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[1] Department of Medicine, St Mary's Hospital, London, UK
[2] Collaborative Centre for Economics of Infectious Disease, Health Services Research Unit, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, UK

* Corresponding author

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Abstract

Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation

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[1] Department of Medicine, St Mary's Hospital, London, UK

[2] Collaborative Centre for Economics of Infectious Disease, Health Services Research Unit, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, UK

* Corresponding author

Objectives: To determine whether combined therapy with interferon-α and ribavirin was more effective and cost-effective than no treatment for patients with mild chronic hepatitis C.

Design: A multicentre, randomised, controlled, non-blinded trial assessed the efficacy of combination therapy. A Markov model used these efficacy data combined with data on transition probabilities, costs and health-related quality of life (HRQoL) to assess the lifetime cost-effectiveness of the intervention.

Setting: A multicentre NHS setting.

Participants: Treatment-naive, adult patients with histologically mild chronic hepatitis C (Ishak necroinflammatory scores <4 and fibrosis scores <3 on liver biopsy).

Interventions: Patients were randomised to receive interferon-α and ribavirin for 48 weeks or no treatment (control).

Main outcome measures: The primary outcome measure was the proportion of patients having a sustained virological response (SVR), measured at 6 months after cessation of therapy. Secondary outcome measures were: the ability of early phase kinetics to predict the eventual outcome of treating mild disease; HRQoL measured using the Short Form 36 and EuroQol (5 Dimensions) questionnaires, and the cost per quality-adjusted life-year (QALY) of interferon-α and ribavirin for mild disease compared with no treatment.

Results: In the treatment group, 32 out of 98 patients (33%) achieved an SVR. Patients infected with genotype 1 had a lower SVR than those infected with genotype non-1 (18% versus 49%, $p = 0.02$). No patients who failed to achieve a 2-log drop in viral load at 12 weeks achieved an SVR. HRQoL fell during treatment and rose with treatment cessation. For patients having an SVR there were modest improvements in HRQoL at 6 months post-treatment. The mean cost per QALY gained was £4535 for 40-year-old patients with genotype non-1 and £25,188 for patients with genotype 1. For patients with genotype 1 aged 65, providing interferon-α and ribavirin for mild disease led to fewer QALYs gained, and a mean cost per QALY of £53,017. The model using efficacy estimates from the literature, showed that the cost per QALY gained from providing pegylated interferon α-2b and ribavirin at a mild stage rather than a moderate stage was £7821 for patients with genotype non-1 and £28,409 for patients with genotype 1.

Conclusions: Based on the evidence collected in this study, interferon-α and ribavirin treatment for mild chronic hepatitis C patients is in general cost-effective at the £30,000 per QALY threshold previously used by policy-makers in the NHS. For patients with chronic hepatitis C aged 65 or over with genotype 1, antiviral treatment at a mild stage does not appear cost-effective. Further research is required on the cost-effectiveness of pegylated interferon and ribavirin, in particular the intervention's long-term impact on HRQoL and health service costs requires further evaluation. Further research is also needed to develop predictive tests, based on pharmacogenomics, that can identify those cases most likely to respond to antiviral therapy. Liver biopsy before treatment no longer appears justified apart from for older patients (aged 65 or over) with genotype 1. However, further research should monitor the impact this strategy would have on costs and outcomes.

Contents

List of abbreviations

ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the curve
BNF	British National Formulary
CEA	cost-effectiveness analyses
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRF	case-report form
CT	computed tomography
DGH	district general hospital
EOTR	end of treatment response
EQ-5D	EuroQol 5 Dimensions
F	female
GGT	γ-glutamyltransferase
HAI	Histological Activity Index
Hb	haemoglobin
HbA_{1c}	glycosylated haemoglobin
HB_sAg	serum hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDU	high-dependency unit
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
INR	international normalised ratio
IPA	Inflammation, Parenchymal damage, Architecture
ITT	intention to treat
IVDU	intravenous drug use
LREC	local research ethics committee
M	male
MCS	mental component summary score
MCV	mean corpuscular volume
MRC	Medical Research Council
MREC	multicentre research ethics committee
MRI	magnetic resonance imaging
NA	not applicable
NB	net benefit
NICE	National Institute for Health and Clinical Excellence
ns	not significant
OLS	ordinary least squares
OR	odds ratio
PCR	polymerase chain reaction
PCS	physical component summary score
PPV	positive predictive value
QALY	quality-adjusted life-year
RBC	red blood cell
RCS	Royal College of Surgeons
RCT	randomised controlled trial
RFLP	restriction fragment length polymorphism
ROC	receiver operating characteristic
SD	standard deviation
SF-36	Short Form 36
SVR	sustained virological response
TIPPS	transjugular intrahepatic portosystemic shunt
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

The objectives of the study were to determine whether combined therapy with interferon-α and ribavirin was more effective and cost-effective than no treatment for patients with mild chronic hepatitis C.

Methods

Design and setting

A multicentre, randomised, controlled, non-blinded trial (RCT) assessed the efficacy of combination therapy. A Markov model used these efficacy data combined with data on transition probabilities, costs and health-related quality of life (HRQoL) to assess the lifetime cost-effectiveness of the intervention.

Participants

Treatment-naive, adult patients with histologically mild chronic hepatitis C (Ishak necroinflammatory scores <4 and fibrosis scores <3 on liver biopsy).

Intervention

Participants were randomised to receive interferon-α and ribavirin for 48 weeks or no treatment (control).

Main outcome measures

The primary outcome measure was the proportion of patients having a sustained virological response (SVR), measured at 6 months after cessation of therapy. Secondary outcome measures were: the ability of early phase kinetics to predict the eventual outcome of treating mild disease; HRQoL measured using the Short Form 36 and EuroQol (5 Dimensions) questionnaires, and the cost per quality-adjusted life-year (QALY) of interferon-α and ribavirin for mild disease compared with no treatment.

Results

In the treatment group, 32 out of 98 patients (33%) achieved an SVR. Patients infected with genotype 1 had a lower SVR than those infected with genotype non-1 (18% versus 49%, $p = 0.02$). No patients who failed to achieve a 2-log drop in viral load at 12 weeks achieved an SVR. HRQoL fell during treatment and rose with treatment cessation. For patients having an SVR there were modest improvements in HRQoL at 6 months post-treatment. The mean cost per QALY gained was £4535 for 40-year-old patients with genotype non-1 and £25,188 for patients with genotype 1. For patients with genotype 1 aged 65, providing interferon-α and ribavirin for mild disease led to fewer QALYs gained, and a mean cost per QALY of £53,017. The model using efficacy estimates from the literature, showed that the cost per QALY gained from providing pegylated interferon α-2b and ribavirin at a mild stage rather than a moderate stage was £7821 for patients with genotype non-1 and £28,409 for patients with genotype 1.

Conclusions

Implications for healthcare

Based on the evidence collected in this study, interferon-α and ribavirin treatment for mild chronic hepatitis C patients with genotype non-1 is effective, and in general cost-effective at the £30,000 per QALY threshold previously used by policy-makers in the NHS. For patients with chronic hepatitis C aged 65 or over with genotype 1, antiviral treatment at a mild stage does not appear cost-effective.

Recommendations for research

- For patients with genotype 1 the estimates of cost-effectiveness were sensitive to the gain in HRQoL following an SVR. Further research is required to investigate the long-term HRQoL for genotype 1 patients who have had an SVR.
- To provide a full assessment of the cost-effectiveness of pegylated interferon-α and ribavirin at a mild compared with a moderate stage, research is needed to assess the impact of pegylated interferon-α and ribavirin on SVRs, HRQoL and health service costs.
- The use of predictive tests based on pharmacogenomics to target therapy to those most likely to respond should now be developed.

- For patients with mild hepatitis C liver biopsy before treatment no longer appears justified apart from for older patients (aged 65 or over) with genotype 1. However, further research should monitor the impact this strategy would have on costs and outcomes.

Chapter 1
Introduction

The scale of the hepatitis C virus epidemic

Natural history

Chronic hepatitis C virus (HCV) infection is present in 0.07% of UK blood donors[1] and 0.7% of the general population.[2] The infection is usually asymptomatic, but carries risks of significant morbidity and mortality with approximately 20% of patients progressing to cirrhosis and hepatocellular carcinoma (HCC) within 20 years.[3]

In two large studies of the natural history of liver fibrosis progression, the median times to develop cirrhosis from time of infection were 30 and 35 years.[4,5] In late-stage disease, frequent outpatient and inpatient support is required and ultimately some patients will require liver transplantation. In Europe and the USA 20–40% of liver transplants are now carried out for cirrhosis related to hepatitis C. Effective therapy before the development of these complications appears to be cost-effective.[6,7] Development of an effective treatment for patients with chronic HCV infection has major public health implications. It will decrease significantly the prevalence of disease among carriers. Furthermore, as it is likely to be many years before an effective vaccine is developed, therapy aimed at effective viral clearance will progressively reduce the viral burden and transmission in the general population.

The future of the HCV epidemic

Two groups, one American and one French, have attempted to describe the future of the HCV epidemic using different methods, but obtaining very similar results. Armstrong and colleagues[8] used data from the Third National Health and Nutrition Examination Study (NHANES III)[9] to estimate the prevalence of HCV in the USA. They then combined this with data on the age-specific incidence of acute non-A non-B viral hepatitis from the Sentinel Counties Study,[10] to model the number of people infected with HCV and the duration of their infection at time-points until 2030. Although the incidence of new infections appears to be falling owing to screening of blood products, the prevalence will continue to rise for some time yet, because of the slow natural history. The number of people infected for 20 years or more will peak around 2020. Dueffic and colleagues[11] used the observed deaths from HCC attributable to HCV from three large French cohorts to back-calculate the number of patients infected in the past, and then used these data to predict the number of HCC deaths related to HCV until 2025. As in the American study, deaths due to HCV are predicted to peak around 2020, with between three and four times the number of HCC cases that are seen currently. On the same basis, the prevalence of decompensated cirrhosis would also be predicted to rise. The increased costs of managing a higher prevalence of end-stage and post-transplant care would lead to added pressure on limited healthcare resources, especially given the scarcity of transplant donors.

The models discussed assume that no treatment will be given. If patients can be cured then the numbers of HCC cases predicted would be reduced. It will be important, however, to treat the 'right' patients, as providing therapy for those destined only to progress very slowly may make little impact on the epidemiological 'hump' of HCC cases, whereas treating those with more rapid fibrosis and a poorer prognosis will impact greatly on morbidity and mortality and may, consequently, be more cost-effective.

The rate of progression to cirrhosis varies between individuals. Cirrhosis is the end result of progressive deposition of fibrous tissue during chronic hepatitis. Different subgroups of patients progress at different rates. An improved understanding of the natural history of HCV would be very valuable. It would enable accurate prognostic information to be given to infected patients. It would also facilitate the planning of healthcare provision, with the prediction, for example, of likely numbers of people with HCC in the future based on the number of infected individuals at present. Cost-effectiveness models require accurate transition rates to estimate the long-term impact of antiviral therapy.

Clinical perspective

Clinical assessment of hepatitis C

The assessment of liver fibrosis in the clinical setting relies on liver biopsy and interpretation by a histopathologist using semi-quantitative scoring systems. Several scoring systems are in use for the various liver diseases and generally comprise a necroinflammatory activity score (grade) and a fibrosis score (stage). Fibrosis ranges from zero (no fibrosis) to a maximum score denoting cirrhosis. Two widely used systems for hepatitis C are the modified Histological Activity Index (HAI)[12] and METAVIR[13] scores. Both systems use the morphological features of the liver biopsy to assign a score based on progression of fibrosis from none to gradual expansion of fibrous tissue in the portal areas followed by formation of septa, which eventually bridge portal tracts and central veins and ultimately form the nodules of cirrhosis (*Tables 1* and *2*). The modified HAI has a necroinflammatory score ranging between 0 and 18. The modified HAI (Ishak)[12] is most frequently used in the UK and is the one used in this study.

Patients chronically infected with HCV pass through these progressive stages of fibrosis. It is generally accepted that 'mild' disease is represented by a fibrosis score of 2 or less and a necroinflammatory score of 3 or less. Cirrhosis is represented by a fibrosis score of 6. 'Moderate–severe' disease represents degrees of fibrosis in between.

TABLE 1 *Fibrosis staging in hepatitis C using the modified HAI system[12]*

Stage	
0	No fibrosis
1	Fibrous expansion some portal areas ± short fibrous septa
2	Fibrous expansion most portal areas ± short fibrous septa
3	Fibrous expansion most portal areas + occasional portal–portal bridging
4	Fibrous expansion most portal areas + marked portal–portal bridging and portal–central vein bridging
5	Marked bridging portal–portal and/or portal–central vein with occasional nodules
6	Cirrhosis

TABLE 2 *Fibrosis staging in hepatitis C using the METAVIR system[13]*

Stage	
0	No fibrosis
1	Portal fibrosis
2	Few septa
3	Many septa
4	Cirrhosis

Mild hepatitis C

The distinction between mild and moderate disease is an arbitrary definition. It is impossible to tell from a single biopsy showing mild disease whether this reflects a good prognosis or early disease that will progress. UK[14–16] and European[17] guidelines advocate that patients with HCV who have only mild histological changes on liver biopsy should not routinely be treated with antiviral agents but should be managed by observation, with periodic liver biopsies to assess for progression. The original guidelines[14] suggesting a watch and wait policy for mild disease were produced at a time when interferon-α monotherapy was the only treatment available for HCV. Interferon-α had low sustained virological response (SVR) rates and high costs.

Currently available antiviral therapies

Definition of complete (sustained) virological response

A complete response is defined as the sustained loss of HCV RNA with normalisation of transaminase values, 6 months after discontinuing treatment: if relapses occur, the majority occur within this time.[18] It is also now recognised that viral levels usually fall as the transaminase levels fall, but HCV RNA may remain detectable at low titre in the presence of normal transaminase values.[19]

Combined interferon-α and ribavirin treatment

Large multicentre studies have confirmed the benefit of combination therapy over interferon monotherapy in treatment-naive[20,21] and relapsed[22] chronic hepatitis C patients. In these studies combination therapy given for 48 weeks showed SVRs of 38–43% compared with response rates of 6–19% for interferon monotherapy. The factors associated with response to treatment were age 40 years or younger, female gender, minimal fibrosis, viral genotype 2 or 3 and baseline viral load less than 2 million copies ml^{-1}. In patients with viral genotype 1, 48 weeks of treatment was associated with a better response than treatment for 24 weeks.

Since this trial began, the increased efficacy of the pegylated interferons over standard interferon-α has been demonstrated in a number of randomised controlled trials (RCTs).[23,24] Manns and colleagues[23] looked at two doses of peginterferon-α-2b plus ribavirin in comparison with standard interferon-α and ribavirin. For genotype 1, the SVRs were 42% and 34% in the higher and lower dose peginterferon groups, respectively, compared with 33% in the standard interferon-α plus ribavirin group. For genotypes 2 and 3 combined the response rates were 82%, 80% and 79%. Fried and colleagues[24] compared peginterferon-α-2b plus ribavirin, standard interferon-α plus ribavirin and peginterferon-α-2b plus placebo. For genotype 1 the SVRs were 46%, 36% and 21%. For genotypes 2 and 3 they were 76%, 61% and 45%. These trials demonstrate clearly the improvement in SVR once ribavirin is combined with interferon-α, and the superior SVR when pegylated interferons are used. In terms of response rates there appears to be little advantage in treating patients with genotypes 2 and 3 with peginterferon, although for genotype 1 the advantage is clear and the peginterferons, with their once weekly dosing, are generally better tolerated by patients.

Retreatment of non-responders and relapsers

Despite considerable treatment advances there are patients who fail to respond to treatment or who initially respond then relapse. Trials addressing the management of these patients naturally lag behind the trials for naive patients. From the literature a number of points are clear: patients who had an initial response but then relapsed on interferon-α monotherapy should receive combination therapy either with standard[22] or pegylated interferon-α and ribavirin;[25] and patients who have had no initial response to interferon monotherapy do not respond as well as those who have relapsed and probably should not be further treated with standard interferon-α based regimens on current evidence, although emerging evidence from peginterferon-α and ribavirin treatment is encouraging.[25] There is no current evidence for people who failed to respond to a combination of interferon-α and ribavirin and these patients should await results of ongoing trials and the development of new agents.

Potential benefits of treating mild hepatitis C

Do those with mild disease progress and therefore need therapy?

Early studies on the natural history of HCV suggested that the majority of those infected would suffer from no long-term sequelae.[26] While this may be true for some patients, increasingly emphasis is turning to the rate of fibrosis within individuals.[4,5] It may be that someone with mild disease has only a short duration of infection and is destined to progress to cirrhosis rapidly.

Are response rates better if treatment is given early in infection?

Treatment of patients (mainly exposed healthcare workers) with acute HCV results in SVRs in excess of 95%,[27] whereas treatment once cirrhosis has been reached is characterised by a poor virological response.[28] These figures need to be seen in the context of a high rate of spontaneous clearance in acute disease but not once infection is established. Previous trials of interferon-α and ribavirin in combination showed a response rate for those with moderate disease that was intermediate. Factors associated with SVR included less severe histology.[21,29] Two small studies have been published specifically addressing the provision of treatment to patients with mild HCV.[30,31] Queneau and colleagues[30] compared interferon-α monotherapy with no treatment in 80 patients with mild disease and achieved an 18% SVR in the treatment group. Verbaan and colleagues[31] compared interferon-α plus ribavirin with interferon-α monotherapy in 116 treatment-naive patients. Fifty-four percent of the patients on dual therapy and 20% of those on monotherapy achieved SVRs. For those patients with genotype 1, SVRs were 28% and 4% for dual and monotherapy compared with 81% and 36% for genotype non-1. Results in this trial were better than the existing published trials for all comers.[20,21]

Seen overall, these studies suggest that SVR rates may fall as fibrosis progresses. Deferment of therapy in individuals with mild disease may therefore be a missed window of opportunity.

Extrahepatic manifestations and impact of HCV on health-related quality of life

It is increasingly clear that hepatitis C has an impact on patients beyond liver damage. Neither of the previous studies looking at mild disease[30,31] included data on health-related quality of life (HRQoL) or the impact of treating mild disease on health service costs. Even patients with liver damage associated with mild hepatitis C report disabling symptoms such as fatigue, malaise, bodily pain and joint symptoms. Reduced HRQoL is common in afflicted individuals[32–34] and is at least partly independent of how the patient acquired the infection.[35] Recently it has been shown that people with hepatitis C have impaired

cognitive function and evidence of CNS involvement.[36,37] Cognitive impairment has also been demonstrated in people with mild liver disease.[38] Studies assessing the impact of treatment with interferon-α on HRQoL show that following successful treatment patients have significant improvement in their total HRQoL score and in individual categories including work and sleep.[33,34,39] Therapy for patients with mild hepatitis C may therefore benefit patients for non-hepatological reasons.

Patient compliance and HRQoL

Interferon-α given at a dose of 3 MU three times weekly and ribavirin for 24–48 weeks appears well tolerated. However, 10% of patients failed to complete therapy in the West London Hepatitis Group,[40] with similar rates in published randomised trials of combination therapy.[20–22] Symptoms such as depression, myalgia, lethargy, influenza-type symptoms, and biochemical and haematological abnormalities are common on treatment and account for much of the dropout in the trials. A fall in HRQoL while on treatment followed by return to baseline after cessation (and improvement in those who achieve an SVR) is well documented.[34] Adherence to therapy is associated with favourable outcome.[41] The ability of patients with mild hepatitis C to tolerate and complete treatment will have implications for the effectiveness and cost-effectiveness of interferon-α and ribavirin therapy.

