, an 18-month course was assumed.
2. Sustained response was the only favourable response considered. All other patients were considered to be non-responders.
3. Non-responders after the first 12 weeks of treatment stopped IFN because a favourable end-of-treatment response would be highly unlikely in such patients.
4. Relapse was not retreated in this model. Thus, the subsequent prognosis of patients who relapsed was assumed, for purposes of the model, to be identical to the pre-treatment prognosis of that histological state of disease.
5. It was assumed that the presence of HCV was an essential requirement for disease progression. Thus, it was assumed that patients who eradicated HCV, either spontaneously or as a result of treatment, did not develop progression of their liver disease. For purposes of the model, patients with a sustained biochemical and virological response were assumed to have a lifelong cure.
6. The effect of age on the rate of liver disease progression could not be determined with certainty from published studies and was therefore not included. However, as preliminary reports suggest that histological progression may be accelerated in patients over the age of 55 years, exclusion of age from the model biases against treatment in older patients.
7. The effects of viral factors, such as genotype and the pre-treatment level of viraemia, were not considered in the model.
8. Serial liver biopsies were not considered in the Bennett model. Thus, although the model describes the potential histological progression, this progression is not observed clinically so the cost of follow-up was assumed to be that of mild chronic hepatitis until subjects were found to be virus negative or presented with decompensated liver disease.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

What is the model time horizon?

Time was represented by annual cycles during which patients might remain in the same histological or clinical state, progress or regress to another histological or clinical state, die from liver disease, or die from other causes based on gender, race, and attained age.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

Hospital costs or adjusted (reduced) charges were used, rather than patient charges, to eliminate regional differences and economic biases that would favour treatment (by making the cost of disease appear greater). Whenever there was a discrepancy for cost (e.g. between actual hospital costs and published costs), the lesser figure was utilized.

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Based on analysis of the pooled database from the two clinical studies, end-of-treatment response was obtained in 61.5% and 50.0% of patients with mild chronic hepatitis without fibrosis treated for 18-24 months or 6 months respectively. Sustained response was achieved in 42.3% and 17.3% for 18-24 months or 6 months respectively. After discounting by 14% to estimate the virological relapse, the sustained viral-negative response rate for mild chronic hepatitis was 36.4% for 18-24 months of treatment and 15.3% for a 6-month course.

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

The wholesale cost of out-patient medications was based upon the 1995 Red Book. The cost of a 6-month course of IFN-α2b at 3MU thrice weekly was $2150 and for an 18-month course, $6450. After including the drug-induced costs for counselling patients, additional follow-up laboratory blood tests and visits, and total cost for a course was increased by $364 for each 6 months of therapy. The model mandated discontinuation of IFN therapy in patients failing to respond to treatment by 3 months and therefore the cost was reduced in these patients to $1257. In patients aged 20-50 years, the discounted marginal cost per year of life gained by long-term IFN treatment ranged from $735 to $8856, and the gain in life expectancy ranged from 4.35 years to 0.75 years respectively, compared with an untreated age-matched cohort. Compared with treatment and healthcare costs, sustained response rates and the rate of progression during early disease were identified as significant variables in sensitivity analysis.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Give results of any statistical analysis of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Owing to the variation in published data and expert estimates, all cost and progression rates were varied over a wide range to assess their effect on the results of the analysis. Wherever appropriate, in the base case or in sensitivity analysis, estimates that biased against IFN therapy were used.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

Each variable in the model was tested over a wide range of possible values.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

For treatment response, the sensitivity analysis included a sustained viral-negative response, ranging from 10-40%, for 6 months of treatment. The analysis included a sustained viral-negative response for 18 months of treatment, which ranged from 15.3-50%. The viral clearance probabilities with 6 and 18 months of therapy varied simultaneously in a linked sensitivity analysis. In another sensitivity analysis, the cost of IFN was varied from 50% of baseline to 150% of baseline.

Conclusions/ Implications

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

The treatment and healthcare costs, sustained response rates and the rate of progression during early disease were identified as significant variables in sensitivity analyses. Longer treatment always showed a survival benefit compared with 6 months of IFN or no treatment, and the cost of longer treatment is reasonable compared with that for a 6-month course.

What are the implications of the evaluation for practice?