Cost-effectiveness

The cost-effectiveness of antiviral therapy has been examined for interferon-α monotherapy,[6] combination therapy with standard interferon-α and ribavirin,[7] and pegylated interferon-α and ribavirin.[42] Each of these studies evaluated the relative cost-effectiveness of treatment for cases with chronic hepatitis C. Although the costs of antiviral therapy may be high, it is recognised that virologically successful interferon therapy will prevent the long-term complications of the disease such as decompensated cirrhosis and hepatocellular carcinoma. These health states are associated with high health service costs, high mortality rates and poor HRQoL. RCTs have insufficient periods of follow-up to assess the impact of antiviral therapy on these long-term consequences of HCV, and so models have been used. These models used epidemiological data on disease progression to extrapolate from trial results and estimate the cost-effectiveness of new interventions over the long term.[6,43–45] The results from these models for chronic hepatitis C suggest that antiviral therapy leads to gains in quality-adjusted life-years (QALYs) that justify the additional costs. The costs per QALY gained were similar to those for other interventions commonly provided by the NHS, such as coronary artery bypass grafting, and treatment of diabetes and hypertension.[46] The National Institute for Health and Clinical Excellence (NICE) has recommended that interferon-α and ribavirin and more recently pegylated interferon-α and ribavirin[47] should be provided for patients with moderate disease or cirrhosis. The decisions to recommend treatment for these later disease stages were based on published trials[20,21,23,24] and cost-effectiveness studies[7,42,48–50] that suggested that these therapies were worthwhile for patients with moderate disease or cirrhosis. However, for patients with mild hepatitis C the absence of data available on the effectiveness and cost-effectiveness of antiviral treatment has meant that treatment is not recommended for these cases.

For patients with mild hepatitis C there is a lack of evidence on the relative cost-effectiveness of antiviral therapy. A previous model for mild hepatitis C suggested that interferon-α monotherapy was likely to be cost-effective.[43] However, this model had certain methodological problems. In particular, there were no effectiveness data specifically for cases with mild hepatitis C, expert opinion was used to estimate HRQoL and healthcare costs, and the rate of disease progression from mild disease was largely unknown. The rate at which mild cases progress is likely to be very important in determining cost-effectiveness, as if patients progress slowly and remain in the mild state for decades, then the costs of the intervention are unlikely to be justified.

In light of this evidence base, a full assessment of the cost-effectiveness of combination therapy (interferon-α and ribavirin) was needed. As part of this study a model was developed specifically for mild hepatitis C (Chapter 4), and costs (Chapter 5) and HRQoL (Chapter 6) were empirically estimated for each disease stage. The results of the cost-effectiveness analysis are presented in Chapter 7.

Viral kinetics: rate of clearance or fall of HCV RNA

Viral kinetics during treatment can be used to predict which patients will have an SVR. Evidence suggests that the early clearance of viral RNA (by the second or third month of treatment) may predict SVR.[51] In addition, the persistence of HCV viraemia during the early period of treatment

predicts those patients who will not derive long-term benefit from therapy.[24,25] Manns and colleagues[23] found that those who failed to achieve at least a 2-log drop in viral load by 12 weeks of therapy with pegylated interferon-α and ribavirin only had a 3% chance of eventual SVR.[23] If the early virological response (either absolute or rate of fall in viral load) can be used to estimate the likelihood of SVR this could reduce the duration of administration of ineffective therapy, by stopping treatment early in those patients unlikely to have an SVR. This would reduce the duration of side-effects and the costs of the intervention.

Studies of early viral kinetics have demonstrated a two-phase decline in viral load following initiation of therapy. The first (steep) phase occurs in the first 24–48 hours and represents the blockage of hepatocytes infection by interferon-α. The second phase decline is due to clearance of infected hepatocytes. The exponent of this second phase (λ) predicts SVR (the steeper the more likely).[52]

Aims of the study

This study was commissioned by the NHS HTA Programme and was conducted within an NHS framework. This is important in this area of healthcare provision, as the levels of supervision and logistical back-up provided by pharmaceutical industry-sponsored studies produce results that may not translate to the NHS setting.

Study design

A UK-based, multicentre RCT assessed the efficacy of combination therapy. A Markov model used efficacy results from the RCT, combined with estimates of transition probabilities and costs of each disease stage, to estimate the lifetime cost-effectiveness of the intervention.

The primary aim is:

- to determine whether the combination of interferon-α (3 MU three times weekly) and ribavirin (1000–1200 mg day^{-1}) for 48 weeks is more effective than no treatment in mild chronic HCV infection.

The secondary aims are:

- to determine the effect of genotype on the probability of responding to the combination of interferon and ribavirin
- to determine whether the early viral kinetics or host factors can predict a long-term response in combination therapy in mild hepatitis C
- to determine the effect of the treatment on HRQoL
- to assess the cost of the treatment regimen: costs of therapy, other costs to the health service of mild disease, and the health service costs of later disease stages
- to assess the potential cost savings from treating patients with mild hepatitis C and preventing disease progression
- to assess the cost-effectiveness of treatment with interferon-α and ribavirin at a mild stage compared with no treatment for patients with mild hepatitis C.

Structure of the report

The structure of the report is as follows. Chapter 2 describes the design of the RCT for measuring the efficacy of the intervention in terms of SVR, HRQoL measured by the Short Form 36 (SF-36), and the use of viral kinetics for predicting response to treatment. Chapter 3 reports the results of the RCT, and these results are then used in the cost-effectiveness model described in Chapter 4. In Chapters 5 and 6, the health service costs and HRQoL estimates for each stage of the disease are reported, before the results of the lifetime cost-effectiveness analysis are presented in Chapter 7. The results of the RCT and the cost-effectiveness model are discussed in Chapter 8. Finally, Chapter 9 provides the overall conclusions of the study and details the areas for further research.

Chapter 2
Design of the RCT

Introduction

This is an RCT in a multicentre NHS setting. The study flow is shown in *Figure 1*. Patients were seen by NHS staff in parallel with their other duties. Where possible, observations were made at the same time-points as for 'standard care'.

Study population

Adult patients with mild chronic hepatitis C (Ishak necroinflammatory score <4, fibrosis score <3) not previously treated with interferon-α or another antiviral regimen were identified. Inclusion and exclusion criteria are shown in *Tables 3* and *4*.

A histological diagnosis consistent with mild chronic hepatitis C was confirmed by the trial histopathologist at the coordinating centre and a report of the pretreatment liver biopsy performed within 1 year of the screening visit was available before screening. Ethics committee approval was obtained both centrally (MREC/98/2/12) and from each local centre committee (LREC). Written informed consent was obtained.

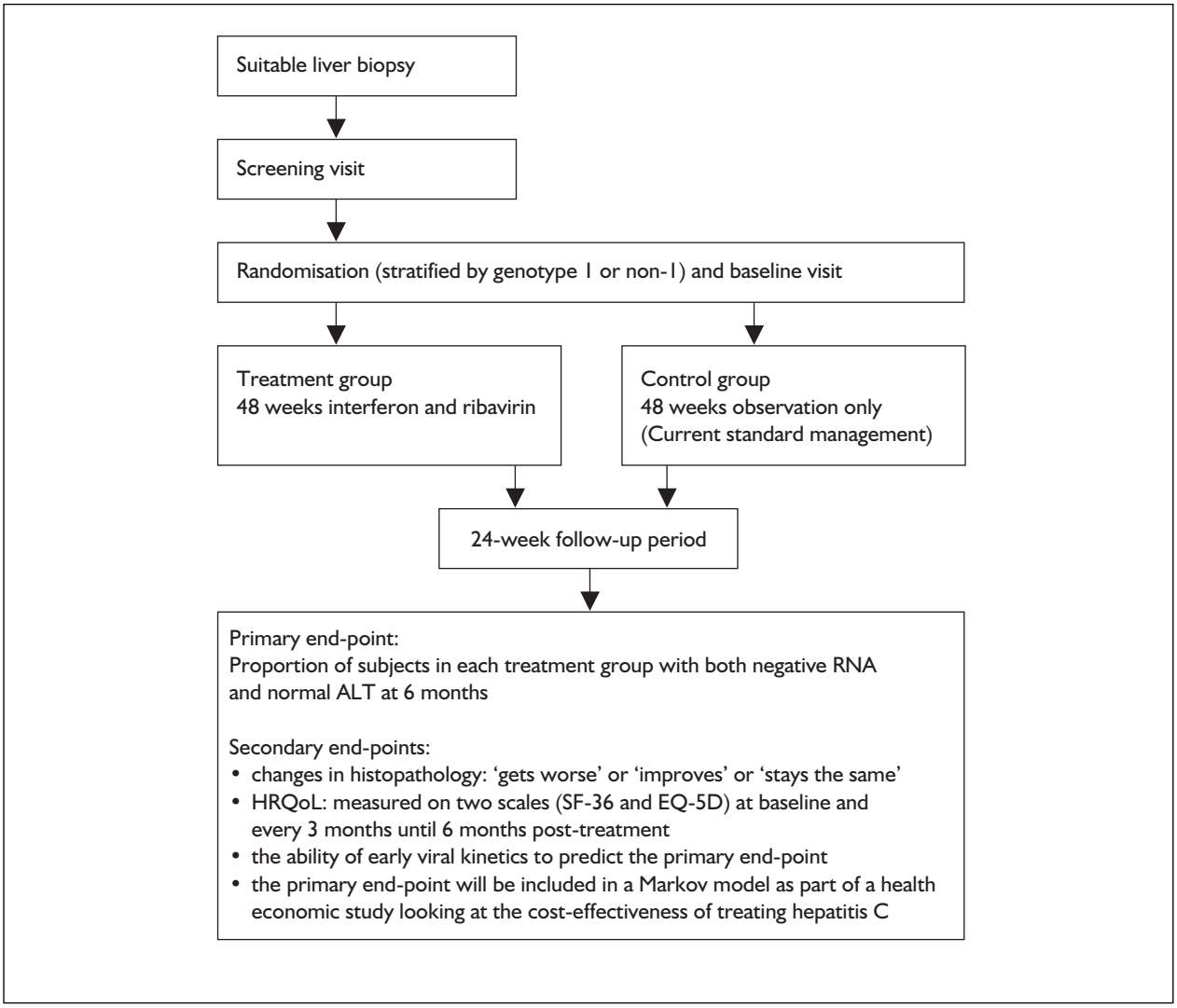

FIGURE 1 *Study flowchart. ALT, alanine aminotransferase; EQ-5D, EuroQol 5 Dimensions.*

TABLE 3 *Inclusion criteria*

Adult, male or female, minimum age of 18 years
Serum positive for HCV by qPCR assay
Liver biopsy within 1 year before entry to the protocol. Histological diagnosis consistent with mild chronic hepatitis (Ishak necroinflammatory score <4, fibrosis score <3)
Compensated liver disease with the following minimum haematological, biochemical and serological criteria at the screening visit:
Hb ≥ 12 g dl^{-1} for women and ≥ 13 g dl^{-1} for men
WBC ≥ 3000 mm^{-3}
Granulocyte count ≥ 1500 mm^{-3}
Platelets ≥ 100,000 mm^{-3}
Prothrombin time/INR within normal limits
Bilirubin within normal limits (unless non-hepatitis-related factors such as Gilbert's disease explain a rise)
Albumin stable and within normal limits
Serum creatinine within normal limits
Fasting blood sugar within normal limits for non-diabetic patients
HbA_{1c} <8.5% for diabetic patients (whether diet controlled or on medication)
TSH within normal limits (patients requiring medication to maintain TSH levels in the normal range were eligible if all other inclusion/exclusion criteria were met)
ANA <1:160
Anti-HIV antibody negative
Serum hepatitis B surface antigen (HB_sAg) negative
Confirmation and documentation that sexually active patients of childbearing potential were practising adequate contraception during the treatment period and for 6 months after discontinuation of therapy. A serum pregnancy test was obtained at entry before the initiation of treatment and had to be negative. Female patients could not breast-feed

ANA, antinuclear antibodies; Hb, haemoglobin; HbA_{1c}, glycosylated haemoglobin; HB_sAg, serum hepatitis B surface antigen; INR, international normalised ratio; qPCR, quantitative polymerase chain reaction; TSH, thyroid-stimulating hormone; WBC, white blood cell count.

Treatment of the study group

Assessments before enrolment in study

All patients were required to attend a screening visit before enrolment in the trial. A complete medical history was taken and a physical examination performed. The following data were recorded: demographic data, vital signs/weight/height, cardiovascular, respiratory and abdominal examinations, hepatitis signs and symptoms, past medical history, current medications, chest X-ray, ECG, ophthalmoscopy (if diabetic or hypertensive) and laboratory observations. All results of the screening evaluations were required before patient randomisation.

Assignment to treatment group

Patient numbers were assigned sequentially and corresponded to a number on a case-report form (CRF). Patients who met the criteria for entry were assigned by a central randomisation procedure (to ensure the balancing of patients between and within sites) by the trial coordination office. Randomisation was stratified within centres according to viral genotype (1 versus non-1) as follows: interferon-α plus ribavirin for 48 weeks or no treatment for 48 weeks.

Administration of study medications

Interferon-α-2b (Shering Plough) was administered subcutaneously at a dose of 3 MU three times a week (3 MU interferon-α-2b solution = 0.2 ml of an 18 MU multidose injection pen). Ribavirin was administered orally and twice daily. Ribavirin dose was based on the patient's body weight as shown in *Table 5*.

Evaluations during treatment

Patients were evaluated by the study staff on days 1, 3, 7, 10 and 14, and then at the end of weeks 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48. The following evaluations were performed at every visit: vital signs/weight, adverse events, concurrent illnesses, concomitant medications, full blood count [Hb, red blood cells (RBCs), mean corpuscular volume (MCV), WBC and differential, platelet count], liver function tests [ALT, alkaline phosphatase, bilirubin, γ-glutamyltransferase

TABLE 4 *Exclusion criteria*

Prior treatment with interferon-α or ribavirin
Hypersensitivity to interferon-α or ribavirin
Participation in any other clinical trial within 30 days of entry to this protocol
Treatment with any investigational drug within 30 days of entry to this protocol
Prior treatment for hepatitis with any other antiviral or immunomodulatory drug within the previous 2 years
Any other cause for the liver disease other than chronic hepatitis C, including but not limited to: – coinfection with hepatitis B virus – haemochromatosis (iron deposition >2+ in liver parenchyma) – α_1-antitrypsin deficiency – Wilson's disease – autoimmune hepatitis – alcoholic liver disease – obesity-induced liver disease – drug-related liver disease
Haemophilia or any other condition preventing the patient from having a liver biopsy, including anticoagulant therapy
Haemoglobinopathies (e.g. thalassaemia)
Evidence of advanced liver disease, such as history or presence of ascites, bleeding varices, encephalopathy
Patients with organ transplants
Any known pre-existing medical condition that could interfere with the patient's participation in and completion of the protocol such as: – pre-existing psychiatric condition (e.g. severe depression, or a history of severe psychiatric disorder) – CNS trauma or seizure disorder requiring medication – significant cardiovascular dysfunction within the past 6 months (e.g. angina, congestive cardiac failure, recent myocardial infarction, severe hypertension or significant arrhythmia) – patients with an ECG showing clinically significant abnormalities – poorly controlled diabetes mellitus – chronic pulmonary disease (e.g. chronic obstructive pulmonary disease) – immunologically mediated disease (e.g. inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune haemolytic anaemia, scleroderma, severe psoriasis, cryoglobulinaemia with vasculitis) – any medical condition requiring, or likely to require during the course of the study, chronic systemic administration of steroids – gout
Substance abuse, such as excessive alcohol intake (>50 g day^{-1}) or erratic use of intravenous or inhaled drugs
Patients with clinically significant retinal abnormalities
Any other condition which in the opinion of the investigator would make the patient unsuitable for enrolment or that could interfere with the patient participating in or completing the protocol

TABLE 5 *Ribavirin dose*

Patient weight	Total daily dose	Regimen	Number of capsules/dose (200 mg each)
≤75 kg	1000 mg	400 mg a.m. 600 mg p.m.	2 caps a.m. 3 caps p.m.
>75 kg	1200 mg	600 mg b.d.	3 caps a.m. 3 caps p.m.

(GGT), total protein, albumin], EDTA for qPCR, serum save and urinalysis (if screening sample abnormal or persistent abnormalities).

The following evaluations were/ are performed at selected visits only:

- questionnaires [SF-36, EuroQol 5 Dimensions (EQ-5D)] at baseline, and weeks 12, 24 and 48. (Data on HRQoL were collected using the EQ-5D, as it provides an appropriate measure of HRQoL for use in the cost-effectiveness model. This is discussed in Chapter 6.)
- biochemistry (sodium, potassium, urea, creatinine, glucose, phosphate, calcium, uric acid, amylase) at weeks 12, 24 and 48, clotting (prothrombin time) at weeks 12, 24 and 48, thyroid function tests (TSH) at weeks 12, 24 and 48, and HBA_{1c} (only if diabetic) at weeks 12, 24 and 48.

Monitoring of patients during post-treatment follow-up

Following the completion of treatment (week 48), patients were evaluated by the study staff at the end of post-treatment weeks 12 and 24. The following evaluations were performed at each visit: questionnaires (SF-36, EQ-5D), vital signs/weight, adverse events, concurrent illnesses, concomitant medications, full blood count (Hb, RBC, MCV, WBC and differential, platelet count), liver function tests (ALT, alkaline phosphatase, bilirubin, GGT, total protein, albumin), EDTA for qPCR, serum save and urinalysis (if persistent abnormalities). A liver biopsy was performed at 24–48 weeks following the end of therapy. Patients who discontinued therapy during the treatment period had clinical and laboratory evaluations performed as at the end of the follow-up period at weeks 12 and 24 after discontinuation of therapy.

Management of adverse events

Trial safety was overseen by the Data and Safety Monitoring Committee. Baseline signs and symptoms were recorded before the start of study medication. During the study, all adverse events including clinically significant laboratory abnormalities were recorded. The date of onset, duration, action taken (if any), relationship to study drug, effect on study drug dosing and degree of severity of the symptoms were recorded. All treatment-emergent adverse events (baseline signs and symptoms that worsened after the initiation of treatment or new adverse events that occurred after the initiation of treatment) were recorded.

TABLE 6 *Management of main adverse events*

	Dose reduction	Discontinuation
Hb	<10 g dl^{-1} (ribavirin)	<8.5 g dl^{-1}
WBC	$<1.5 \times 10^9$ l^{-1} (interferon)	$<1.0 \times 10^9$ l^{-1}
Granulocyte count	$<0.75 \times 10^9$ l^{-1} (interferon)	$<0.5 \times 10^9$ l^{-1}
Platelet count	$<50 \times 10^9$ l^{-1} (interferon)	$<25 \times 10^9$ l^{-1}
Bilirubin		$>2.5 \times$ ULN
Creatinine		$>1.5 \times$ ULN

ULN, upper limit of normal.

TABLE 7 *Dose reduction*

	Protocol dose	Reduced dose
Interferon	3 MU three times per week	1.5 MU three times per week
Ribavirin	1000 mg per day	600 mg per day
Ribavirin	1200 mg per day	600 mg per day

Management of adverse events was generally achieved by dose reduction as shown in *Tables 6* and *7*. Patients returned for assessment at a minimum of every 2 weeks until the adverse event resolved or the patient stabilised. If the laboratory adverse event persisted but did not fall into the range for permanent discontinuation, the reduced dose of either the interferon-α or ribavirin (whichever had been reduced) was continued. After resolution of the laboratory adverse event, the dose could be increased to the full protocol dose. If the laboratory adverse event recurred, the patient was maintained at the previously tolerated reduced dose of the study medication or, at the discretion of the investigator, had their treatment discontinued.

Guidelines for dose modifications following adverse events

The following guidelines were used to determine when dose modification for an adverse event should be implemented.

Grade 1 (mild) adverse events (awareness of sign, symptom, or event but easily tolerated)

No dose adjustment for a grade 1 adverse event was required. However, more frequent evaluation was sometimes required until the adverse event resolved or the patient stabilised.

Grade 2 (moderate) adverse events (discomfort enough to cause interference with usual activity and may warrant intervention)
Patients who developed grade 2 adverse events could continue interferon-α and ribavirin at the full protocol dose. However, more frequent evaluation was required until the adverse event resolved or the patient stabilised. If, in the opinion of the investigator, dose reduction was required to maintain the patient in the study, the dose of both drugs was reduced (*Table* 7) until the adverse event remitted, at which time treatment with the full protocol dose could be resumed.