Appendix 20 – Wong and Koff: economic evaluation data extraction and critical appraisal

Reference

Wong and Koff (2000)[92]

Study Characteristics

Research question

What are the stated objectives of the evaluation?

To compare no antiviral treatment, periodic liver biopsy with subsequent antiviral treatment for moderate hepatitis or cirrhosis, and immediate antiviral therapy.

Study population

What definition was used for mild chronic hepatitis C?

Patients had elevated levels of serum aminotransferase, known genotype, and liver biopsy revealing histologically mild liver inflammation (defined as Knodell periportal inflammation scores of 0 to 1).

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

Age	Mean age (yr) 40.1 ± 8.9
Sex	Female (%) 34.6 ± 0.1
Race (if appropriate)	
Genotype	Genotype 2 or 3 (%) 31.7 ± 0.1
Other characteristics	See table 1: Baseline data

Interventions and comparators

What number of interventions/ strategies were included?

The authors compared the risks and benefits of periodic biopsy with antiviral treatment alone by considering four strategies.

Was a no treatment/ supportive care strategy included?

Natural history with no antiviral treatment was included

Describe interventions/ strategies

Intervention/ strategy 1: Natural history with no antiviral treatment Intervention/ strategy 2: Watchful waiting with liver biopsy every 3 years and combination therapy in patients found to have cirrhosis on liver biopsy Intervention/ strategy 3: Watching waiting with liver biopsy every 3 years and combination therapy in patients found to have moderate hepatitis on liver biopsy Intervention/strategy 4: Immediate empirical combination therapy Treatment consisted of combination therapy for 24 weeks in patients with genotype 2 or 3 and liver biopsy showing no cirrhosis. All other patients received combination therapy for 48 weeks, bus treatment was discontinued in patients who had not responded at 24 weeks.

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

Societal perspective, assuming that quality of life adjustments considered time or indirect costs.

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

Cost-effectiveness analysis

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

Hospital setting

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

All costs were inflated from 1995 to 1998 US$ by using the Medical Care component of the Consumer Price Index.

Data Sources

Effectiveness
Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single study		
a review/ synthesis or combination of previous studies	√	Clinical trial data and published studies (two large clinical trials)
expert opinion		

Give the definition of treatment effect used in the evaluation

Give the size of treatment effect used in the evaluation

include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)

Intervention Costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	Post-treatment costs were based on previously published actual variable costs, wholesale drug costs, and charges adjusted with cost to charge ratios for patients with hepatitis C.
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion	√	To reflect the morbidity associated with some states of health, life expectancy for quality of life was adjusted on a scale from 0 (dead) to 1 (perfect health) on the basis of assessments by an expert panel of senior hepatologists familiar with treatment and liver disease.

List the utility values used in the evaluation

See Table 3: One-way sensitivity analysis: quality-adjusted life year

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation)

A decision analytic Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

A previously described and validated Markov simulation model was used to estimate the long term prognosis of each cohort with chronic hepatitis C.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

The model was used to estimate the long-term prognosis of each cohort with chronic hepatitis C. The Markov model tracked cohort members as they moved through alternative states of health determined by clinical and histological descriptors.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

Within the model, patients may 1) remain in the same histological or clinical state; 2) progress to another histological or clinical state; 3) die of liver disease; 4) die of other causes based on sex, ethnicity, and attained age; or 5) undergo liver biopsy. The simulations continued until all patients died.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

What is the model time horizon?

Time was represented by annual cycles across the patients' lifetime.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

Because immediate combination therapy has higher current costs and its benefits occur in the future, discounting reduced the benefit of immediate therapy and increased its relative costs compared with future biopsy or no antiviral therapy. Immediate therapy increased lifetime discounted costs by $7000 and life expectancy by 1.0 discounted QALY, yielding a marginal cost-effectiveness ratio of $7000 per discounted QALY gained compared with no antiviral therapy. When discounted at 5%, this ratio increased to $13,500 per discounted QALY gained.