Grade 3 (severe) adverse events (incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention)
Patients who developed grade 3 adverse events (except for 'flu-like symptoms) had their doses of both drugs reduced (*Table* 7) until the adverse event returned to grade 1 or below, at which time treatment with the full protocol dose could be resumed. More frequent evaluations were required until the adverse event resolved or the patient stabilised.

If a poorly tolerated or severe adverse event persisted, despite use of the reduced dose, both the interferon-α and ribavirin therapy could be interrupted up to a maximum of 2 weeks (if therapy was interrupted for more than 2 weeks, the patient was discontinued from the study permanently). After resolution of the adverse event, treatment could be restarted at the reduced doses (*Table* 7). If these doses were tolerated for at least 2 weeks, they could be increased to the full protocol dose.

If the adverse event recurred, the patient could be maintained at the reduced doses of both drugs or, at the discretion of the investigator, be discontinued from treatment.

Grade 4 (life-threatening) adverse events (immediate risk of death)
Patients who developed grade 4 adverse events, with the exception of flu-like symptoms, had their interferon-α and ribavirin therapy discontinued permanently. The patient returned for follow-up evaluation(s) as clinically indicated or in a maximum of 2 weeks and remained under medical observation until the adverse event resolved.

Other reasons for withdrawal of patients from study
A patient could be removed from the study for any of the following reasons:

- The patient had a serious or life-threatening adverse event.
- The investigator felt that it was in the best interest of the patient.
- The patient wished to withdraw.
- The patient failed to comply with the dosing, evaluations or other requirements of the study.

Study medication

Interferon solution
Interferon-α-2b was administered by multidose injection pen subcutaneously, after attaching a needle and dialling the prescribed dose on the multidose pen. A new needle was used for each dose and was discarded safely after use.

Ribavirin capsules
Each capsule contains ribavirin 200 mg. Ribavirin capsules were stored at room temperature (15–25°C).

Health-related quality of life

HRQoL was evaluated using the SF-36, administered at baseline, treatment weeks 12, 24 and 48, and follow-up weeks 12 and 24. The SF-36 is a multipurpose, generic health status survey of general health items which uses a profile of eight dimensions and provides summary physical and mental component scores. The eight concepts are physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health.

The SF-36 was scored according to the method of the developer;[53] each scale (dimension) was scored separately and transformed to a scale ranging from 0 (worse possible score) to 100 (best possible score). Mental and physical summary scores were constructed as described in the health services research units publication.[54] Administration of the self-administered questionnaires was according to the following guidelines: only the patient was allowed to answer the questionnaires; the patient completed the questionnaire in the clinic before he or she saw the healthcare professional, before being asked about adverse events or concurrent illnesses, or undergoing clinical procedures and in ignorance of current laboratory results (i.e. ALT or HCV RNA PCR); the questionnaires were completed and left with the healthcare professional who reviewed them for completeness.

Virology

EDTA whole blood samples were sent by post and separated within 5 days, and plasma aliquots stored frozen until testing. HCV viral RNA has been shown to be stable in EDTA whole blood for up to 5 days at room temperature.[55]

Qualitative PCR was performed using the Amplicor HCV v2.0 MWP assay (Roche Molecular Systems, Pleasanton, CA, USA) with an automated nucleic acid extraction using the BioRobot 9604 (Quiagen, Hilden, Germany).[56] Results are expressed as IU ml^{-1} (1 IU = approximately 5 RNA copies). Viral genotyping was performed using restriction fragment length polymorphism (RFLP) of the 5' non-coding region.[57] Quantitative virology was performed using an automated nucleic acid extraction on the BioRobot 9604 with amplification and detection by real-time TaqMan PCR in the Prism 7000 (Applied BioSystems, Foster City, CA, USA).

Statistical plan and methods

Calculation of the power of the studies

The two large trials by Poynard and colleagues[21] and McHutchison and colleagues[20] in patients with chronic hepatitis C reported an SVR of approximately 40% for patients treated with interferon-α and ribavirin for 48 weeks. Untreated patients would have a spontaneous response rate of no more than 2% during the study period. The present study aimed for 230 patients, which would be able to estimate the treatment effect, expected to be 38%, with a precision of ±5%.

Analysis was by intention to treat (ITT). All patients randomised who received at least one dose of study medication were included in the analysis. For control patients this meant attendance at the baseline visit.

Baseline data

Baseline demographic characteristics (age and gender) and other baseline measurements (SF-36 score, method of acquisition, genotype) are summarised as appropriate by mean, median, standard deviation (SD), interquartile range, and range for continuously distributed data. Frequency counts and percentages used for categorical data. For repeated data the appropriate summaries (as above) are made and tabulated at each time-point including subjects with missing values. For continuous data (e.g. SF-36) the time-course of each subject was plotted out in treatment groups. The mean and 95% confidence interval (CI) for an individual observation were plotted against time. For categorical data (e.g. clearance) the frequency count at each time-point was tabulated.

Objectives

The objectives of this study were to compare the SVR rates for the treatment and control groups and to evaluate the safety profiles of the treatment.

Primary end-point

The primary end-point was the SVR at 24 weeks post-treatment. The viral clearance rate was defined as the proportion of patients in each treatment group with both negative RNA and normal ALT at 24 weeks post-treatment. Patients who dropped out before the final follow-up visit were classified as having failed to respond. (Patients with no data were classified as 'no clearance'.)

Secondary end-points

The secondary end-points are listed below.

Baseline factors predicting SVR

Logistic regression was used to estimate the effect of treatment on SVR adjusting for genotype, age and gender. The regression analysis reported odds ratios (ORs) and 95% confidence intervals.

Changes in histopathology

In the initial protocol, patients were to have a repeat liver biopsy 48 weeks after cessation of treatment with changes in histopathology defined as 'gets worse', 'improves' or 'stays the same'. However, because of the slow progression of the disease, a lack of power and the risk of mortality and morbidity, this was not pursued.

HRQoL

HRQoL was measured using the SF-36 at baseline and every 3 months up to 12 months post-treatment. The SF-36 score was normally distributed, and the appropriate analysis was analysis of covariance (ANCOVA) to test for differences in treatment with adjustment for baseline factors such as mode of transmission, gender and genotype. Baseline HRQoL was compared for all patients in the trial with data obtained from the Oxford Healthy Life survey.[58] HRQoL measurements before, during and after treatment and the effects of therapy upon it, were analysed between treatment and control groups and between those achieving SVR and those not.

Viral kinetics: the relationship of early viral kinetics to final treatment outcome

The viral load was plotted as a log scale against time for each individual patient. Sensitivity and specificity for the 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 for prediction of SVR was determined by receiver operating characteristic (ROC) curves.

Adverse events

Adverse events were tabulated and compared between treatment and control groups.

Chapter 3
Results of the RCT

Patient numbers and characteristics at trial baseline

Trial entry

The flow of patients in the trial is detailed in *Figure 2*. In total, 286 patients attended for the screening visit. Of these, 204 fulfilled the inclusion criteria and were randomised (100 to treatment and 104 to control). The main reasons for failing screening were refusal to participate, biopsy more than 1 year from the baseline date and ongoing intravenous drug use (IVDU).

Ninety-eight patients in each of the treatment and control groups attended their baseline visit and hence were included in the ITT analysis. In the control group 11 of the 98 declined to participate further after learning of their randomisation allocation to no treatment. The treatment and control groups were well matched at baseline with no statistically significant demographic, histological, haematological or biochemical differences (*Tables 8* and *9*).

Baseline HRQoL data were also well matched on all eight categories of the SF-36 scale (*Table 10*). There were no differences between individuals according to route of infection (Appendix 1).

Patient flow through the trial

End of treatment follow-up was available for 97/98 patients in the treated group and 87/98 patients in the control group. The length of time on therapy was variable and not all patients were

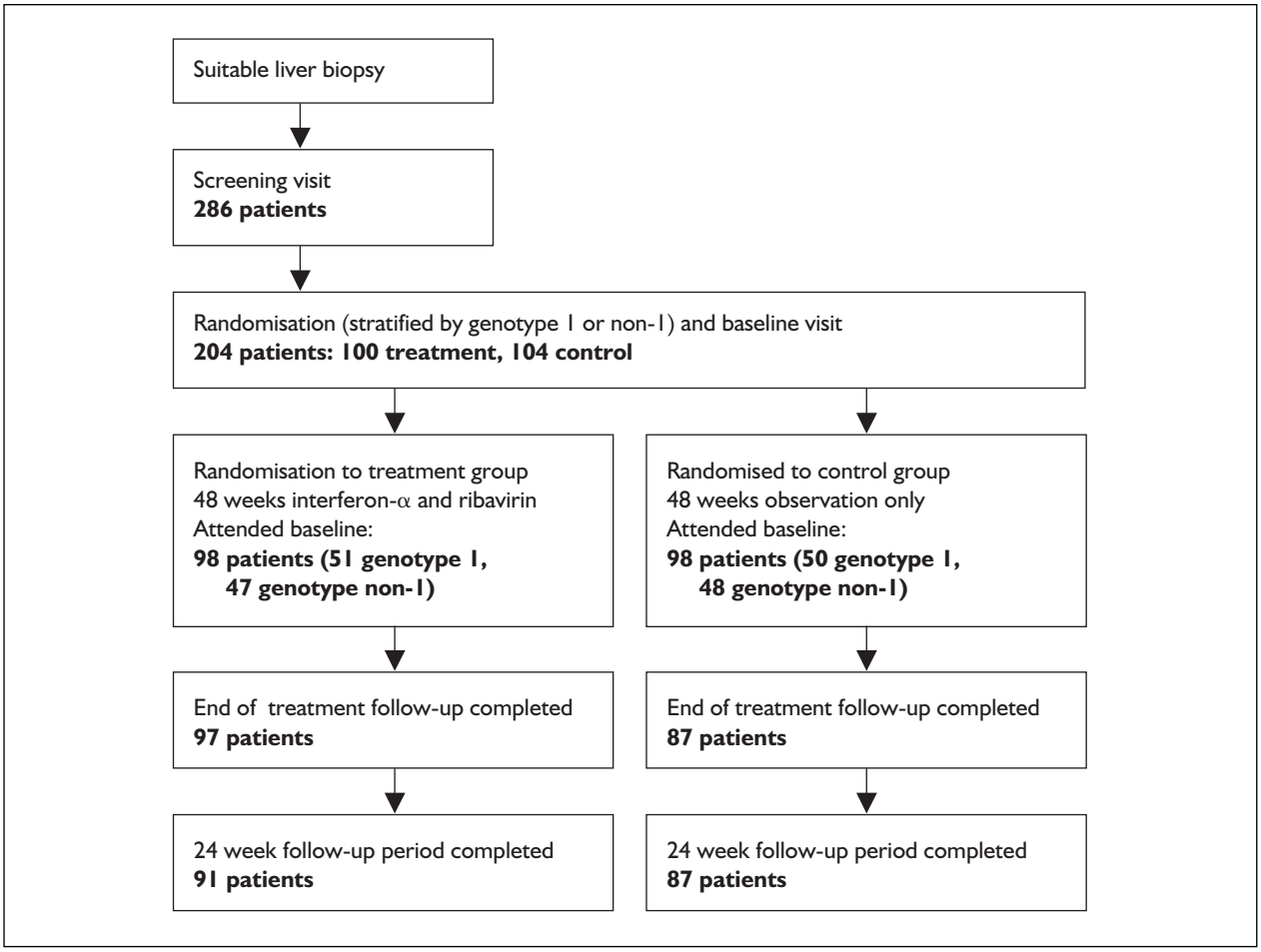

FIGURE 2 *Patient flow through the trial*

TABLE 8 *Baseline demographic details*

	Number of patients		
	Treatment	**Control**	***p***
Gender			
Male	63	56	$p = 0.306^a$
Female	35	42	
Viral genotype			
1	51	50	$p = 0.995^a$
Non-1	47	48	
Ethnic group			
White	90	87	$p = 0.156^a$
Non-white	7	7	
Not recorded	1	4	
Source of infection			
IVDU	52	52	$p = 0.545^a$
Blood products	13	18	
Unknown	33	28	
Age			
Mean (SD)	40.68 (8.82)	40.71 (8.29)	$p = 0.5^b$
Range	23–67	21–58	
Fibrosis score			
Mean (SD)	1.01 (0.77)	1.18 (0.79)	$p = 0.127^b$
Range	0–2	0–2	
Necroinflammatory score			
Mean (SD)	1.96 (1.06)	2.2 (0.99)	$p = 0.474^b$
Range	0–3	0–3	

[a] χ^2.
[b] Independent samples *t*-test.

TABLE 9 *Baseline biochemical and haematological variables*

	Treatment	**Control**	***p*** [a]
ALT (<40)	65.9 (61)	58.6 (58)	$p = 0.39$
Alkaline phosphatase (30–130)	100.3 (58)	108.9 (118)	$p = 0.52$
Bilirubin (<17)	9.8 (4.2)	11.2 (6.4)	$p = 0.08$
GGT (11–50)	45.4 (73)	46.5 (65)	$p = 0.91$
Total protein (60–80)	70.5 (18)	67.3 (26)	$p = 0.34$
Albumin (35–51)	44.1 (7.5)	41.6 (10.8)	$p = 0.06$
Hb (M 13.4–16.6, F 11.5–15.1)	14.0 (3.1)	14.0 (3.0)	$p = 0.97$
Total white cell count (5–11)	7.1 (5.7)	6.8 (2.6)	$p = 0.65$
Platelets (140–400)	234 (75)	239 (74)	$p = 0.61$
Neutrophils (2–7)	3.9 (2.2)	4.5 (5.7)	$p = 0.29$
Lymphocytes (1.3–3.7)	2.0 (0.86)	2.3 (3.3)	$p = 0.51$

Data are shown as mean (SD).
[a] Independent samples *t*-test.
M, male; F, female.

able to complete the full treatment protocol. In the treatment arm 62 patients were able to complete more than 36 weeks of the protocol and 77 completed at least 24 weeks. Twelve patients completed less than 12 weeks of combination therapy (*Figure 3*). The control group demonstrated a similar pattern of attendance at trial visits.

Reasons for, and implications of attrition among the patient groups are discussed in Chapter 8. There was no difference in attendance duration between patients infected by blood products and those infected by intravenous drugs.

At the end of the trial 13 patients in the treatment group failed to attend for their post-week 24 visit.

TABLE 10 *Baseline HRQoL data measured by the SF-36*

Parameter	Treatment group	Control group	*p*
Physical functioning			
Number	94	88	$p = 0.81$
Mean (SD)	84.5 (21.9)	83.8 (20.4)	
Role – physical function			
Number	90	86	$p = 0.50$
Mean (SD)	67.2 (40.5)	71.2 (37.5)	
Bodily pain			
Number	93	87	$p = 0.56$
Mean (SD)	66.3 (29)	68.7 (27.1)	
General health			
Number	94	86	$p = 0.76$
Mean (SD)	58.4 (22.4)	57.4 (22.8)	
Vitality			
Number	94	88	$p = 0.86$
Mean (SD)	52.1 (23.5)	52.7 (22.9)	
Social functioning			
Number	94	87	$p = 0.18$
Mean (SD)	71.6 (27.6)	65.8 (29.8)	
Role – emotional function			
Number	92	85	$p = 0.58$
Mean (SD)	70.3 (40.2)	66.7 (45.4)	
Mental health			
Number	94	88	$p = 0.06$
Mean (SD)	67.0 (20.74)	61.2 (20.2)	

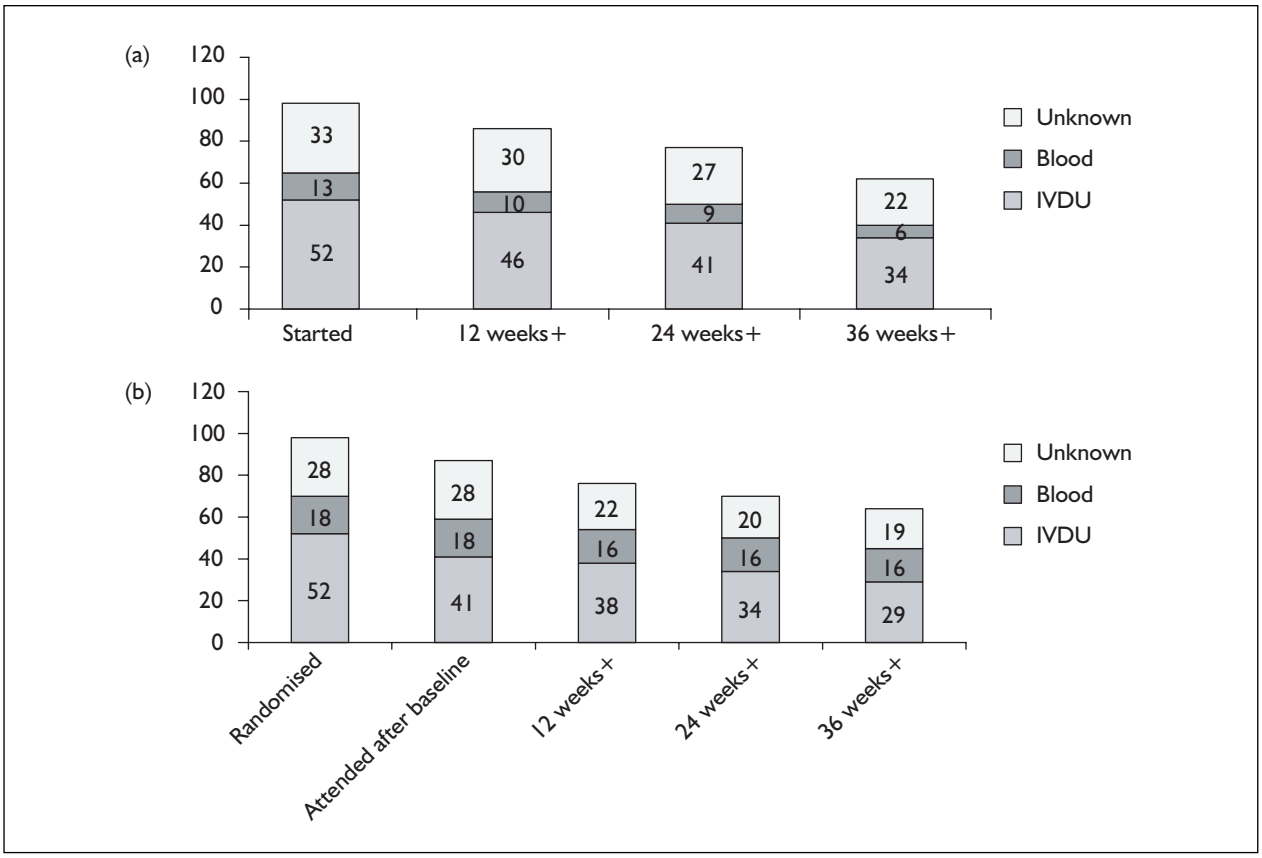

FIGURE 3 *Length of time spent on therapy by treatment group (number of patients at various times after start of therapy). (a) Length of time on therapy by risk factor (treatment group). (b) Length of time on active follow-up in the control group by risk factor.*

Seven of these patients had been PCR positive at the end of treatment visit and were coded as such for the end of follow-up analysis. Of six who had been PCR negative at the end of treatment, two were imprisoned during the treatment phase of the trial and were released and untraceable by the end of follow-up. The remaining four patients had discontinued therapy early during treatment. All six were recorded as having become PCR positive by the end of follow-up in line with the ITT principle. In the control group 28 patients failed to attend their final visit. All were recorded as being PCR positive in line with the ITT principle. In the control group 11 patients declined to continue in the trial after learning their randomisation status at the baseline visit.

Virological end-points

For the primary end-point, ITT analysis demonstrated a 44% end of treatment response (EOTR) and a 33% SVR in the group as a whole. No PCR-negative results were observed in the control group (*Table 11*). Analysis by viral genotype demonstrated a 30% EOTR and an 18% SVR for patients infected with genotype 1 and a 60% EOTR and 49% SVR for those infected with genotype non-1 ($p = 0.0009$). No significant differences in EOTR or SVR were demonstrated between genders, age less than or greater than 40 years, raised or normal ALT at baseline, or baseline viral load above or below 4×10^5 IU ml^{-1} (*Table 12*).

Logistic regression analysis of all treated patients showed that out of age, gender, ALT, viral genotype and baseline viral load, only viral genotype was independently associated with having an SVR ($p = 0.002$). This remained true if the analysis was performed only on those patients completing 24 weeks of therapy. There was no interaction between viral genotype and baseline viral load.

When virological response was analysed according to the length of time the patient continued treatment, as expected, longer treatment durations were associated with better outcomes (*Table 13*).

A very high SVR (86%) was seen in genotype non-1 patients who took between 24 and 36 weeks of therapy. In those with genotype non-1 who took more than 36 weeks of therapy, the SVR was 59%. The explanation for this apparent discrepancy lies in the deliberate cessation of treatment (by patients or their physicians) after 6 months, if the patient was PCR negative. This was not part of the protocol but nevertheless occurred in light of evidence from other RCTs that were published during the course of our trial, which showed that SVRs were not improved beyond 24 weeks. Thus those that were still PCR positive at 24 weeks were unlikely to respond. A more representative figure is for all genotype non-1 patients treated for at least 24 weeks (*Table 14*) with an SVR of 65%. Patients with genotype 1 treated for between 24 and 36 weeks had only a 14% SVR compared with 25% if they were treated for more than 36 weeks.

Early viral kinetics and treatment outcome

Individual viral load plots are shown in Appendix 2. Quantitative virology was performed on patients who had attended all, or had missed

TABLE 11 *Virological response by the end of treatment (EOTR) or control period and the end of follow-up (SVR) according to group*

Treatment response	Interferon and ribavirin		Control
Loss of HCV RNA			
End of treatment/ control	43/98 (44%)		0/98
End of follow-up	32/98 (33%)		0/98
ALT response			
End of treatment	81 Normal, 17 raised		38 Normal, 58 raised, 2 missing
End of follow-up	45 Normal, 31 raised, 22 missing		27 Normal, 41 raised, 30 missing
Overall response	SVR	No SVR	
(Clearance of HCV RNA and normalisation of ALT)	27 Normal ALT 1 Raised ALT 4 Missing	18 Normal ALT 30 Raised ALT 18 Missing	27 Normal ALT 39 Raised ALT 32 Missing ALT

TABLE 12 *SVR according to baseline characteristics*

Baseline characteristic	Interferon and ribavirin	Control	*p* (Subgroups of treatment arm)
Genotype			
1	9/47 (19%)	0/50	$p = 0.0009$
Non-1	23/44 (52%)	0/48	OR = 0.22
Gender			
Male	23/59 (39%)	0/56	$p = 0.3$
Female	9/32 (28%)	0/42	OR = 1.63
Age			
>40 years	14/44 (32%)	0/47	$p = 0.52$
<40 years	18/47 (38%)	0/51	OR = 0.75
ALT			
Normal	12/35 (34%)	0/42	$p = 0.89$
Raised	20/56 (36%)	0/56	OR = 0.94
Viral load IU ml^{-1}[a]			
$< 4 \times 10^5$	19/56 (34%)		$p = 0.82$
$> 4 \times 10^5$	13/42 (31%)		OR = 1.1
Cross-tabulations			
Males			
Genotype 1	5/31 (16%)		$p = 0.0002$
Genotype non-1	18/28 (64%)		OR = 9.36
Females			
Genotype 1	4/16 (25%)		$p = 0.69$
Genotype non-1	5/16 (31%)		OR = 1.36
Genotype 1			
Viral load $<4 \times 10^5$	6/24 (25%)		$p = 0.3$
Viral load $>4 \times 10^5$	3/23 (13%)		OR = 0.45
Genotype non-1			
Viral load $<4 \times 10^5$	13/28 (46%)		$p = 0.3$
Viral load $>4 \times 10^5$	10/16 (63%)		OR = 1.92
Males			
Viral load $<4 \times 10^5$	12/29 (41%)		$p = 0.71$
Viral load $>4 \times 10^5$	11/30 (37%)		OR = 1.22
Females			
Viral load $<4 \times 10^5$	7/23 (30%)		$p = 0.64$
Viral load $>4 \times 10^5$	2/9 (22%)		OR = 1.53

[a] 1 IU is equivalent to approximately 5 RNA copies.

TABLE 13 *SVR according to length of time the patient had treatment*

Duration of antiviral therapy	End treatment viral response (treatment group)		SVR (treatment group)	
<12 weeks	1/10 (10%)		0/11	
12–24 weeks	3/9 (33%)		1/8 (12.5%)	
24–36 weeks	9/15 (60%)		7/14 (50%)	
	Genotype 1 2/7 (29%)	**Genotype non-1** 7/8 (88%)	**Genotype 1** 1/7 (14%)	**Genotype non-1** 6/7 (86%)
36–48 weeks	30/62 (48%)		24/59 (41%)	
	Genotype 1 12/34 (35%)	**Genotype non-1** 18/28 (64%)	**Genotype 1** 8/32 (25%)	**Genotype non-1** 16/27 (59%)

TABLE 14 *Response in those taking treatment for more than 24 weeks*

End of treatment response		**SVR**	
41/77 (53%)		31/73 (42%)	
Genotype 1	**Genotype non-1**	**Genotype 1**	**Genotype non-1**
14/41 (34%)	25/36 (69%)	9/39(23%)	22/34 (65%)

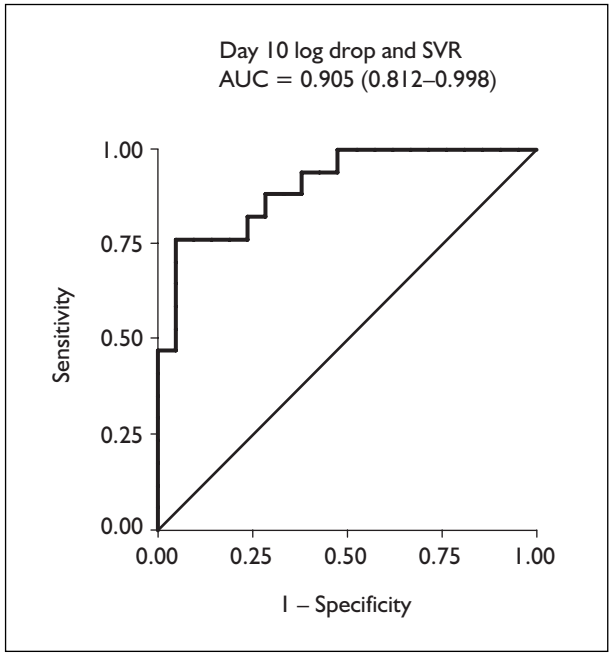

FIGURE 4 *Drop in viral load (IU ml^{-1}) at day 10 and SVR: ROC curve*

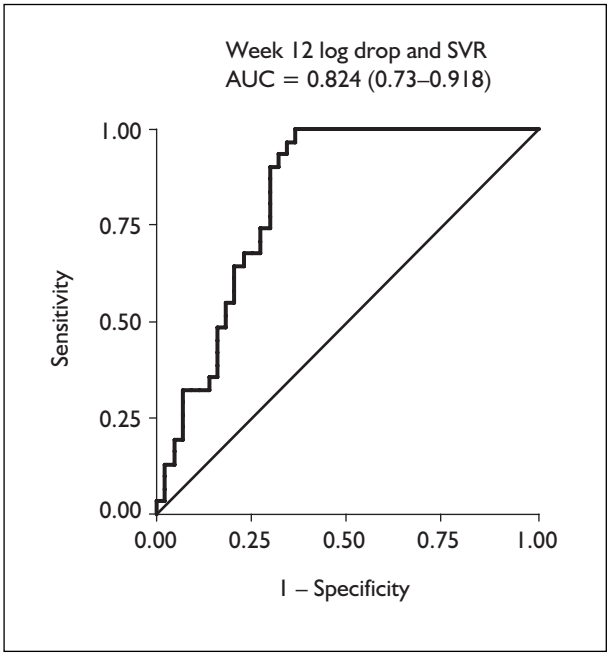

FIGURE 5 *Drop in viral load (IU ml^{-1}) at week 12 and SVR: ROC curve*

only one of their initial early visits (day 0, 3, 7, 10 and 14, and week 12) and for whom there was a follow-up sample at 24 weeks post-completion of therapy. Seventeen control patients and 51 active treatment patients fulfilled these criteria. A week 12 quantitative sample was available for 75 of the treated patients. Viral load is expressed as IU ml^{-1} (1 IU is equivalent to approximately 5 viral copies). Change in viral load is expressed logarithmically.

In the control patients there was very little variation in the viral load from baseline. In the treated patients there was, in most cases, a fall in viral load associated with the commencement of antiviral therapy. The degree of fall in viral load was examined for its relationship to final outcome at the different time points using receiver operating characteristic (ROC) curves. The area under the ROC curve represents the probability that the log drop in viral load predicts the outcome with greater accuracy than a random number. An area of one represents complete discrimination and an area of 0.5 represents a test of no diagnostic value. ROC curves for viral load drop at day 10 and week 12 are shown in *Figures 4* and *5*. The curves plot sensitivity and specificity of detecting the end-point at each level of viral load. Viral load drop gave the best area under the curve (AUC) at day 10 followed by week 12. Rates of SVR predicted by a 2-log drop at each time-point are shown in *Table 15* for all patients and subdivided by genotype in *Table 16*.

A 2-log drop at 10 days gives a positive predictive value of 81% for eventual viral clearance, while patients failing to achieve a 2-log drop had only an 18% chance of SVR. If measured at 12 weeks, no patient failing to achieve a 2-log drop went on to SVR, with a 57% positive predictive value (PPV) if the drop occurred.

Viral genotype non-1 with a 2-log drop at 12 weeks had an 82% chance of SVR compared with 31% for genotype 1 (*Table 16*).

TABLE 15 *Early viral load change and treatment outcome*

Baseline characteristic	Interferon and ribavirin		% with SVR
	No SVR	SVR	
Viral load change at 3 days			
Undetectable or 2-log drop	2	4	66%
<2-log drop	23	20	47%
Viral load change at 7 days			
Undetectable or 2-log drop	2	14	88%
<2-log drop	22	9	29%
Viral load change at 10 days			
Undetectable or 2-log drop	3	13	81%
<2-log drop	18	4	18%
Viral load change at 14 days			
Undetectable or 2-log drop	5	15	75%
<2-log drop	22	9	29%
Viral load change at 12 weeks			
Undetectable or 2-log drop	23	31	57%
<2-log drop	21	0	0%

TABLE 16 *Early viral load and treatment outcome by genotype*

Baseline characteristic	Interferon and ribavirin		% with SVR
	No SVR	SVR	
Genotype 1			
Viral load change at 3 days			
Undetectable or 2-log drop	1	0	0%
<2-log drop	18	3	14%
Viral load change at 7 days			
Undetectable or 2-log drop	2	3	60%
<2-log drop	16	3	16%
Viral load change at 10 days			
Undetectable or 2-log drop	2	3	60%
<2-log drop	14	1	7%
Viral load change at 14 days			
Undetectable or 2-log drop	3	3	50%
<2-log drop	18	3	14%
Viral load change at 12 weeks			
Undetectable or 2-log drop	18	8	31%
<2-log drop	14	0	0%
Genotype non-1			
Viral load change at 3 days			
Undetectable or 2-log drop	1	4	80%
<2-log drop	5	10	67%
Viral load change at 7 days			
Undetectable or 2-log drop	0	11	100%
<2-log drop	6	6	50%
Viral load change at 10 days			
Undetectable or 2-log drop	1	10	91%
<2-log drop	4	3	43%
Viral load change at 14 days			
Undetectable or 2-log drop	2	12	86%
<2-log drop	4	6	60%
Viral load change at 12 weeks			
Undetectable or 2-log drop	5	23	82%
<2-log drop	7	0	0%

Effect of antiviral treatment on HRQoL

SF-36 questionnaires were completed at baseline, week 12, 24 and 48, and at end of follow-up. The baseline SF-36 data are shown in *Table 10*. Tables comparing scores between the treatment group and controls for subsequent visits are shown in Appendix 1. Approximately 60% of trial participants completed questionnaires at each time-point.

Key comparisons

Baseline

There were no differences between the treated patients and controls in any of the eight domains of the SF-36 or in the mental and physical summary scores at baseline (*Table 10*). The baseline scores showed substantial impairments in well-being in all eight domains of the SF-36 in the study group compared with data acquired from a UK normal population (*Figure 6*).[58]

During treatment

There were marked decreases in SF-36 scores during therapy, which were most pronounced in the physical function, role–physical function, social function and role–emotional function domains (*Figure 7*). The mean scores returned to pretreatment levels by 24 weeks post-treatment.

End of follow-up

Comparisons between baseline and post-week 24 scores were made for patients across three groups: SVR, treatment failures (non-SVR) including non-responders and responder-relapse patients, and the control group. The individual differences between the baseline and post-week 24 scores for the eight scales of the SF-36 and the two summary scales were compared across the three groups. Data were available for 24/32 (75%) of the SVRs, 44/68 (65%) of the non-SVRs and 58/98 (59%) of the control group. Continuous parametric data were tested with analysis of variance (ANOVA), and the Kruskall–Wallis test was used when the data departed from a normal distribution. Pairwise comparisons were made using a Student's *t*-test or Mann–Whitney *U*-test as appropriate. The χ^2 test was used to test categorical data.

At 24 weeks after the end of treatment, there was a mean improvement in 7/8 of the SF-36 scales in the SVRs, in 6/8 in the non-SVRs and in 0/8 in the control group, where substantial reductions were

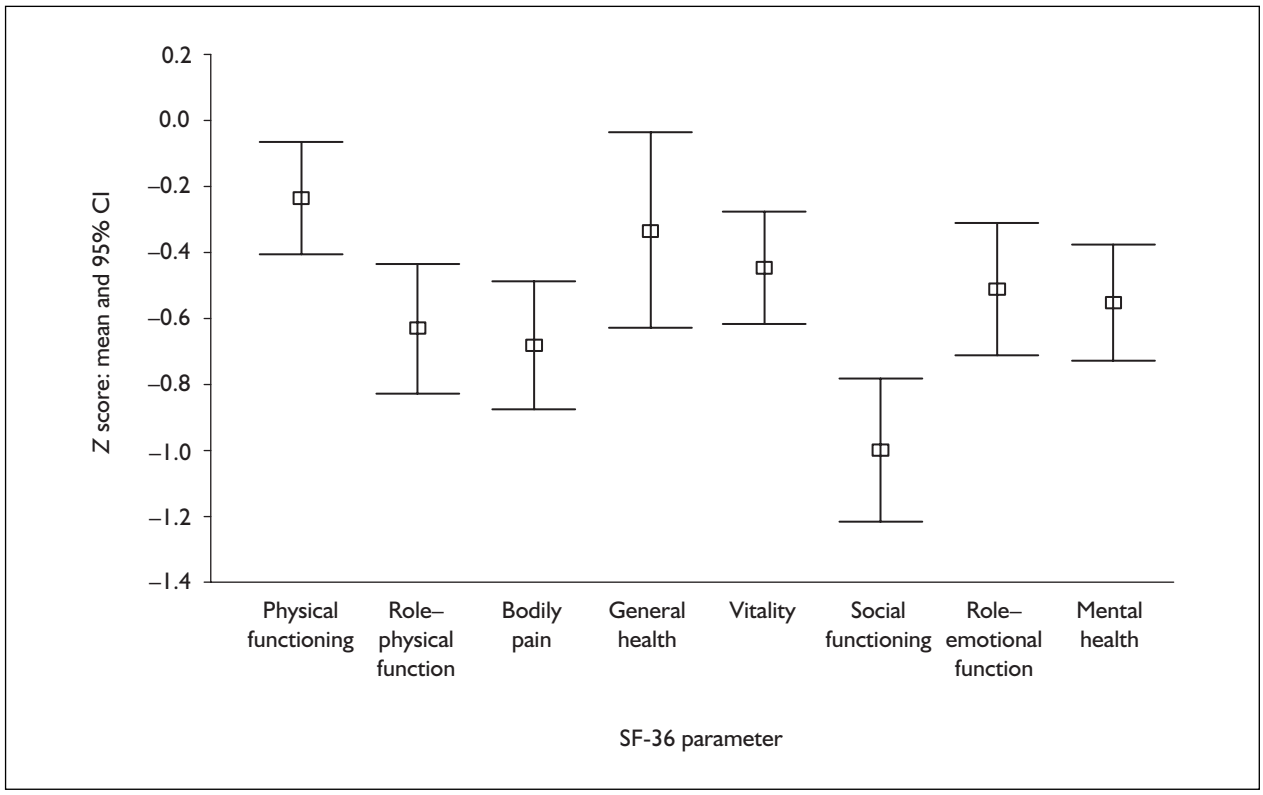

FIGURE 6 *Baseline SF-36 scores versus population norms. The Z score represents the number of standard deviations by which the population under study differs from the normal population (the normal population mean would by definition have a Z score of zero).*

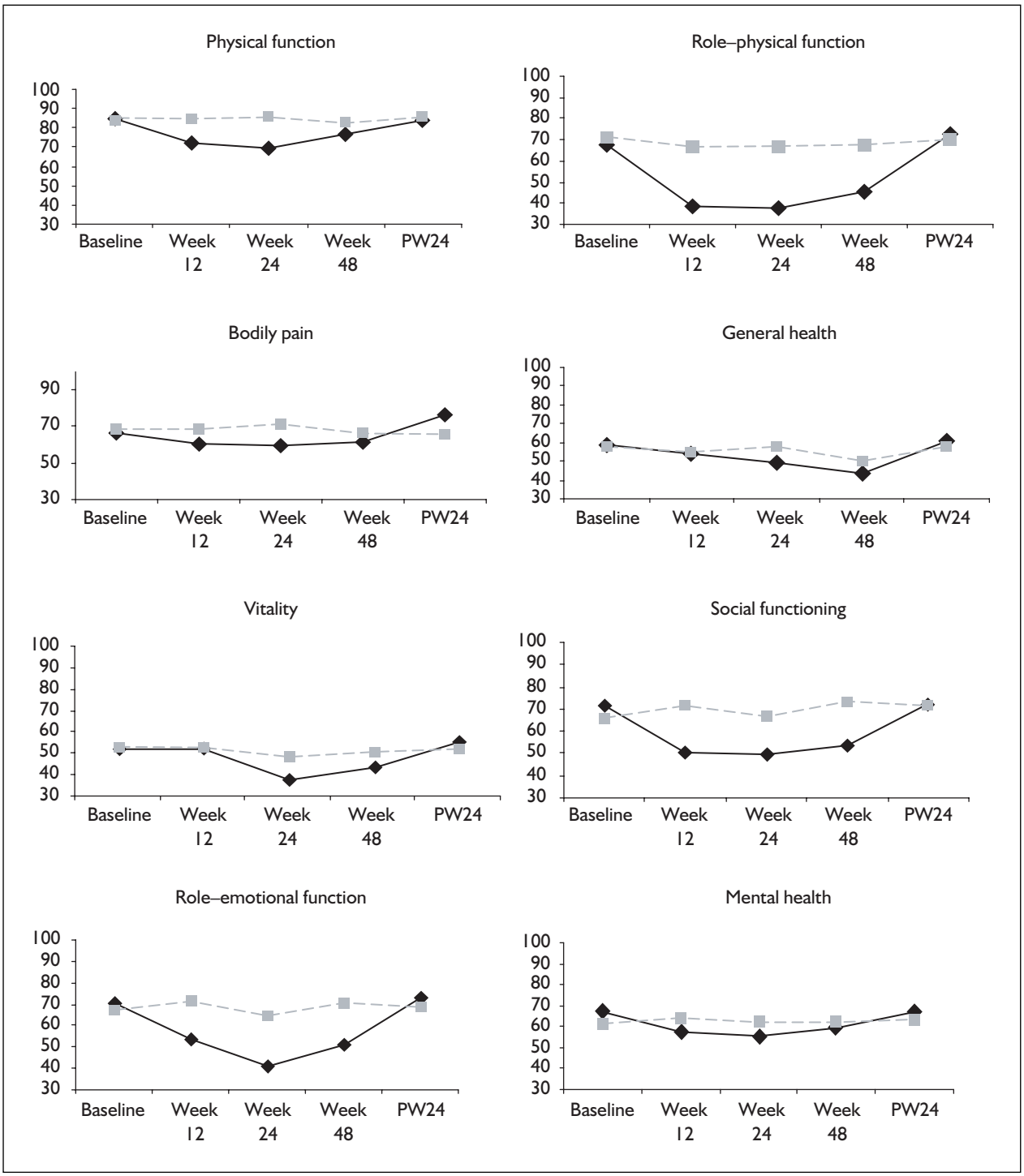

FIGURE 7 *Effect of antiviral therapy on HRQoL. The dashed lines represent controls and the solid lines the treatment group. PW24, 24 weeks post-treatment.*

seen (*Figure 8*). Similarly, the mean change in the physical and mental component summary scores (PCS and MCS) showed improvements in the SVR and non-SVR groups with deterioration in the controls (*Figure 9*). The changes in the PCS were more marked than in the MCS, with 16/24 (67%) of the SVRs, 27/44 (61%) of the non-SVRs and 24/58 (41%) of the controls reporting an improvement ($p < 0.05$ for SVRs and non-SVRs compared with controls). There were no statistical differences in the MCS.