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

Antiviral drug costs were based on average wholesale costs of $6.20 for 200mg ribavirin and $11.64 per million U of interferon, but were adjusted for the actual drug dose received in the trial, which reflected patient weight, dose reduction due to side effects, and drug discontinuation in patients who tested positive for HCV after 24 weeks of therapy.
Although watchful waiting reduced costs of antiviral therapy by $3400, costs of biopsy reached $6200. After including the cost of potential future HCV related complications, the lifetime cost of biopsy management exceeded the lifetime cost associated with immediate therapy by at least $5100. Because immediate therapy also prolonged life while reducing costs, it dominated biopsy management and was cost saving.
Post-treatment costs were based on previously published actual variable treatment costs, wholesale drug costs, and charges adjusted with cost to charge ratios for patients with hepatitis C.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Give results of any statistical analysis of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

One way sensitivity analysis and Monte Carlo sensitivity analysis

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

To examine the extent to which the results varied with alternative assumptions, additional analyses were performed for clinical subgroups. In addition, a Monte Carlo analysis was performed, in which all parameters are varied simultaneously over probability distributions defined by the 95% CIs or reasonable ranges. A unique set of random values was sampled for each variable (including patient characteristic, liver disease progression rates, treatment response rates, and costs). For each unique set of values, the simulation projected the discounted quality-adjusted life expectancy and lifetime cost results for each strategy using four identical cohorts of 10,000 patients. These analyses were repeated 1000 times.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

Results of the one-way analysis are provided in Table 3. Results of the Monte Carlo sensitivity analysis are provided in Table 4.

Conclusions/ Implications

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

For histologically mild chronic hepatitis C, initiation combination therapy compared with periodic liver biopsy should reduce the future risk of cirrhosis, prolong life, and be cost-effective.

What are the implications of the evaluation for practice?

The analysis suggests that biopsy management would avoid treatment in many patients, especially over the next 20 years. Compared with immediate antiviral treatment, however, biopsy management permitted an increased cumulative incidence of cirrhosis and decreased survival.

Appendix 21 – Grieve and Roberts: economic evaluation data extraction and critical appraisal

Reference

Grieve and Roberts (2002)[93]

Study Characteristics

Research question

What are the stated objectives of the evaluation?

To determine whether a combination of alpha interferon and ribavirin is cost-effective for patients with mild HCV.

Study population

What definition was used for mild chronic hepatitis C?

No definition was provided for mild chronic hepatitis C.

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

Age	40 years
Sex	Not reported
Race (if appropriate)	Not reported
Genotype	Not reported
Other characteristics	Mild HCV

Interventions and comparators

What number of interventions/ strategies were included?

Alpha interferon and ribavirin was compared with no treatment.

Was a no treatment/ supportive care strategy included?

A no treatment strategy was included.

Describe interventions/ strategies

Intervention/ strategy 1: Alpha interferon and ribavirin in the treatment of patients with HCV. Intervention/strategy 2: No treatment

Analytical perspective

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

Health service perspective (costs falling on social services, the patient and their carer were excluded from the analysis).

Study type

Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost-effectiveness

Institutional setting

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

Hospital/health care setting

Country/ currency

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

All costs were converted from UK pounds into EURO's using official exchange rates (£ = 1.58 EURO's).

Data Sources

Effectiveness

Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single study		
a review/ synthesis or combination of previous studies	√	A literature review was undertaken.
expert opinion		

Give the definition of treatment effect used in the evaluation

Give the size of treatment effect used in the evaluation

include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)

Intervention Costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	Model costs were taken from the literature.
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Table 2 presents the costs used in the model.

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	Values used were taken from the literature
expert opinion	√	The estimates were derived by asking health care professionals to state the utility associated with being in the health states of interest.

List the utility values used in the evaluation

Table 2 states the costs and quality of life values used in the model.

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation)

A Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

The model structure was developed from the model previously outlined in Dusheiko and Roberts (1995). However, certain changes to the original structure were undertaken to take account of the aim of the model.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

The aim of the model was to evaluate anti-viral therapy for patients with mild rather than chronic HCV. Also, a separate sub-stage was included for hepatocellular carcinoma.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

The model assumed that all cases were treated if they progressed to moderate disease or cirrhosis as recommended by UK guidelines.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

A literature review was undertaken to find the best available estimates of disease progression rates for patients with HCV. Although there appeared to be a general consensus in the literature about the transition probabilities between later disease states, such as cirrhosis and decompensated cirrhosis, there was much less agreement about the rate of progression between mild and moderate disease. The transition probabilities, which were felt to be most appropriate to the HCV population in the UK, were included in this version of the model. These are listed, along with their sources in Table 1.