There was substantial variation in the magnitude and direction of change in the SF-36 scores from baseline to 24 weeks post-treatment. Despite this variation, the mean change in PCS was significantly

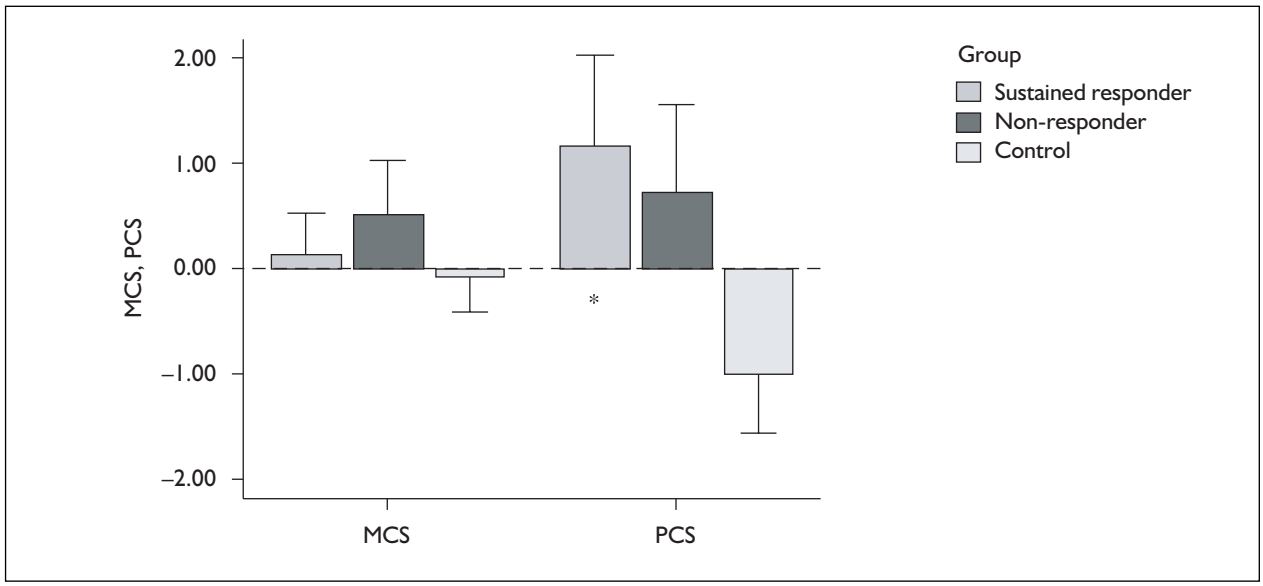

FIGURE 8 *Mean changes in the mental (MCS) and physical (PCS) component scores of the SF-36 in the three treatment groups. Bars represent the standard error of the mean.* *p = 0.04.

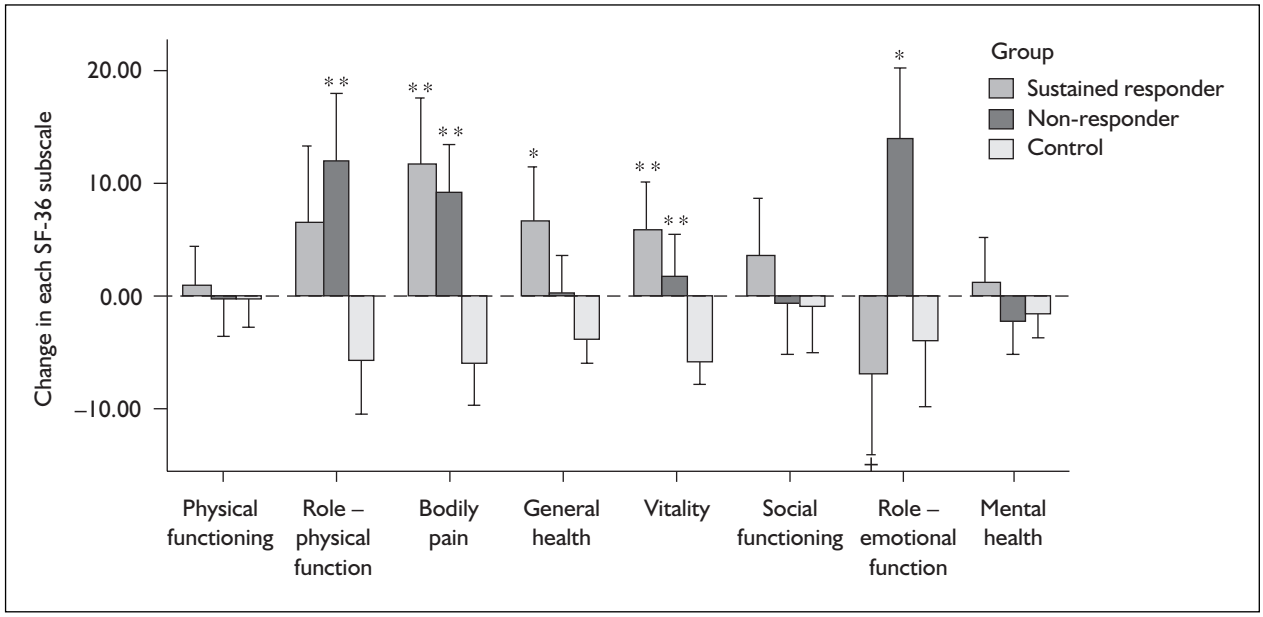

FIGURE 9 *Mean changes in the eight subscales of the SF-36 in the three treatment groups. Bars represent the standard error of the mean.*** p < 0.02, * p < 0.04 compared with controls. † p < 0.04 compared with non-SVRs.*

greater in the SVRs than in the controls ($p = 0.04$) (*Figure 8*). There were no statistical differences between non-SVRs and SVRs or controls, although there was a trend towards greatest improvement in the SVRs. This is likely to be due to the relatively small sample sizes. There were significant improvements in 3/8 of the SF-36 subscales (bodily pain, general health and vitality, $p = 0.01$) in the SVRs compared with the controls (*Figure 9*). These are reflected in the PCS. There was an overall deterioration in only one subscale (role–emotional function) in the SVRs, which was significantly different to the improvement seen in the non-SVRs ($p < 0.05$).

Multivariate analysis was used to test whether age, gender, mode of acquisition, baseline scores and virological treatment outcome were independently associated with improvement or deterioration in PCS 24 weeks after treatment. Virological treatment outcome ($p = 0.04$) and baseline PCS ($p < 0.01$) were independently associated with

TABLE 17 *Baseline SF-36 scores and duration of treatment tolerated*

Parameter	<12 weeks	12–24 weeks	24–36 weeks	36–48 weeks	*p* ANOVA
Physical component summary score					
Number	12	10	15	57	0.36[a]
Mean (SD)	44.4 (5.29)	48.6 (4.92)	47.4 (5.14)	47.4 (6.4)	0.136[b]
Mental component summary score					
Number	12	10	15	57	0.015[a]
Mean (SD)	47.1 (2.9)	50.7 (2.76)	49.9 (2)	49.5 (2.92)	0.011[b]

[a] Linear trend; [b] <12 weeks vs 36 weeks.

improvement or deterioration in PCS. 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 before 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.

Baseline SF-36 scores were compared between patients according to how long they had treatment. There was a non-significant trend suggesting that those who only had short treatment durations had impaired HRQoL at baseline compared with those who continued for the full duration (*Table 17*).

Adverse events and dose modifications

Adverse events

Adverse events were recorded in both treatment and control groups and are shown in *Table 18*. As expected owing to the nature of the treatment, there was an excess of events in the treatment group and these were similar to those demonstrated in other trials of interferon-α and ribavirin. A significant number of adverse events was reported in the control arm of the study, despite there being no placebo component.

There were four hospitalisations among trial patients, all in the treatment arm. These are recorded in *Table 19*. Patient number 1 had completed 36 weeks of therapy, but a diagnosis of gastric carcinoma was made and he died before the end of follow-up. The remaining three were discontinued in accordance with the protocol. Two patients were admitted following episodes of self-poisoning. Patient number 2 had a history of

TABLE 18 *Adverse events among trial patients*

	Treatment (*n* = 98)	Control (*n* = 87)
Flu-like symptoms	41	9
Depression/low mood	48	14
Hair loss	19	0
Hypothyroidism	6	0
Metallic taste	11	2
Insomnia	20	21
Irritability	9	6
Sensitive skin	51	16
Sensitive eyes	11	2
Dizzy	19	3
Fevers/rigors	12	5
Gastrointestinal upset	13	4
Blood abnormality	31	0
Other	224	125
Abdominal pain	7	11
Totals	522	218

TABLE 19 *Hospitalisations during the treatment period*

Patient found to have metastatic gastric carcinoma after completion of therapy	Subsequently died of disease
Overdose of sleeping pills	Uneventful recovery; patient had history of depression
Overdose of ribavirin	Uneventful recovery; patient had history of depression
Severe vomiting in the week following commencement on therapy	Admitted to hospital with Mallory Weiss tear

previous suicide attempts, but failed to disclose this at either the screening or baseline visits. This patient did not attend subsequent follow-up visits. Patient number 3 was known to have a history of mild–moderate depression, but had been assessed as suitable for treatment by a senior psychiatrist. Both patients 3 and 4 were followed up and were well at completion of follow-up.

Dose adjustments resulting from adverse events

Adverse events resulted in 56 recorded dose adjustments. Ten patients were withdrawn completely, 16 required reduction of interferon-α alone, four required reduction of both interferon-α and ribavirin, and 26 required reduction of ribavirin alone.

Chapter 4

Cost-effectiveness model for mild hepatitis C: structure and transition probabilities

Introduction

The main finding from the RCT was that a combination of interferon-α and ribavirin was effective in achieving an SVR for 33% of cases with mild hepatitis C. HRQoL deteriorated during the treatment, but for those patients who had an SVR, there were on average modest improvements in HRQoL. This raises the question: is antiviral treatment worthwhile for patients with mild disease? The main aim of the health economics assessment was to assess whether interferon-α and ribavirin therapy was relatively cost-effective for patients with mild hepatitis C. A cost-effectiveness model was developed to assess the long-term impact of the intervention on costs and outcomes, and empirical data were collected to provide the costs and HRQoL estimates needed to populate the model.

In this chapter the key features of the cost-effectiveness model are described: the cost-effectiveness literature in this area is reviewed and an overview of the cost-effectiveness methodology is given, before the model structure is detailed. The central issue of the early transition probabilities used in the model is covered, followed by the later transition probabilities; then the key issues to emerge during the model's development are discussed. The following chapters cover the measurement of health service costs (Chapter 5) and HRQoL (Chapter 6), before Chapter 7 reports the results of the cost-effectiveness analysis. Chapter 8 includes a discussion of the overall methodology and results of the cost-effectiveness model and offers some conclusions and areas for further research.

Cost-effectiveness analyses in hepatitis C

Conducting cost-effectiveness analyses (CEA) in hepatitis C is challenging as patients may progress through a number of disease stages over a long period.[59] Data from RCTs are insufficient, mainly because the follow-up periods are too short to capture the differential costs and benefits associated with antiviral therapy. To resolve this problem economic assessments in hepatitis C have used Markov models to extend the effectiveness data from RCTs and evaluate the cost-effectiveness of new antiviral treatments over a longer time-horizon.[6,7,42,44,45,48–50,59] Markov models are probabilistic models that can use estimates of disease progression to estimate lifetime costs and outcomes.[60] These models divide the natural history of the disease into a series of health states. Patients are assigned a probability of moving between the various health states during each Markov cycle. The length of the Markov cycle (e.g. 1 year) and the duration of the model (e.g. 30 years) are set by the analyst. Markov models have been widely used in economic analyses of chronic diseases.[60–63]

To populate Markov models, data are required on the probability of moving between the various health states, the short-term effectiveness of the intervention, the total costs of each disease stage and the HRQoL associated with each disease state. Previous cost-effectiveness models for hepatitis C are reviewed briefly below.

Markov models for hepatitis C

An early model for economic assessment in hepatitis C by Dusheiko and Roberts, in 1995, compared interferon-α and ribavirin to no treatment for patients with chronic hepatitis C.[6] Expert opinion was used to estimated HRQoL, and UK clinical protocols and expert opinion were used to estimate resource use. Costs and effects were estimated over 30 years, and the model predicted that interferon-α for patients with chronic hepatitis C was likely to be cost-effective.

Subsequent models have also used a Markov structure to estimate the cost-effectiveness of interferon-α,[43,45,64] interferon-α and ribavirin[42,50] and most recently pegylated interferon-α and ribavirin.[42,50] The model developed by Wong[64] has been used for each of these purposes. This model has been used to estimate the cost-effectiveness of interferon-α monotherapy and interferon alpha with ribavirin for cases with mild hepatitis C.[43,65] The authors concluded that antiviral therapy

compared with a no-treatment alternative was likely to be cost-effective.

These studies have suffered from important limitations. In particular, the models have not been based on empirically estimated transition probabilities. The models have estimated transition probabilities based on published disease progression rates. Progression rates from the literature vary widely, and the choice of which data to use to estimate transition probabilities is an important issue when developing a Markov model in this area. For a model of mild disease the choice of transition probabilities for progressing through the early stages of the disease is particularly important. This study therefore aimed to improve on previous attempts to model the cost-effectiveness of antiviral therapy by using accurate estimates of transition probabilities. For the early transition probabilities, new estimates of transition probabilities are presented, based on UK data.

The remainder of this chapter gives an overview of the CEA, presents the structure of the model for mild hepatitis C, and details the choice and estimation of the transition probabilities.

Overview of the methodology for the CEA

Study question

The purpose of the CEA was to evaluate whether treating patients at a mild stage was cost-effective compared with waiting until they reached moderate disease before providing treatment. The choice of comparator (no treatment until they reach moderate hepatitis C) was based on recommended practice in England and Wales.[15] It was assumed that neither group was retreated. There was no evidence to suggest that retreatment following non-response to interferon-α and ribavirin therapy was effective for patients with mild or moderate hepatitis C. (The comparator group is referred to during the remainder of the document as either the control group, no-treatment cohort or moderate treatment cohort. These terms are used interchangeably; in each case patients in this group were monitored during the mild disease stage and then given interferon and ribavirin treatment if they reached moderate disease.)

Perspective and duration of analysis

Following recent NICE guidelines,[66] a health service perspective was taken to the inclusion of costs, which meant that broader societal costs were excluded from the analysis. Although previous hepatitis C models have assumed a time-horizon for the model of 20 or 30 years,[6,7,42,44,45,48–50] the base-case analysis uses a lifetime duration. For cases who enter the model aged 40 years, the model runs until they reach 90 years old; a time-horizon of 50 years. Patients are subjected to the probability of all-cause death, so that towards the end of the analysis period most cases have died and therefore exited the model. (By this time, the probability of all-cause death is very high, and any differences in costs or HRQoL between the treatment and no-treatment cohorts are minimal.) The justification for taking a lifetime perspective is that guidelines for economic evaluations suggest that the time-horizon for the analysis should be sufficient to capture the differential costs and effects associated with the intervention.[66] In this case adopting a shorter time-horizon would mean that costs and effects resulting from antiviral treatment would be excluded. However, to allow comparison with previous studies, various methodological scenarios were run in the sensitivity analysis (Chapter 7) adopting shorter time-horizons.

Efficacy data

The short-term efficacy for interferon-α and ribavirin was based on data from the mild hepatitis C RCT, so on average 33% of cases were assumed to have an SVR (Chapter 3). For patients who had moderate disease it was assumed that all patients were treated and the same proportion of patients had an SVR as for the patients with mild disease. Although previous trials that included a majority of patients with moderate hepatitis C had slightly higher response rates,[20,21] these were multinational studies and the results may not apply to the UK NHS.

Study end-point

The end-point of the CEA was the incremental cost-effectiveness of providing antiviral therapy at a mild rather than a moderate stage, summarised by the additional cost per QALY gained. The cost per QALY was chosen as the end-point to reflect the gains and losses in HRQoL that occur as a result of the intervention. Using the QALY as an outcome measure allowed these to be captured together with any changes in life expectancy.

Costs and HRQoL data

Information on the costs and HRQoL associated with each stage in the model were required. Previous models in hepatitis C have lacked empirical data on these parameters and instead

relied on expert opinion. This can lead to inaccurate estimates of model inputs and hence cost-effectiveness. To counter this problem empirical estimates of the costs and HRQoL associated with each disease stage were used and details are provided in Chapters 5 (costs) and 6 (HRQoL).

A model was therefore required that could incorporate these empirical estimates and project the incremental cost per QALY of antiviral therapy for mild hepatitis C over the patients' lifetime. The next section details the structure of the model developed.

Model structure

Overview of model structure

A new model was developed for estimating the cost-effectiveness of combination therapy for cases with mild hepatitis C. The model structure was based on a previous Markov model developed by Dusheiko and Roberts,[6] which divided the natural history of the disease into a series of health states. An important change was made to this model's structure to evaluate treatment specifically for patients with mild hepatitis C. For the new model, the chronic state was divided into two histologically separate states: mild and moderate hepatitis C. The later stages of hepatitis C were categorised into cirrhosis, decompensated cirrhosis, HCC and liver transplantation (*Figure 10*). From the later three health states patients faced a probability of liver-related death, and from all the earlier health states patients faced a probability of all-cause death.

Progress through the model

Two cohorts of 1000 patients were entered into the model, one a treatment cohort, the other a control cohort. All patients were assumed to start with mild hepatitis C and each cohort was assumed to have the average characteristics of the mild hepatitis C trial population at trial entry (Chapter 3). The parameters used to populate the model (e.g. transition probabilities) were chosen and where possible adjusted to reflect the characteristics of the trial population.

Patients faced an annual probability of progressing through the model. During the first cycle the costs of investigating and staging the hepatitis C were included for both cohorts (e.g. costs of liver biopsy). The cycle length of the model was 1 year, and at the end of each cycle patients faced a probability of moving to a subsequent health state. After the first cycle the treated cohort entered the mild treatment state and had the costs and HRQoL associated with this health state. Following antiviral treatment, those patients who had an SVR moved to the SVR health state and had the ensuing costs and HRQoL. Following an SVR it was assumed that patients no longer face a probability of progressing through the disease. This is consistent with end of treatment biopsies from previously reported trials that did not find any evidence of disease progression following an SVR.[67]

Patients who did not have an SVR faced the same annual probability of progressing from mild to moderate disease as if they had not received antiviral treatment. This is a conservative assumption as there is some evidence to suggest that antiviral treatment, even in the absence of an SVR, can delay disease progression.[67]

The model structure was similar for the mild no treatment cohort, and during the first cycle this cohort also faced the costs of investigating and staging the disease (e.g. costs of having a liver biopsy). In subsequent cycles, this cohort faced a probability of moving onto moderate disease. Those patients who progressed to moderate disease were all assumed to have antiviral therapy (interferon-α and ribavirin). These patients faced the same probability of having an SVR as the cases in the mild treatment cohort.