What is the model time horizon?

The model time horizon was not reported.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

All costs were discounted at 6% and outcomes at 1.5% as recommended by recent guidelines from the UK Department of Health (1998)

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

The results suggested that CMB for mild HCV is likely to prove a relatively cost-effective intervention. The projected cost per QALY for cases with mild HCV was 8,490 EUROs. This compares favourably with many other interventions which, are routinely provided.

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

The model predicted that on average, the intervention will mean 55 fewer deaths from liver disease for 1000 cases, which will lead to an average gain of 1.2 life years. Apart from the reduction in mortality, CMB also reduced morbidity by preventing disease progression.

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

The average lifetime costs for mild HCV were higher following treatment (33,228 EUROs) compared to no treatment for cases with HCV (18,346 EUROs). This is mainly because of the high treatment and monitoring costs associated with anti-viral therapy for mild HCV (21,534 EUROs). The incremental cost-effectiveness ratio for the base case, was 12,089 EUROs per life year or 8,490 EUROs per QALY.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Measures of health related quality of life (HRQOL) were included for each of the health states included in the model. The incremental cost-effectiveness ratio (ICER) was calculated for CMB compared with no treatment.

Give results of any statistical analysis of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Sensitivity analyses were run to examine the impact of changing assumptions on the progression rate rates, and effectiveness of the intervention on the estimated cost-effectiveness of the intervention.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

The sensitivity analysis looked at the impact of changing various parameters on the cost per QALY. These scenarios tested included: sub group genotype 1; sub group genotype non-1, slow progression to cirrhosis and fast progression to cirrhosis.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

The analysis showed that the cost-effectiveness ratio varied widely according to certain parameters. E.g. for cases with genotype 1, the intervention was much less effective than for cases with genotype non-1 so the cost-effectiveness ratio was much higher. Similarly, for those cases who would progress from mild to moderate disease and then to cirrhosis at a fast rate (10% per year) without the intervention, then the cost-effectiveness ratio is more favourable than for those who would progress slowly through the illness.

Conclusions/ Implications

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

These preliminary results suggest that CMB for mild HCV is likely to prove a relatively cost-effective intervention. The projected cost per QALY for cases with mild HCV was 8,490 EUROs. This compares favourably with many other interventions which are routinely provided.

What are the implications of the evaluation for practice?

Before results from the model are used to recommend that anti-viral treatment should be provided for patients with mild HCV, certain concerns about the model need addressing.

Appendix 22 – Saloman and colleagues: economic evaluation data extraction and critical appraisal

Reference

Saloman (2003)[91]

Study Characteristics

Research question

What are the stated objectives of the evaluation?

To examine the clinical benefits and cost-effectiveness of newer treatments for chronic hepatitis C infection in a population of asymptomatic, HCV seropositive but otherwise healthy individuals.

Study population

What definition was used for mild chronic hepatitis C?

Patients had elevated levels of alanine aminiotransferase, positive results on quantitative HCV RNA assays and serologic tests for antibody to HCV, and no histological evidence of fibrosis on liver biopsy.

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

Age	
Sex	
Race (if appropriate)	
Genotype	
Other characteristics	Baseline values are reported in Table 2.

Interventions and comparators

What number of interventions/ strategies were included?

Five strategies for HCV infection were included.

Was a no treatment/ supportive care strategy included?

A no treatment strategy was included.

Describe interventions/ strategies

Intervention/ strategy 1: No treatment Intervention/ strategy 2: Monotherapy with interferon alpha-2b Intervention/ strategy 3: Monotherapy with pegylated interferon alpha-2b Intervention/ strategy 4: Combination therapy with interferon and ribavirin Intervention/ strategy 5: Combination therapy with pegylated interferon and ribavirin.

Analytical perspective

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

A societal perspective was adopted (although patient-time costs were excluded).

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

The comparative efficiencies of alternative treatment strategies were measured by the incremental cost-effectiveness strategy.