The patients in both cohorts who did not have an SVR following treatment faced a probability of progressing to cirrhosis and its complications. Unlike other models for hepatitis C,[43] decompensated disease was kept as a single health state rather than subdivided into its different clinical manifestations, such as ascites, hepatic encephalopathy and hepatorenal syndrome, because it is possible for an individual to have several of these complications. A requirement of the Markov structure is that a particular patient cannot be in more than one health state at any one time.

A separate health state was included for patients with HCC, as previous studies suggested that this was a distinct health state with its own particular health service costs and HRQoL.[45] In the model it was assumed that patients had to reach cirrhosis or decompensated disease before they faced a probability of moving to HCC.[45]

Patients with decompensated cirrhosis and HCC were assumed to face an annual probability of

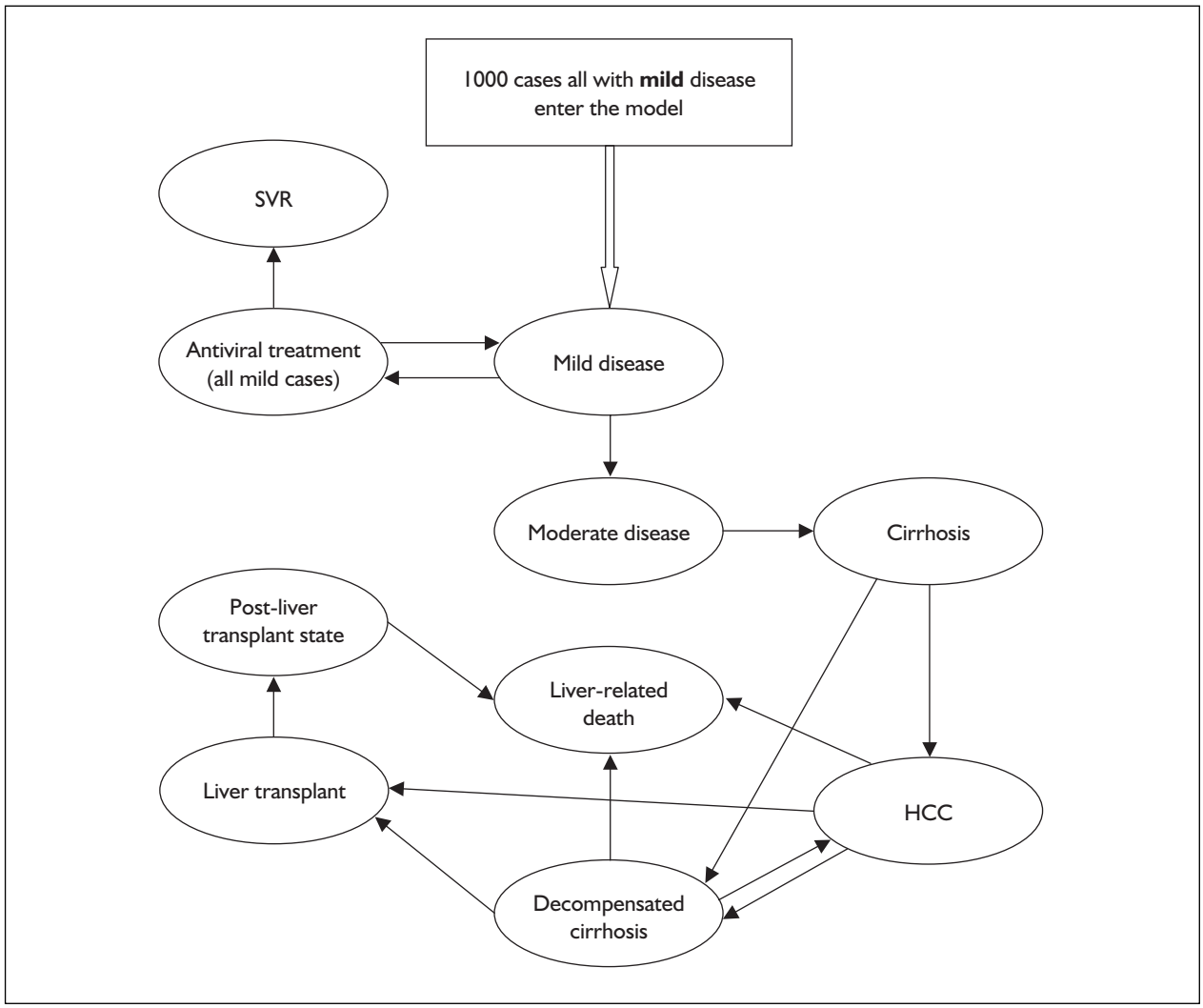

FIGURE 10 *Structure of Markov model for mild hepatitis C, showing disease transitions between the main health states included in the model, for the mild treatment group*

receiving a liver transplantation. Following a liver transplantation patients faced a probability of death or moving to the post-transplantation phase. In the post-transplantation phase patients remained at a higher risk of death compared with the general population.

The model assumed time-independent disease transition probabilities. Thus, the probability of moving between, say, mild and moderate disease was independent of the time in the mild disease state. This is consistent with the current understanding of hepatitis C progression, which suggests that although disease progression may vary by cofactors such as age at infection and gender, there is no evidence to suggest that length of time in a particular health state is associated with disease progression.[4,5]

The HRQoL and costs of being in each health state were multiplied by the number of patients in that health state, to give the total costs and total QALYs for each model cycle. For each cohort of patients the total lifetime costs and total QALYs were calculated by summing across the model cycles (50 in the base-case analysis) to give the total lifetime costs and QALYs following treatment and no treatment of mild hepatitis C. (Further details on the model analysis are given in Chapter 7.)

Early transition probabilities

The structure of the model meant that two early transition probabilities were required to represent the movement from mild to moderate disease and

TABLE 20 *Estimates of mean prevalence of cirrhosis after 20 years of infection (from Freeman and colleagues[3]) and estimated annual probabilities of progression*

Study description	No. of studies	Mean subjects	Estimated cirrhosis prevalence after 20 years of HCV infection Mean (95% CI)	Estimated annual transition probabilities Mean (95% CI)	
				Mild–moderate disease	Moderate disease–cirrhosis
Liver clinic	33	482	21.9% (17.9 to 25.9%)	0.046 (0.041 to 0.052)	0.046 (0.041 to 0.052)
Post-transfusion	5	72	23.8% (11.0 to 36.6%)	0.049 (0.03 to 0.067)	0.049 (0.03 to 0.067)
Blood donors	10	65	3.7% (0.8 to 6.5%)	0.016 (0.007 to 0.022)	0.016 (0.007 to 0.022)
Community	9	231	6.5% (3.5 to 9.5%)	0.022 (0.016 to 0.028)	0.022 (0.016 to 0.028)

then from moderate disease to cirrhosis. A literature review was conducted to find appropriate early transition probabilities. The literature review highlighted that there were certain general problems with the literature estimates of disease progression.[68] The recent discovery of the virus means that most estimates of progression rely on retrospective natural history data.[69–71] Most of the retrospective cohort studies have not used liver biopsies to assess fibrosis and have therefore used the incidence of clinically defined cirrhosis to estimate progression.[69–71] Prospective studies are by their very nature only of short duration, and therefore of limited use for providing the estimates of disease progression required over the model's analysis period.[72,73] The rate at which patients progress through stages of fibrosis is difficult to measure as chronic hepatitis C may last for decades and most longitudinal studies have relatively short durations of follow-up.[5] Often cases do not have a known date of infection, so duration of infection, and therefore the rate of disease progression, have to be estimated.[4,5,10,74] It is also difficult to use recent data on the natural history of the disease as many patients have now received antiviral therapy.

The review revealed that there was considerable uncertainty surrounding the rate of progression from mild hepatitis C to cirrhosis.[26,68,75] It is unclear what proportion of cases will develop cirrhosis and which subgroups of patients are most likely to progress.[4,5,10]

Reasons for variability in progression to cirrhosis

The published natural history studies have a number of different study designs, with different types of data collection and consequently widely variable conclusions. Various factors compromise results; in particular, the source of patients included in the study is likely to be important. Clinic populations, screened populations and cohorts followed from a known date of infection are not comparable. Groups are selected in various ways, and differ in their general background health and in how they contracted the virus.

These points are illustrated by Freeman and colleagues' systematic review of 57 epidemiological studies (*Table 20*).[3] Each study had a different mean duration of infection for the study subjects ranging from 3 to 26 years. The authors divided the published studies into four categories according to the their population: liver clinic series, post-transfusion studies, blood donor studies and community-based studies. The authors estimated the prevalence of cirrhosis at 20 years for each study and then estimated the mean prevalence of cirrhosis for each group of studies. After 20 years of infection with hepatitis C, the mean proportion of cases with cirrhosis was 22% in the liver clinic series, 24% in the post-transfusion cohorts, 4% for the blood donor series and 7% for the community-based cohorts.

The prevalence of cirrhosis in a particular population with a known duration of infection can be used to estimate the early transition probabilities required by the cost-effectiveness model, provided that it is assumed that there is a constant rate of disease progression from infection to cirrhosis. The estimated prevalence of cirrhosis at 20 years was used for each group of studies, assuming a constant rate of disease progression to estimate the required transition probabilities

(using the XL solver command). Using the estimates of cirrhosis prevalence from the Freeman study gave a wide range of estimates for the early transition probabilities across the groups concerned (*Table 20*). This meant that the choice of transition probabilities from the literature was sensitive to the study population.

The choice of transition probabilities for the model was driven by the model's purpose, which was to estimate the cost-effectiveness of antiviral treatment for cases with mild hepatitis C. To be considered for treatment in the UK, patients with hepatitis C are currently required to attend a liver clinic and have a liver biopsy. In light of this, it would seem most appropriate to use transition probabilities estimated from liver clinic cases. The transition probabilities from the liver clinic series data summarised by Freeman and colleagues[3] would therefore seem to provide the best available estimates from the literature; however, there are certain concerns about the use of literature-based estimates in the mild hepatitis C cost-effectiveness model.

Potential problems with using transition probabilities from the literature for the mild HCV model

Several problems surrounded the use of probabilities from the literature for the mild hepatitis C model. First, separate estimates were not available for the transition probability of mild to moderate disease and then moderate disease to cirrhosis. Instead, it was necessary to assume a constant rate of progression from mild disease to cirrhosis, which may not be realistic.

Another problem is that the studies may not be relevant to the model's target population. In particular, rates from studies in Japan, the USA or even other European countries, may not be relevant because the characteristics of the patients and the styles of clinical management may differ. The characteristics of patients, in particular age at infection, alcohol and gender, have been shown to be associated with disease progression.[4,5] Following these findings, cost-effectiveness models for hepatitis C should present subgroup analyses for different patient characteristics, as the cost-effectiveness of an intervention is likely to vary according to different progression rates. However, the extent to which adjustment can be made for different cofactors is limited, when using estimates from the literature. For example, although the Freeman study[3] illustrated that cofactors were associated with disease progression, details were not provided in a usable form for estimating transition probabilities by cofactor.

In light of these problems with using published transition rates for the model, the authors collaborated with a separate Department of Health-funded study to produce empirical estimates of disease transition, for use in the cost-effectiveness model.

Empirical estimates of early disease transition

The authors collaborated with colleagues at the Medical Research Council (MRC) Biostatistics Unit (Cambridge) working on a separate Department of Health study estimating the burden of hepatitis C which required empirical estimates of transition probabilities.[76] The early transition probabilities required by the cost-effectiveness model were estimated using methodology developed as part of the Department of Health study. A second Markov model was used to estimate rates of progression through fibrotic stages of hepatitis C. Such models have been extensively used to estimate disease progression for HIV infection and AIDS,[77–79] diabetic retinopathy,[80] bronchiolitis obliterans syndrome,[81] hepatic cancer[82] and also recently hepatitis C.[83] This study used a data set from a previously published retrospective cohort study,[5] which estimated fibrosis progression in hepatitis C. These patients had all attended St Mary's Hospital, the lead centre for the mild hepatitis C trial, and had had at least one liver biopsy between 1 January 1990 and 30 June 2001. All patients were known to be HCV antibody and RNA positive. Exclusion criteria were HCC, other types of liver disease in addition to their hepatitis C, HIV infection, treatment before first biopsy and non-interpretable biopsy.

In total, 430 patients were enrolled in the St Mary's cohort; 57 were missing date of infection and were excluded from the analysis, leaving 373 patients in the analysis sample. Data were collected on patient demographic details (gender, date of birth, age at infection, current alcohol intake, risk factor, ethnic origin), histological (dates and scores) and virological features (HCV genotype) and antiviral therapy (dates and types). Biopsy data following antiviral treatment were not used in the analysis. The characteristics of the patients included (*Table 21*) were similar to those recruited to the mild hepatitis C trial (*Table 8*).

Markov model to estimate transition probabilities

At each liver biopsy the fibrosis stage was recorded using the modified HAI (Ishak) scale, the fibrosis stages were then grouped into three categories:

TABLE 21 *Characteristics of the patients included in the analysis*

Characteristic		*n* (%) unless stated otherwise
No. of patients		373
No. of liver biopsies	1	372
	2	49
	3	5
	4	1
Time between infection and first biopsy (years), mean (range; median)		16.6 (1.0–55.0; 16.3)
Time between first and second biopsies (years), mean (range; median)		2.6 (0.2–6.0; 2.4)
Gender		
Male		226 (61%)
Female		147 (39%)
Age at infection (years), mean (range; median)		25.3 (1.0–62.0; 22.0)
Viral genotype		
1		109 (29%)
Non-1		50 (13%)
Unknown		214 (57%)

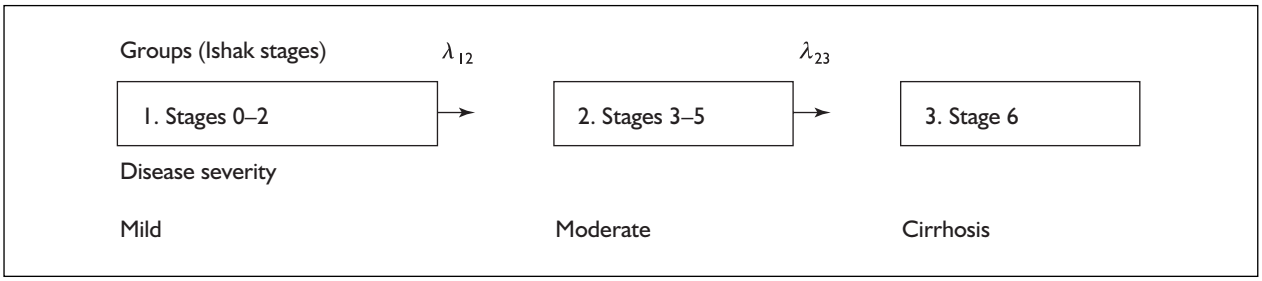

FIGURE 11 *Markov model for fibrosis progression*

mild (F0–2), moderate (F3–5) and cirrhosis (F6) (*Figure 11*).

This grouping allowed the rates of progression required by the cost-effectiveness model to be estimated. Forward progressions were allowed between neighbouring groups. Any observed regressions were treated as misclassifications. The stages in the model were labelled 1, 2 and 3. All patients were assumed to have no fibrosis at infection and entered the model in stage 1. Progressions between the stages could then occur between the date of infection and the first liver biopsy (this is how the majority of the transitions observed occurred, given that the majority of cases only had one biopsy), and between the first and subsequent biopsies for those cases with data from several liver biopsies. The model used the number of transitions observed over the period of follow-up to estimate transition intensity. The transition intensity [λ_{rs}] represents the instantaneous risk of moving from state r to s, hence $\lambda_{rs}\delta t$ is the probability of moving from state r to s in a small time interval δt, so for example λ_{12}, where $\delta = 1$, gives the annual transition probability of moving from mild to moderate disease. It was assumed that disease progression only depends on the current state occupied, and that the transition intensities are constant over time. Unlike the estimates derived from the literature, an important advantage of this modelling approach was that it allowed the transition probability of moving from mild to moderate disease to differ from moderate disease to cirrhosis. Estimates of the annual transition probabilities were obtained using maximum likelihood (see Appendix 3 for further details).

Results: estimates of transition probabilities

Forty-two patients (11%) progressed to cirrhosis during follow-up. Two-hundred and forty-one patients (65%) showed no signs of progression to moderate disease. Male gender ($p = 0.008$), older age at infection ($p < 0.001$) and alcohol consumption greater than 40 units per week ($p = 0.022$) were all associated with increased disease progression in a univariate analysis.

TABLE 22 *Annual transition probabilities, predicted for the main group characterising the trial population and relevant subgroups*

	Mild–moderate Estimate [SE] (95% CI)	Moderate–cirrhosis Estimate [SE] (95% CI)
Main group		
Age 25 at infection 50% genotype 1 60% male	0.025 [0.004] (0.02 to 0.031)	0.037 [0.007] (0.025 to 0.053)
Subgroup		
Age 25 at infection 100% genotype non-1 100% male	0.031 [0.007] (0.022 to 0.042)	0.045 [0.011] (0.028 to 0.071)
Age 25 at infection 100% genotype non-1 100% female	0.021 [0.005] (0.015 to 0.031)	0.031 [0.009] (0.019 to 0.051)
Age 50 at infection 100% genotype non-1 100% male	0.081 [0.021] (0.050 to 0.123)	0.094 [0.039] (0.039 to 0.219)
Age 50 at infection 100% genotype non-1 100% female	0.057 [0.016] (0.034 to 0.092)	0.066 [0.028] (0.026 to 0.158)

No significant associations were found for viral genotype 1 ($p = 0.649$), Caucasian ethnic origin ($p = 0.997$) or past hepatitis B virus infection ($p = 0.135$).

The multivariate analysis included the covariates gender, age at infection, weekly alcohol consumption and viral genotype. Although viral genotype was not associated with the rate of fibrosis it was included in the analysis because it is associated with the effectiveness of antiviral therapy, and is therefore an important parameter in the cost-effectiveness model.

The estimated 1-year transition probabilities for different patient subgroups were obtained and *Table 22* gives the annual transition probabilities for the relevant groups for the cost-effectiveness model. All the results are presented for patients consuming less than 40 units of alcohol per week, as this was an inclusion criterion for the trial. The overall trial population was 60% male, with 50% having genotype 1 and the mean age at infection was 25. The mean estimated annual probability of progression for this the main group of interest, was 0.025 for mild to moderate disease and 0.037 for moderate disease to cirrhosis. The predicted probability of progression was highest for patients aged 50 at infection, who were male with genotype non-1. *Figure 12* shows that using these transition probabilities, the probability of staying cirrhosis free for the main group of interest was predicted to be about 0.8 after 30 years of infection.

Interpretation of results

The multivariate analysis found, in line with previous studies of progression, that the probability of transition between health states varied according to patient cofactors.[4,5,74] Importantly, transition probabilities could then be estimated specifically for the trial (and hence the model) population. Usually Markov models of cost-effectiveness have to rely on using the most relevant transition probabilities for their population of interest from the literature, and rarely have the opportunity of customising the transition probabilities in this way. The analysis was also able to estimate transition probabilities for various subgroups, which will allow cost-effectiveness analyses to be conducted for the subgroups of interest.

One concern with models of this type is whether they have predictive validity. Part of the analysis tested whether the model made valid within-sample predictions of transition probabilities. The validation model using 245 patients gave similar transition intensities and covariate effects to the model using all of the data. The resulting model gave predicted state occupancies for the remaining 128 patients. *Table 23* presents the observed and predicted number of patients in each state for each observation, and shows that the model had good predictive validity.

The results suggested that the transition probability for moderate disease to cirrhosis is

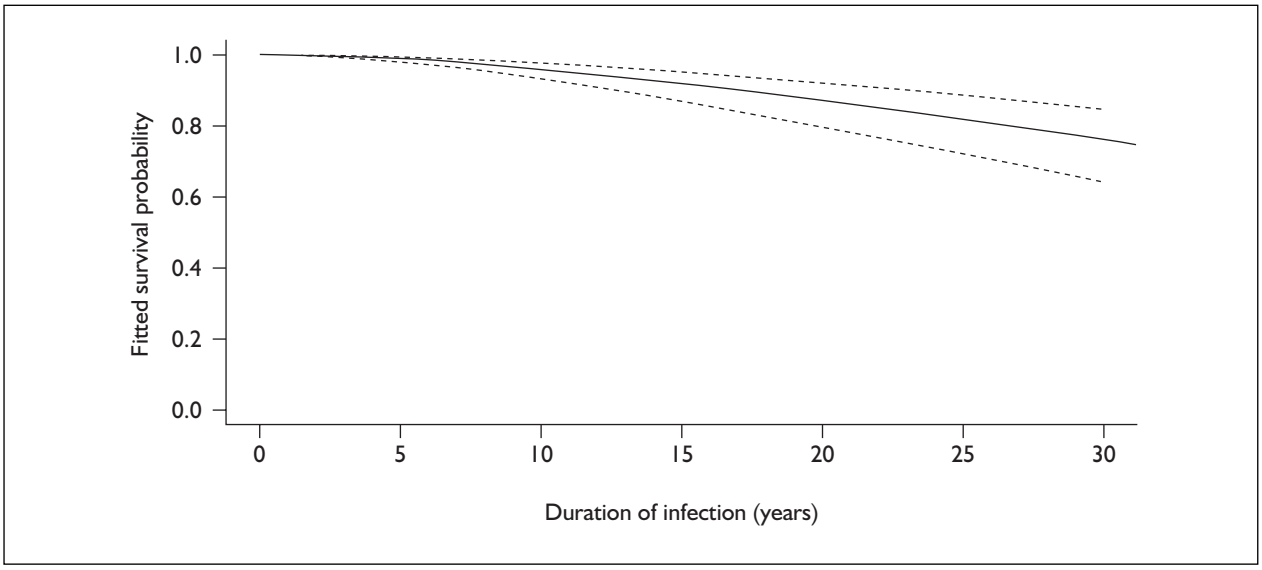

FIGURE 12 *Probability of staying cirrhosis free if untreated, for a subgroup of patients aged 25 years at infection; 60% are male and 50% are genotype 1*

TABLE 23 *Observed and predicted states for a third of the St Mary's cohort (using the other two-thirds to fit the model)*

	State 1 (F0–2)	State 2 (F3–5)	State 3 (F6)
First biopsy	84 (83.2)	29 (28.4)	14 (15.4)
Second biopsy	11 (11.7)	5 (3.9)	0 (1.5)
Third biopsy	1 (0.6)	0 (0.3)	0 (0.1)

lower than from mild to moderate disease (*Table 22*). Thus, allowing for a differential rate between these disease stages would appear to be important, and therefore using these estimates rather than those based on the literature would appear to improve the model. Different transition rates from mild to moderate and moderate to cirrhosis may occur because some individuals with very slow rates of fibrosis may never develop moderate disease. Only those individuals with faster rates of transition enter the moderate to cirrhotic stage. This does not imply that fibrosis progression increases as the disease progresses; the model still assumes that progression from mild or moderate disease is constant over time. To test whether this assumption is valid a study with sequential liver biopsies over a long period of follow-up would be required. Such a data set is not likely to be available for the UK in the foreseeable future.

In conclusion, the empirical analysis of early transition probabilities provided the best estimates of transition probabilities for the cost-effectiveness model.

Other transition probabilities

Postcirrhosis

The main emphasis in this chapter has been on choosing or estimating appropriate early disease transition probabilities. For a cost-effectiveness model for mild hepatitis C these were particularly important. However, the model also required transition probabilities to be selected for later disease transitions. A literature review was conducted to identify appropriate studies for estimating these transition probabilities. The study by Fattovitch and colleagues was found to be the most appropriate,[84] as it included the requisite information to estimate annual transition probabilities and was based on cases with cirrhosis related to hepatitis C. Patients were identified retrospectively from seven European centres, importantly including a UK tertiary referral centre. The study was a retrospective cohort study of 384 compensated cirrhotics (other published studies in cirrhotics of similar size frequently contain a variety of aetiologies). Patients were assessed at least annually for a mean of 5 years until death or the end of the study. The probability

of survival, developing HCC or decompensated disease was plotted using survival analysis.

The Fattovitch study found that the cumulative probability of developing HCC from either cirrhosis or decompensated cirrhosis was 4% at 3 years, 7% at 5 years and 14% at 10 years. Using these data it was possible to calculate that the annual probability of HCC from either cirrhosis state was 0.014 during the first 5 years. Similarly, the results from the Fattovitch study were used to estimate the annual probability of death from decompensated cirrhosis (0.13) and HCC (0.427) (*Table 24*).

The model also allowed for the possibility of liver transplantation following either decompensated cirrhosis or HCC. To estimate the probability of transplantation, data are required on the number of hepatitis C-related liver transplantations each year, and on the prevalence of decompensated cirrhosis and hepatitis C. Although there are data on the total number of hepatitis C-related liver transplantations performed each year in the UK (national transplantation register),[85] data have not been collected on the national prevalence of hepatitis C-related cirrhosis or HCC. In the absence of these data the authors followed the approach of Siebert and colleagues,[42] who took an estimate of the rate of liver transplantation for hepatitis C cases in the USA, and based on European transplant registry data, revised the estimate downwards to 2%, as the USA is likely to have a higher rate of transplantation than most centres in Europe, including the UK.[85]

For the probability of death following transplantation a survival analysis of UK liver transplant registry data was used, conducted by colleagues based at the Royal College of Surgeons (RCS). This gave a probability of death in the year following transplantation of 0.15, and then 0.03 in subsequent years.[85]

All-cause death rates

It was assumed that the age-specific all-cause death rates for patients with hepatitis C were the same as those from the general population. There is evidence to suggest that cases with hepatitis C are generally at similar risk of all-cause death as the general population.[86] Even though certain subgroups of the hepatitis C population (e.g. those who are involved in active IVDU) are at higher risk of all-cause death, these cases were excluded from the mild hepatitis C trial, and indeed from treatment in general, and are not relevant for the model.

The probabilities of all-cause death were taken from UK life tables published on the Government Actuary's Department website (http://www.gad.gov.uk).[87] The data are age and gender specific, and for this model the relative proportions of men and women included in the trial were used to weight the probability of death at each age. In the base-case analysis the entry age for the model was set at 40 years, approximately the mean age at trial entry. Subsequent subgroup analyses were run varying the age at model entry from 20 years up to 65 years, and the appropriate age-specific all-cause death rates were then adjusted accordingly.

Discussion

A model was developed to evaluate the cost-effectiveness of interferon-α and ribavirin for patients with mild hepatitis C. The model development conformed to recent guidance for cost-effectiveness modelling;[88–91] the assumptions made and the choice of transition probabilities were made explicit. The transition probabilities reported for early progression are lower and more conservative than those previously used in cost-effectiveness modelling for hepatitis C. The previous estimates were based on clinical opinion or small samples of cases, and used data that may not be relevant to the UK. The findings support recent suggestions that previous estimates may have overestimated the rate of disease progression,[3] and hence the relative cost-effectiveness of new interventions to prevent disease progression in hepatitis C.

The model takes a lifetime perspective in the base-case analysis, although the results will also be presented for shorter time-horizons for comparability with other studies in hepatitis C. The model makes certain assumptions that are widely used in hepatitis C models; for example, for patients treated with interferon-α and ribavirin who have had an SVR, it is assumed that patients do not progress through the disease; this assumption is supported by trial evidence.[67] It is also assumed that patients who are treated, but do not have an SVR, have the same probability of disease progression as the no-treatment cohort. This is a conservative assumption as it may be that antiviral treatment reduces the probability of disease progression even in the absence of an SVR.[67]

The model makes the widely used assumption in Markov modelling that the probability of moving

TABLE 24 *Summary of the transition probabilities used in the model*

Transition probability	Best estimate	Source
Effectiveness		
Mild disease–SVR (interferon-α and ribavirin)	0.33	Mild hepatitis C RCT (Chapter 3)
Moderate disease–SVR	0.33	Mild hepatitis C RCT (Chapter 3)
Disease transitions		
Mild–moderate disease	0.025	MRC biostatistics[76]
Moderate disease–cirrhosis	0.037	MRC biostatistics[76]
Cirrhosis–decompensated cirrhosis	0.04	Fattovitch, 1997[84]
Cirrhosis or decompensated cirrhosis–HCC	0.014	Fattovitch, 1997[84]
Decompensated cirrhosis–death	0.13	Fattovitch, 1997[84]
HCC–death	0.43	Fattovitch, 1997[84]
Decompensated cirrhosis/HCC–liver transplant	0.02	Siebert, 2003[42]
Liver transplant–death (year 1)	0.15	RCS, 2003[85]
Liver transplant–death (subsequent years)	0.03	RCS, 2003[85]
All-cause death	0 to 0.19	Government Actuary's Department (2000)[87]

from a health state is independent of the time in the health state. Studies of progression in hepatitis C have generally made an even more stringent assumption: that the rate of fibrosis progression is constant over time.[4,5] When applied to cost-effectiveness models this would mean that the mild to moderate transition is the same as the transition from moderate disease to cirrhosis. This restrictive assumption was not supported by empirical work on the early transition rates. This suggested that the transition probability of progressing from mild to moderate disease was low, but for the minority who progressed to moderate disease, there was a correspondingly higher probability of progressing to cirrhosis.

In the empirical study the patients who reached moderate disease were more likely to be men and older at infection. The use of empirical data allowed different transition probabilities to be specified for different subgroups of patients. This will allow the cost-effectiveness model to assess the relative cost-effectiveness of mild treatment for different groups of patients.

Although this substudy provided the best and most relevant estimates of disease transition rates available to the researchers, it still has limitations. In particular, the analysis currently only uses patients who had had a liver biopsy and attended a tertiary referral centre, and may not be broadly representative. At present, patients are required to have a liver biopsy before being considered for treatment, so using biopsied cases would seem relevant, and most patients are treated within tertiary referral centres. The results from this empirical analysis would seem to improve on estimates available from the literature and provide the best possible source of early transition rate data for the cost-effectiveness model. It would be desirable to extend the modelling approach outlined to a wider range of hospital settings and this is part of research currently in progress.[76]

To conclude, for most of the transition probabilities the best available estimates from the literature were used in the cost-effectiveness model. However, for the key transitions between mild disease and cirrhosis, the transition probabilities from the literature were not suitable and transition probabilities were estimated using the most appropriate data available. Uncertainty always surrounds the assumptions and parameters used in cost-effectiveness models, and the sensitivity of the results to the rates of disease progression and the modelling assumptions made will need to be tested as part of the cost-effectiveness analysis.

Chapter 5

The costs of different stages of hepatitis C

Introduction

To estimate the cost-effectiveness of antiviral therapy for mild hepatitis C the model requires information on the costs of each disease stage. There is, however, a lack of empirical evidence on the costs of the various stages of hepatitis C;[59] previous cost-effectiveness studies in hepatitis C have been limited by this lack of good quality cost data.[6,7,43,44,48–50,64,65] These studies have relied on costs derived from health professionals' assessments of the resources required to provide 'good practice'. These estimates may be inaccurate; for example, some patients may fail to complete antiviral treatment regimens specified by clinical protocols. This approach also fails to incorporate variability in resource use between patients, and may therefore provide a false sense of certainty about the results of the cost and cost-effectiveness analyses. It is therefore important to collect cost data so that accurate costs associated with disease progression can be used in the cost-effectiveness analysis. In light of this gap in the literature an important objective of this study was to measure the costs associated with the various stages of hepatitis C.

This chapter of the report is split into three main sections: the first section details the costing methodology used, the second reports the results, and the third presents the discussion and conclusions. The methodology section is divided into separate subsections on data collection for patients with mild disease and later disease (moderate disease, cirrhosis and decompensated cirrhosis). There are then general sections on the measurement of unit costs and the statistical analysis. The results section reports the resource use and total costs separately for the mild disease and later disease stages, before reporting the results of the statistical and sensitivity analysis across all disease stages.

Costing methodology

Overview of costing methodology used

To assess the cost-effectiveness of antiviral treatment at a mild compared with a moderate stage, cost data were required for the relevant disease stages (*Table 25*). For each disease stage detailed resource-use data were collected for a sample of patients to enable empirical cost estimates to be constructed and used in the cost-effectiveness model.

For the stages related to mild disease, resource-use and cost data were collected alongside the mild hepatitis C RCT. For the moderate, cirrhosis and decompensated cirrhosis stages a separate observational costing study was conducted. For all disease stages, rather than attempting to measure costs across all the liver centres recruited to the trial, detailed costs were estimated for patients attending three centres in London, Newcastle and Southampton. Each of these centres has a large teaching hospital, which provides a range of hepatology services to the local community.

For the liver transplantation stages, costs were made available from the national Department of Health-funded liver transplantation study.[92]

All costs were measured from a health-service perspective. Inpatient and outpatient resource use incurred at both the study hospitals and other hospitals that the patients attended were included.

Data collection for mild disease stages

Patients and resource use included

There were 196 patients included in the mild hepatitis C trial, of whom 83 patients (44 treatment,

TABLE 25 *Disease stages in the model requiring cost estimates*

Mild disease stages	Later disease stages
Work-up for mild hepatitis C patients	Monitoring moderate disease
Monitoring for mild hepatitis C	Antiviral treatment moderate disease
Treatment for mild hepatitis C	Monitoring following SVR
Monitoring following SVR	Management of cirrhosis
Monitoring following non-SVR	Management of decompensated disease
	Management of HCC
	Liver transplantation
	Follow-up following transplantation

39 control) attended the three centres included in the detailed costing study. For each of these cases, detailed resource-use information was collected covering inpatient and outpatient care, investigations, procedures and drug use. The resource-use data were collected from patients' case notes and computer databases. Consideration was given to including a broad range of resource use beyond the hepatology services provided, by including available information on the use of other related services such as psychiatric services. Resources were also included if consumed in hospitals outside the study hospital, for example in local district general hospitals (DGHs). These data were obtained by requesting discharge summaries, or separate case notes containing the required resource-use information from the relevant hospitals.

Definition of mild disease substages

To provide the cost data required by the model, the patients' resource use during the mild phase had to be split into certain substages (*Table 26*). For all cases the resource use incurred, between the date of screening and the date of randomisation, that was related to hepatitis C was defined as initial investigation costs.

For patients in the control group resource use was attributed to this substage from the date of randomisation until the date they were due to have their last follow-up visit. Following randomisation, 44 cases were allocated to receive interferon-α and ribavirin. The resources used during the treatment phase were recorded on a separate form, and attributed to the intervention. The treatment phase included all the relevant resources consumed while the patient was taking antiviral therapy, and in the 6 months following cessation of therapy. Any resource use related to side-effects of the intervention was included.

Following the PCR test at 6 months post-treatment patients were defined as entering either the SVR state (PCR+) or the non-SVR state (PCR–). For both of these substages resource use was measured from the date when the patient was entered into the substage until the last possible date of follow-up. In some cases this was 48 weeks post-treatment, but in other cases no further information was available from an earlier date, and therefore the patients' resource-use consumption was censored accordingly. For a minority of patients (five in the non-SVR state and one in the SVR state) no information was available after the patient completed treatment; these cases were therefore excluded from this aspect of the analysis.

Excluding trial-based resource use

For each patient and each substage careful consideration was given to measuring those resources that would be consumed in routine practice. In RCTs resources are used for administrative purposes, which would not be consumed in routine practice; these resources should generally be excluded from cost analysis.[93] The healthcare professionals in each centre were therefore asked to identify those visits specified by the trial protocol that would not be provided as part of routine practice care. These visits, and their associated resource use (blood tests and other investigations) were therefore excluded from the analysis. (At each of the centres treatment protocols specifying the frequency of patient visits during treatment were available based on patients with moderate disease; these were applied to the mild hepatitis C treatment group. Patients' resource consumption was therefore limited to the level specified by these protocols, although if further visits, tests, investigations or hospitalisations occurred as a result of the treatment or the disease these were included. Similarly, for control patients the centres concerned usually specified one or two visits per year for the patient. Again, this protocol was followed unless there were indications in the patients' case notes of more frequent visits due to the patients' hepatitis C rather than as required by the trial protocol.) One resource-use item that was left unadjusted in the main analysis was the duration of therapy, which was reported as the duration observed during the trial. This was the therapy duration associated with the measure of patients' outcome (proportion of

TABLE 26 *Definition of substages related to mild hepatitis C*

Substage	Definition	*n* (complete data)
Initial investigation	Date of screening to date of randomisation	83 (83)
Control	Date of randomisation to end of follow-up	39 (39)
Treatment	Date of start of therapy to 6-month PCR	43 (43)
SVR	Date of 6-month post-treatment PCR– to end of follow-up	16 (15)
Non-SVR	Date of 6-month PCR+ to end of follow-up	27 (22)

TABLE 27 *Patients considered for inclusion in the observational study*

	No. of patients who met study criteria	Patients considered for inclusion	Notes accessed
Moderate disease	310	190	183
Cirrhosis	128	128	122
Decompensated cirrhosis	60	60	53
Unclassified	773	0	0
Total	1271	378	358

cases having an SVR) used in the cost-effectiveness model. However, the trial protocol allowed for treated patients to have up to 1 year of therapy, whereas in routine practice patients with genotype non-1 would only have a maximum of 6 months of therapy. The impact of limiting treatment duration to a maximum of 6 months for patients with genotype non-1 was considered as part of the statistical analysis.

Data collection for later disease stages

Patients included

To calculate the costs of later disease stages, patients were again recruited from three hepatology centres, in London, Southampton and Newcastle. Patients were considered for inclusion if they attended any of the three study hospitals for an inpatient admission related to hepatitis C, or for an outpatient appointment at the liver clinic, between 30 March 1998 and 1 April 2000. The patient admission system, local virology and histopathology databases were used to recruit patients. Duplicates and patients who had not tested PCR positive were excluded. Patients considered for inclusion were categorised into the different stages of hepatitis C. Patients were defined as having decompensated cirrhosis if they were admitted to hospital with an International Classification of Diseases (ICD-10) diagnosis code related to decompensated cirrhosis. Patients were categorised as having cirrhosis if they had a fibrosis score of 6 (Ishak scale) from a recent liver biopsy (after 1 January 1996) or if a diagnosis of cirrhosis was given in a letter from the patient's outpatient doctor to the GP. [These letters were reviewed by a member of the research team (MW) and where the diagnosis of cirrhosis was uncertain the patient's case notes were recalled. In particular, it was sometimes uncertain whether the patient had cirrhosis or decompensated cirrhosis. From information available in the patient's case notes it was possible to categorise the patients using the Child–Pugh score into cirrhosis (Child Pugh A) or decompensated cirrhosis (Child Pugh B or C).] To identify patients with mild or moderate disease it was necessary to have results from a recent liver biopsy available. Fibrosis and necroinflammatory scores based on the Ishak scale were then used at the centres in London and Newcastle to identify which patients had moderate rather than mild disease (Fibrosis score >2 or Necroinflammatory score >3). For patients in the third centre (Southampton) the IPA (Inflammation, Parenchymal damage, Architecture) scoring system was used to identify patients with moderate disease. (This scale is based on the Metavir scale; scores based on this scale have been found to be highly correlated with those based on the Ishak scale.[5])

For 773 patients who met the initial inclusion criteria, a recent biopsy was not available and there was no information to suggest they might have cirrhosis or decompensated cirrhosis. These patients were defined as unclassifiable and were excluded from the study. A previous audit into management of hepatitis C also found a high proportion of patients referred for their hepatitis C who had not had a liver biopsy. The distribution of patients included in the observational study is listed in *Table 27*.