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

Hospital setting

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

Currency was presented in US dollars

Data Sources

Effectiveness
Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single study		
a review/ synthesis or combination of previous studies	√	Estimates for treatment efficacy were based on pooled results of randomised controlled trials. Presented in Table 2.
expert opinion		

Give the definition of treatment effect used in the evaluation

Give the size of treatment effect used in the evaluation

include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)

Intervention Costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	Treatment costs were based on mean wholesale drug costs, combined with previously published cost estimates for clinic visits, laboratory tests, and the treatment of adverse events.
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study	√	Annual costs for patients in each of the clinical states in the model were derived from a published study that included detailed estimates of resource utilisation
a review/ synthesis or combination of previous studies		
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies	√	For the base case analysis previously published quality weights were applied to each health state.
expert opinion		

List the utility values used in the evaluation

Table 2 presents health-related quality of life weight. Table 4 presents incremental costs per life-year and quality adjusted life-year saved or combination therapy with pegylated compared with standard interferon.

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation)

A Markov model was developed.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

The model was newly developed. Natural history parameter values were in the model were derived from the authors' previous empirical calibration study (Saloman, 2002). Values for the additional parameters demanded by the more detailed structure of the model were derived from the empirically calibrated parameters (listed in Table 1), combined with other estimates from the literature.

What was the purpose of the model (i.e. why was a model required in this evaluation)?

The structure of the Markov model used in this decision analysis included a more detailed specification of the complications of cirrhosis than did the model used for empirical calibration to build on an existing body of cost-effectiveness work, including published data pertaining to annual costs of care for specific states of ascites, variceal haemorrhage, and hepatic encephalopathy.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

To be consistent with current guidelines it was assumed that: 1) monotherapy was administered for 48 weeks; 2) combination therapy was administered for 48 weeks in patients with HCV genotype 1 and 24 weeks in patients with all other HCV genotypes; 3) treatment was discontinued in patients with detectable HCV RNA levels after either 12 weeks or receiving monotherapy or 24 weeks of receiving combination therapy.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

Transition probabilities determined the movements of patients through different health states until all members of the cohort had died. Each year, patients faced probabilities of fibrosis progression, complications from cirrhosis, and competing mortality risks from decompensated cirrhosis, HCC, and other causes unrelated to HCV infection.

What is the model time horizon?

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

All costs and clinical consequences were discounted at a rate of 3%.

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

The incremental costs for each strategy ranged from $2000 to $4000, with incremental gains in life expectancy ranging from 1 to 2 months. Interferon therapy was weakly dominated by pegylated interferon therapy, and the incremental cost-effectiveness ratios of the combination strategies were between $24000 and $35000 per QALY gained.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Give results of any statistical analysis of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Sensitivity analysis was performed.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

Sensitivity analyses were performed on costs, treatment efficacy, and health-related quality of life.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

The results were insensitive to variation in annual costs or managing chronic hepatitis C or its complications, and relatively insensitive to assumptions about the efficacy of different treatment regimens. If costs of a specific treatment regimen for HCV infection were to vary within a range of ±50%, the given strategy typically would be dominated or be dominated by adjacent strategies at the extreme values of the ranges. Results were sensitive to the discount rate used; with no discounting, the incremental cost-effectiveness of all treatment strategies were all lower than in the base case by approx. 60-80%. Results were highly sensitive to plausible alternative assumptions about the impact of chronic HCV infection and treatment of quality of life. Results were also sensitive to alternative assumptions about the decrements of quality of life associated with treatment.

Conclusions/ Implications

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

While newer treatment options for hepatitis C appear to be reasonably cost-effective on average, these results vary widely across different patient subgroups and depend critically on quality-of-life assumptions.

What are the implications of the evaluation for practice?

As the pool of persons eligible for treatment for HCV infection expands to the more general population, it will be imperative for patients and their physicians to consider the assumptions from this study, in making individual-level treatment levels.

Appendix 23 – Grieve and colleagues: economic evaluation data extraction and critical appraisal

Reference

Grieve and colleagues (2005)[12]

Study Characteristics

Research question

What are the stated objectives of the evaluation?

To assess whether anti-viral therapy (either interferon α or peginterferon α combined with ribavirin) is cost-effective at a mild stage compared to waiting and only treating those cases who progress to moderate disease.

Study population

What definition was used for mild chronic hepatitis C?

Cases with mild chronic hepatitis C

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

Age	40 yrs
Sex	60% male
Race (if appropriate)	
Genotype	50% genotype 1
Other characteristics	

Interventions and comparators

What number of interventions/ strategies were included?

Four interventions were included

Was a no treatment/ supportive care strategy included?

A no treatment strategy was included.

Describe interventions/ strategies

Intervention/ strategy 1: mild disease: no treatment; moderate disease: interferon α-2b + ribavirin Intervention/ strategy 2: mild disease: interferon α-2b + ribavirin; moderate disease: no treatment Intervention/ strategy 3: mild disease: no treatment; moderate disease: peginterferon α-2b + ribavirin Intervention/ strategy 4: mild disease: peginterferon α-2b + ribavirin; moderate disease: no treatment

Analytical perspective

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

A health service perspective was taken to costing; the inpatient and outpatient costs incurred from hospital care were included.

Study type

Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost –effectiveness study

Institutional setting

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

Hospital or liver clinics

Country/ currency

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

All costs were reported in 2002-2003 prices (£), and the main cost results were converted into US dollars using 2002-3 purchasing power parties to assist with the interpretation of results (OECD, 2004).

Data Sources

Effectiveness

Were the effectiveness data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single study	√	The effectiveness data for interferon α-2b and ribavirin from a mild hepatitis C RCT were used as a basis for estimating the likely effectiveness of peginterferon α-2b and ribavirin in routine clinical practice.
a review/ synthesis or combination of previous studies		
expert opinion		

Give the definition of treatment effect used in the evaluation

Give the size of treatment effect used in the evaluation

include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)

Intervention Costs
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Total costs were calculated by multiplying each patient's resource use by the relevant unit cost.

indicate the source for individual cost values (if appropriate)

Other Direct Costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study	√	The costs of liver transplantation were taken from a UK study of the costs and outcomes following liver transplantation (Longworth, 2003).
a review/ synthesis or combination of previous studies		
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used.

indicate the source for individual cost values (if appropriate)

Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included:

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued)

indicate the source for individual cost values (if appropriate)

Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	Were the methods for deriving these data adequately described (give sources if using data from other published studies)?
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion		

List the utility values used in the evaluation

indicate the source for individual cost values (if appropriate)

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation)

A Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.

The model's structure and main assumptions were similar to previous models for hepatitis C and have previously been described (Grieve, 2002).

What was the purpose of the model (i.e. why was a model required in this evaluation)?

The model was required to estimate the lifetime cost-effectiveness of anti-viral treatment for patients with mild chronic hepatitis C.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

The Markov model required the natural history of the disease to be divided into a series of health states. Two hypothetical cohorts with the characteristics of the UK mild hepatitis C trial population were entered into the model and faced annual probabilities of progression to subsequent health states. The cases in the 'treatment group' were all assumed to have antiviral therapy at a mild stage, with a proportion having a SVR and no longer facing a probability of progression. Patients in the 'no treatment group' did not receive treatment at a mild stage; those cases predicted by the model to reach moderate disease were assumed to have anti-viral treatment in accordance with recent UK recommendations.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

The transition probabilities for mild to moderate disease, and moderate disease to cirrhosis were estimated by re-analysing data from UK cross sectional and longitudinal datasets. Subsequent transition probabilities were taken from the literature. Annual transition probabilities are shown in Table 1. The transition probabilities were based on studies that recruited patients from a hospital rather than a community setting, in order to fit in with the perspective of the study. The transition probabilities used for progression from mild to moderate disease and moderate disease to cirrhosis were compared to estimates (Wright et al, 2005) from a recent systematic review of progression rates in hepatitis C. These were lower than those derived from other studies that recruited cases from liver clinics, but higher than estimates from community-based studies.

What is the model time horizon?

The model duration is up to 50 years, The duration of treatment for all patients is 52 weeks.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

All estimates were discounted at a rate of 3.5%

Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

Unit costs for antiviral therapy and all other medication use were taken from the BNF. All other unit costs were collected from the finance departments at the three centres concerned.

Synthesis of costs and benefits –are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

Give results of any statistical analysis of the results of the evaluation.

Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Multivariate Monte Carlo sensitivity analyse were used to consider the random variation across the input parameters and to report cost-effectiveness acceptability curves.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

In further sensitivity analysis, certain assumptions made in the base case model were examined; the treatment duration was reduced to a maximum of 24 weeks for patients with genotype non-1, and to 12 weeks for patients identified as having insufficient change in viral load at week 12. The impact of assuming different levels of improvement in HRQOL and using a 30 year time horizon was also considered.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

Conclusions/ Implications

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

For patients with chronic hepatitis C and genotype on-1, antiviral treatment compared to no treatment at a mild stage, is cost-effective. For patients with genotype 1, antiviral therapy at a mild disease stage is not cost-effective.

What are the implications of the evaluation for practice?

For patients with mild chronic hepatitis C and genotype non-1, where treatment with interferon α or pegylated interferon α and ribavarin is cost-effective, liver biopsy prior to treatment is no longer justified. For patients with genotype 1, where early intervention is not cost-effective, monitoring by liver biopsy and providing pegylated interferon and ribavarin only to those cases that progress to moderate disease is the most cost-effective strategy.

Appendix 24 – Costing protocols for patient evaluation and for monitoring during and post treatment

Evaluation Of A New Patient With Confirmed HCV

ITEM		(£)
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
Clinic administration (pulling notes etc)		£3.58
STAFF cost for outpatient appointment		£35.59
Tests and investigations		
Hepatitis C Screen (HCV RNA)	Virology	£11.33
HBV (for 50% of patients)	Virology	£5.18
LIVER FUNCTION TESTS	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		£236.90

FURTHER INVESTIGATIONS OF A PATIENT WITH HCV CONSIDERED FOR TREATMENT

ITEM		(£)
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
Clinic administration (pulling notes etc)		£3.58
STAFF cost for outpatient appointment		£24.54
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		£0.00
Additional costs for time on ward estimated at 10%		£0.00
TOTAL		£635.95

MONITORING DURING ACTIVE TREATMENT WITH INTERFERON ALFA (24 WEEKS)

ITEM		(£)
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
Clinic administration (pulling notes etc)		£3.58
STAFF cost for outpatient appointment		£44.43
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		**£210.74**

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
Clinic administration (pulling notes etc)		£3.58
Staff cost for appointment		£15.72
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		**£27.36**

Hence total cost for basic assessments	£136.82

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
Clinic administration (pulling notes etc)		£3.58
Staff cost for appointment		£15.72
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		**£29.76**

Hence total cost for 4 & 8 week assessments	£59.53

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
Clinic administration (pulling notes etc)		£3.58
Staff cost for appointment		£19.58

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		**£200.50**

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
Clinic administration (pulling notes etc)		£3.58
Staff cost for appointment		£23.44
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		**£70.62**

MONITORING DURING INTERFERON ALFA TREATMENT (48 weeks)

All patients would receive the treatments as per the 24 week patients		
First appointment		£210.74
Basic assessments (weeks 1,2,6,16 and 20)		£136.82
Week 4 and week 8 assessments		£59.53
Week 12 assessment		£200.50
Week 24 assessment		£70.62
Total		£678.21
Subsequent assessments: Weeks 28, 32, 40 & 44 (as basic assessments, plus pregnancy test)		
Per assessment		£27.61
Total assessments		£110.44
Week 36 (as week 12, excluding Viral load)		£48.23
Week 48 (as week 24)		£70.62

Total monitoring cost for 48 week patient	**£907.50**

SURVEILLANCE OF PATIENTS FAILING, REFUSING OR UNSUITABLE FOR TREATMENT (PER YEAR)

ITEM		(£)
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		(£)
4 weeks post treatment		
Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)		£10.48
Clinic administration		£3.58
Total staff costs		£14.06
FBC	Haematology	£2.20
INR	Haematology	£2.40
U & Es	Chem Path	£5.60
LFT	Chem Path	£3.60
Pregnancy test (5%)	Chem Path	£0.25
TOTAL		**£28.10**

12 weeks post treatment		
Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)		£10.48
Clinic administration		£3.58
Total staff costs		£14.06
FBC	Haematology	£2.20
U & Es	Chem Path	£5.60
LFT	Chem Path	£3.60
AFP	Chem Path	£1.31
Pregnancy test (5%)	Chem Path	£0.25
TOTAL		**£27.01**

24 weeks post treatment

Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)		£10.48
Clinic administration		£3.58
Total staff costs		£14.06
U & Es	Chem 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		**£84.14**

Total monitoring costs per year	£139.25

Appendix 25 – Variables and probability distributions used in the probabilistic model.

Description	Distribution type, parameters and expected value
Transition probabilities	
TP: mild to moderate CHC	Beta, alpha = 38.0859, beta = 1485.3516; Expected value: 0.025
TP: moderate CHC to compensated cirrhosis.	Beta, alpha = 26.9050, beta = 700.2582; Expected value: 0.037
TP: cirrhosis to HCC	Beta, alpha = 1.9326, beta = 136.1074; Expected value: 0.014
TP: cirrhosis to decompensated disease	Beta, alpha = 14.6168, beta = 360.1732; Expected value: 0.039
TP: cause-specific excess mortality for decompensated disease	Beta, alpha = 147.0300, beta = 983.9700; Expected value: 0.13
TP: HCC excess mortality	Beta, alpha = 117.1033, beta = 155.2300; Expected value: 0.43
TP: DC to liver transplant	Beta, alpha = 6.5256, beta = 210.9945; Expected value: 0.03
TP: LT to Death	Beta, alpha = 16.2762, beta = 61.2294; Expected value: 0.21
TP: post-LT to death	Beta, alpha = 22.9017, beta = 378.8825; Expected value: 0.057
Health State Costs	
Cost of SVR state	Gamma, alpha = 28.8141, beta = 8.9887; Expected value: 259
Cost of mild CHC state	Gamma, alpha = 25.6995, beta = 5.3698; Expected value: 138.0011751
Cost of moderate CHC state	Gamma, alpha = 88.8502, beta = 8.0698; Expected value: 717
Cost of compensated cirrhosis state	Gamma, alpha = 24.2342, beta = 46.9584; Expected value: 1138
Cost of decompensated cirrhosis state	Gamma, alpha = 36.0249, beta = 253.1582; Expected value: 9120
Cost of hepatocellular carcinoma state	Gamma, alpha = 18.1081, beta = 448.8045; Expected value: 8127
Cost of liver transplant	Gamma, alpha = 89.7536, beta = 304.5004; Expected value: 27,330
Cost of care in year in which transplant occurs	Gamma, alpha = 13.7788, beta = 686.4168; Expected value: 9458
Cost of care in years after liver transplant occurs	Gamma, alpha = 15.2189, beta = 91.0053; Expected value: 1385
Health State Utilities	
utility of SVR (SVR from mild CHC health state)	Beta, alpha = 65.8678, beta = 14.4588; Expected value: 0.82
utility of SVR (SVR from mild CHC health state)	Beta, alpha = 58.0608, beta = 22.5792; Expected value: 0.72
utility of mild CHC state	Beta, alpha = 521.2375, beta = 155.6943; Expected value: 0.77
utility of mild CHC state while on treatment (non-Peg IFN!)	Beta, alpha = 115.7063, beta = 59.6063; Expected value: 0.66
utility of moderate CHC state	Beta, alpha = 168.2461, beta = 86.6723; Expected value: 0.66
utility of compensated cirrhosis state	Beta, alpha = 47.1021, beta = 38.5381; Expected value: 0.55
utility of decompensated cirrhosis state (and also HCC/ LT1)	Beta, alpha = 123.7500, beta = 151.2500; Expected value: 0.45
Treatment effects	
Non-pegylated interferon treatment effect for SVR - from mild Hep C trial	Beta, Integer parameters only, n = 98, r = 32; Expected value: 0.33
SVR for non-peg IFN in moderate/ severe disease	Beta, Integer parameters only, n = 453, r = 198; Expected value: 0.44
SVR for peg IFN in mild disease	Beta, Integer parameters only, n = 110, r = 55; Expected value: 0.50
SVR for peg IFN in moderate/ severe disease	Beta, Integer parameters only, n = 444, r = 247; Expected value: 0.56
Treatment duration mean and std dev from mild Hep C trial	Normal, Mean = 37.8, Std Dev = 15.6/sqrt(98); Expected value: 37.8