For the patients with moderate disease a large number of cases was recruited (n = 310). Rather than devoting excessive research resources to measuring costs for each of these patients, a random sample of 190 cases was taken over the three centres. For the patients with cirrhosis and decompensated cirrhosis all the cases available were included in the study. In total, 378 patient observations were considered for inclusion. Some patients were included in more than one stage, as during the observation period their disease progressed, for example from cirrhosis to decompensated cirrhosis. Medical records were unavailable for a total of 23 patients, who were excluded from the analysis, leaving a total of 355 observations for analysis. For patients with cirrhosis or decompensated cirrhosis, case notes were used to ascertain whether the patient had been diagnosed as having HCC. Where a diagnosis of HCC was made any subsequent resource use was recorded as a separate substage.

Resource-use measurement

Patients were required to have attended a study hospital between March 1998 and April 2000 to be included in the study; however, this period did not define the duration of resource-use measurement. Instead, to make most use of the data available for each disease stage, resource use was measured for the maximum time for which information was available for each stage. The date of entry into a particular stage was defined as the date when the patient first attended the study hospital and there was evidence that the patient had reached the stage in question, for example from a liver biopsy. The date of exit from a stage was defined as the date when the patient moved to the next stage, died or was lost to follow-up.

All of the resource use related to hepatitis C between the dates of stage entry and exit was recorded from hospital case notes, and from histopathology, virology and pathology databases. To decide which resources were attributable to hepatitis C, resource use was allocated into three categories. The list of items for inclusion in each category was decided upon through discussion with the project steering group and by piloting the resource-use measurement tools in each centre. Certain resource-use items (e.g. healthcare consultations with hepatologists, PCR tests, endoscopies and use of antidepressants) were defined as being attributable to hepatitis C and were included. Certain other resource use (e.g. inpatient admission related to hip fracture) was defined as definitely not related to hepatitis C and was excluded from the analysis. A third category of resource use was defined as resource use that could potentially have been attributable to hepatitis C (e.g. consultations with a dietitian). Healthcare professionals at each centre were asked to judge for individual cases whether the resource use was hepatitis C related or not, and on this basis resource use that fell into this third category was either included or excluded. For patients with moderate disease, resource use related to antiviral treatment and to any subsequent SVR following antiviral treatment was recorded on a separate form, to enable the costs associated with these disease substages to be reported separately.

Unit costs for all disease stages

The sources used for estimating unit costs are summarised in *Table 28*. Drug costs were taken from the British National Formulary (BNF).[94] This source is recommended for providing drug costs that are likely to be applicable in general to the UK.[95] To measure the unit costs of outpatient visits, to both doctors and nurses, site visits were undertaken in each centre. Healthcare professionals were asked to estimate the average time required by them to provide a consultation for a hepatitis C patient. Staff costs per hour were collected for each grade of staff from each hospital's finance department, and combined with the estimated staff time to give the staff costs of a consultation. The costs of London weighting were excluded to improve the generalisability of the unit costs. The proportion of outpatient direct costs that were allocated to overheads and capital was not available for the hospitals considered. Instead, the proportions of direct costs allocated to overheads and capital were taken from a recent detailed study on the costs of hospital-acquired infection.[96]

The costs of investigations were taken from the finance departments at each of the study hospitals. The finance departments were asked to provide the unit cost that they would charge another NHS provider, as this would be most likely to reflect the total cost to the NHS of providing the intervention. For each investigation appropriate additions for overheads and capital were included.

Costs were unavailable from finance departments on the costs of most procedures, and where they were available there was concern about the accuracy of the costs reported. To address this, site visits to each centre were undertaken to estimate the staff time involved in providing each procedure for an 'average' hepatitis C patient. Staff were also asked to estimate the consumables typically involved in providing each procedure.

TABLE 28 *Summary of unit costing approach*

Cost category	Sources for unit costing
Drug costs	BNF, 2002[94]
Outpatient visits	Site visits to assess staff time specifically for hepatitis C cases Staff costs from finance departments Previous study for allocation of overheads and capital[96]
Investigations	Finance departments in individual centres
Procedures	Site visits to assess staff time specific for hepatitis C cases Previous study for additional allocation of overheads and capital[96]
Inpatient days	Site visits and bed-day allocation for staff time Staff costs from finance departments Allocation of overheads and capital from finance department

The costs of overheads and capital were again allocated based on the proportion of overheads and capital reported in the hospital-acquired infection study.[96]

For the cost of each hospital day, a separate unit cost was constructed for each ward attended by the hepatitis C patients included in the database. To estimate the hotel cost component of each hospital day it was necessary to allocate certain costs (nursing time, medical time, overheads, capital) from the relevant department to the individual bed-day. To do this, the proportion of the overall expenditure for each item that was relevant to the provision of inpatient care was first identified. This was done by asking the healthcare professionals concerned to allocate a proportion of their working week into different categories. For example, clinicians were asked to estimate the proportion of their time spent working in inpatient care rather than research, teaching and outpatient care. This proportion was then used to estimate the total cost of medical time in the relevant department. The relevant total costs for inpatient care were then allocated to the individual inpatient day. This was done by dividing the relevant total annual costs (e.g. medical inpatient costs) by the total number of bed-days consumed in the department or ward concerned, to give an average cost per bed-day. This assumes that the patient with hepatitis C consumes the average level of these resource items in the ward or department concerned. This was repeated for all elements of staff time. The total costs of consumables, overheads and capital relevant to inpatient care in the particular department were identified from finance department records. These were then allocated to the individual bed-day by dividing the total annual cost in each category by the number of bed-days in each department.

The unit costs estimated (e.g. liver unit day) were the sum of each cost component (e.g. staff costs per day, consumables costs per day, overhead and capital costs per day). All unit costs were adjusted using an appropriate price index[97] and reported in 2002/03 prices.

Statistical analysis

For each patient and each disease stage, the resources consumed were multiplied by the relevant unit costs to give a total health service cost over the period of observation. For certain costs (e.g. antiviral treatment costs and initial investigation costs), the duration of the observation period corresponded to the duration of the stage in the model. In this case the mean costs were estimated directly for the stage in question. These mean costs were then used directly as inputs to the model. However, most costs needed adjustment as the observation period was longer or shorter than the 1-year period required by the model. These costs were therefore annualised, by dividing the total costs observed for an individual patient by the duration of the observation period (in years) for that patient, to give an annual cost for each patient in each disease stage. So, for example, if the costs for a moderate patient were measured over 2 years, these costs were divided by 2 to give annual costs. This assumes that the intensity of the resource consumption over the observation period is representative of the annual cost associated with the disease stage. Where the observation period was defined as too short to give meaningful cost estimates (less than 40 days) the patient was excluded from the analysis. The annual total costs for all patients included in the disease stage were divided by the number of patients in each disease stage, to give the average annual total health service costs for each disease stage.

An ordinary least squares (OLS) regression analysis was undertaken to extrapolate the results of the mild treatment costs to the trial centres not included in the mild costing study. This was done by using the OLS regression model to estimate the relationship between total treatment costs and treatment duration and patient cofactors for those cases included in the mild costing study. On the basis of this observed relationship, and the value of the above covariates in the excluded patients, the treatment costs were predicted for the patients excluded from the costing study.

OLS regression analysis was undertaken to estimate whether the health service costs within each disease stage varied according to patient factors. The purpose of this analysis was to predict mean costs for different subgroups of interest for the cost-effectiveness analysis (different ages, genders and genotypes). For patients with mild hepatitis C the analysis was undertaken assuming that the treatment duration was as observed during the trial. This analysis was repeated, but assuming instead that the treatment duration for patients with genotype non-1 was limited to 24 weeks, in line with typical clinical practice in the UK.

Finally, OLS regression analysis was used to test the hypothesis that health service costs varied according to the disease stage. The regression model included health service cost as the

TABLE 29 *Mild hepatitis C stages: patient characteristics and duration of antiviral treatment*

	Sample included (n = 83)	Sample excluded (n = 113)	p-Value
Age mean (SD)	42.1 (7.9)	38.3 (8.5)	<0.01
% Men	48	54	0.43
Source of infection			
% IVDU	58	50	
% Blood products	18	14	
% Unknown	24	36	0.19
Genotype			
% 1	65	58	
% Non-1	35	42	0.47
Treatment group			
% Treatment	53	48	
% Control	47	52	0.29
% SVR in treatment group	39	28	0.26
Treatment duration (weeks),[a] mean (SD)	38.9 (14.6)	35.8 (15.9)	0.32

[a] Reported on trial CRFs.

dependent variable and disease stage and patient covariates as independent variables. The patient covariates included were patient characteristics that were likely to be associated with cost differences but not with disease progression.

Results

Mild disease

Patient characteristics

In the three centres where detailed resource use and cost data were collected, 83 mild cases were included in the analysis. The characteristics of the patients included are presented in *Table 29*, and are reasonably similar to those of the patients excluded from the main cost analysis, with only age being significantly different. Importantly, for the estimation of the costs of antiviral treatment, the duration of treatment was similar in the cases included and excluded from the main cost analysis.

Resource-use measurement

During the work-up period, each of the patients included in the costing study (n = 83) had a liver biopsy, a genotype test, a PCR and other blood tests, and on average 1.2 visits were made to a hospital doctor during this period.

For the patients who had antiviral treatment, the mean (SD) duration of interferon-α and ribavirin use was 37.8 (15.6) and 37.6 (15.3) weeks. The mean (SD) duration of the observation period related to treatment (see definition in *Table 26*) was 1.09 (0.46) years and for the control group was 1.72 years (0.83). The main items of resource use are shown in *Table 30*. During the treatment period there were four hospital admissions related to interferon-α. These included one for a further liver biopsy (1 day), one for sickness and vomiting related to the intervention (1 day) and two for attempted suicides (1 day and 40 days). Each of the hospital admissions was adjudged to be related to the intervention and hence the costs of these hospital admissions were attributed to the intervention. Apart from the higher inpatient resource use during the treatment phase, outpatient visits to the doctor and particularly the nurse increased in accordance with the need to monitor the intervention and its side-effects (*Table 30*).

TABLE 30 *Resource use during the treatment and control stages*

	Treatment (n = 44) Mean (SD)	Control (n = 39) Mean (SD)
Hospital days	1.26 (7.00)	0
Visits to doctor	2.54 (1.33)	1.27 (1.00)
Visits to nurse	8.90 (5.47)	0.47 (0.68)
PCR tests	1.98 (1.20)	0.08 (0.18)
Liver biopsies	0.04 (0.19)	0.01 (0.09)

At the end of the treatment phase, patients were defined as either having an SVR or not having an SVR. The main resource use during each of these two treatment substages is described in *Table 31*. Although the numbers of cases were small, the

TABLE 31 *Mean annual resource use during the SVR compared with the non-SVR phases*

	SVR (n = 17) Mean (SD)	Non-SVR (n = 22) Mean (SD)
Hospital days	0.13 (0.50)	0 (0)
Visits to doctor	0.70 (0.58)	1.63 (2.41)
Visits to nurse	0.50 (0.52)	0.47 (0.68)
PCR tests	0.63 (1.02)	0.08 (0.18)
Liver biopsies	0.07 (0.21)	0.01 (0.09)

results illustrate that resources relevant to hepatitis C continued to be used by the SVR group. For example, one patient had a hospital episode (attempted suicide) that was adjudged to be related to their previous hepatitis C. Patients were also likely to have PCR tests and other blood tests related to hepatitis C.

Unit costs: all disease stages

A selection of the unit costs used in the study for both the mild and severe disease stages is given in *Table 32*, with a more extensive list given in Appendix 4. The unit costs were reasonably similar across the three centres included in the study, reflecting the consistent costing methodology applied and the general agreement about the resource inputs required to provide each of the items concerned. For certain items (e.g. liver unit day) there was a wide discrepancy in the unit cost, with the centre in Southampton having a much lower unit cost. The main driver for this was the nursing input, which was much lower for the liver unit in this centre. This may reflect a less severe case mix of patients in this centre than in the other two centres.

Total costs for mild disease

The mean (SD) total cost of the initial investigation stage for patients with mild disease was £684 (£219); the majority of the costs were for investigations (£254) and procedures (£382). The mean (SD) total costs incurred during the treatment stage were £7141 (£2852). The costs during the treatment period were dominated by the costs of antiviral therapy which, on average, accounted for 91% of the costs of the treatment phase. There was important variability about this average, however, which reflected variability in the duration of treatment and also the high hospitalisation costs incurred by a few patients (*Table 33*). The mean annual costs (SD) for the control or no-treatment group were £138 (£170) per year. All of these patients had had a liver biopsy as part of the initial investigation, so the only recurrent costs were for further investigation and monitoring of their hepatitis C. During the observation period none of these patients was admitted to hospital for reasons related to hepatitis C.

TABLE 32 *Selection of unit costs (£) used in the study*

Item of resource use	Unit cost (£)		
	London centre	Southampton centre	Newcastle centre
1 week of interferon-α (3 mu three times a week)	49	49	49
1 week of ribavirin (1000 mg per day)	148	148	148
Outpatient visit			
Doctor	19	15	20
Nurse	16	14	19
PCR test (quantitative)	63	70	36
Liver biopsy (day case)	243	233	271
Diagnostic endoscopy (upper gastrointestinal tract, day case)	98	124	109
Hepatic angiography	300	315	351
TIPPS	2192	2213	2542
Inpatient day			
ICU	1131	1141[a]	1131
HDU	278	323	367
Liver unit	246	119	228
General medical ward	141	130	138

[a] For the Southampton centre unit costs were unavailable for ICU and high-dependency unit (HDU) days, so the mean value from the other two centres was used instead. Only two cases in the data set used these bed-days in this centre.
TIPPS, transjugular intrahepatic portosystemic shunt.

TABLE 33 *Mean annual total health service costs (£) during treatment and control stages*

	Treatment (*n* = 44) Mean (SD)	Control (*n* = 39) Mean (SD)
Visits to doctor	50 (26)	24 (19)
Visits to nurse	148 (89)	8 (11)
Investigations	240 (111)	29 (19)
Procedures	11 (49)	65 (155)
Antiviral therapy	6514 (2659)	0 (0)
Other drugs	33 (80)	12 (72)
Hospital days	144 (854)	0 (0)
Total	7141 (2852)	138 (170)

TABLE 34 *Mean annual total health service costs (£) following SVR versus non-SVR*

	Non-SVR (*n* = 22) Mean (SD)	SVR (*n* = 16) Mean (SD)
Visits to doctor	32 (48)	13 (10)
Visits to nurse	1 (3)	1 (1)
Investigations	23 (24)	152 (60)
Procedures	53 (93)	18 (40)
Other drugs	2 (5)	52 (165)
Hospital days	8 (30)	23 (92)
Total	118 (121)	259 (193)

Patients during the SVR and non-SVR periods were only observed for 42 weeks and 57 weeks, respectively. Nevertheless, certain interesting trends emerge. First, at least in the initial period after the SVR, health service costs did not seem to fall, in fact they rose (*Table 34*). This reflected the high use of blood tests (especially PCRs), antidepressant medication and that one patient was hospitalised during this period for reasons related to their hepatitis C.

Later disease

Patient characteristics

Compared to the patients with mild disease (Chapter 3, *Table 8*) a higher proportion of cases included in the later disease study were male (*Table 35*), and in the cirrhotic and decompensated groups, patients were older and had had the disease for longer. The proportion of patients with blood products as the principal risk factor was higher than observed in general populations,[86] and may reflect the study's sampling strategy. The relatively low proportion of IVDU may be because patients in this group are less likely to attend follow-up appointments to have a liver biopsy.[32] Data were available on average over a 4- and 3-year period for the moderate and cirrhotic groups, but for less than 2 years for the decompensated cases. These patients were likely to have their costs censored earlier, because they either died or had a liver transplantation.

TABLE 35 *Demographic and case-mix characteristics at entry to the observational study*

	Moderate disease	Cirrhosis	Decompensated cirrhosis
No. of patient observations	183	122	53
% Males	66	71	79
Age (years), mean (SD)	41.0 (11.0)	47.4 (11.3)	51.6 (12.0)
Primary risk of infection[a]			
% Blood products	29	35	19
% IVDU	63	57	71
% Other	9	9	10
Age at infection (years),[b] mean (SD)	25.8 (10.7)	27.3 (11.8)	24.1 (8.9)
Duration of infection (years), mean (SD)	15.5 (9.2)	19.6 (9.3)	24.4 (9.5)
Time since diagnosis (years), mean (SD)	1.4 (0.6)	1.3 (2.3)	2.1 (2.7)
% Cases with HCC	0	6.6	23.1
Centre			
% London	36	43	38
% Southampton	32	27	27
% Newcastle	32	30	35
Time in study (years), mean (SD)	3.6 (6.2)	3.3 (2.0)	1.7 (1.3)

[a] The risk factor for infection was unknown or missing for 21 moderate cases, 30 cirrhotic and 21 decompensated cases.
[b] Data on date of infection were unavailable for 34 cases with moderate disease, 40 cases with cirrhosis and 22 cases with decompensated cirrhosis.

For the patients with moderate disease, the main resource use was in the outpatient setting; on average patients visited a doctor at outpatients four times per year for reasons related to their hepatitis C (*Table 36*). Patients with cirrhosis made more frequent visits to outpatients, and on average spent two days in hospital per year. Some of these patients had endoscopies and hepatic angiographies. For patients with decompensated cirrhosis, resource use was substantially higher than for those with either moderate disease or cirrhosis. In particular, patients with decompensated disease, who did not have HCC, were admitted to hospital for on average 21 days per year. Patients with HCC were even more likely to be admitted to hospital, staying on average for 23 days each year.

For the patients with moderate disease and cirrhosis the resource use during antiviral treatment and following an SVR was documented separately. For patients with moderate disease a total of 37 cases received a combination of interferon-α and ribavirin. The mean (SD) duration of treatment for these cases was 28 (17) weeks. This was a much shorter duration than for the patients with mild disease (duration, on average: 38 weeks). This reflects that for the moderate patients antiviral therapy was being provided in a routine clinical setting rather than alongside an RCT. A total of 17 moderate patients who had antiviral therapy had an SVR and the mean number of visits per year was 2.85. This supports the cost data collected for the mild hepatitis C patients, which also showed that following an SVR patients still incur costs related to their previous hepatitis C.

Later disease costs

The mean annual total cost of moderate disease was £717 and the highest cost items were outpatient visits and procedures (*Table 37*). The moderate disease costs were much higher than the mild disease costs (*Table 33*), which reflected the higher use of investigations, procedures and outpatient visits during this disease stage.

The average total cost for managing patients with cirrhosis was £1138. The higher costs compared

TABLE 36 *Mean (SD) annual resource use for patients with moderate disease, cirrhosis and decompensated cirrhosis*

	Moderate disease	Cirrhosis	Decompensated cirrhosis	HCC
No of observations	183	115	40	20
No. of admissions	0.27 (0.78)	0.57 (1.20)	3.10 (3.96)	3.70 (4.66)
Inpatient days	0.69 (3.13)	2.26 (8.13)	21.10 (10.39)	22.64 (31.52)
ICU days	0.03 (0.37)	0.01 (0.13)	0.22 (0.09)	0 (0)
HDU days	0 (0)	0 (0)	0.23 (0.10)	0 (0)
Liver unit days	0.38 (1.71)	1.84 (8.07)	13.41 (9.21)	10.89 (25.33)
Other days	0.28 (1.93)	0.40 (1.54)	7.24 (2.90)	11.74 (17.35)
No. of TIPPS	0 (0)	0 (0)	0.16 (0.06)	0 (0)
No. of hepatic angiographies	0 (0)	0.13 (0.73)	0.18 (0.07)	0.65 (1.00)
No. of endoscopies	0.10 (0.41)	0.31 (0.79)	2.27 (0.94)	0.46 (0.68)
No. of liver biopsies	0.66 (1.14)	0.26 (0.48)	0.07 (0.16)	0.30 (0.60)
No. of outpatient visits				
Doctor	3.81 (3.22)	4.08 (3.86)	5.36 (8.50)	5.36 (8.50)
Nurse	0.58 (1.24)	0.54 (1.14)	0.38 (0.15)	0.38 (0.15)

TABLE 37 *Mean (SD) annual costs (£) of severe disease*

	Moderate disease	Cirrhosis	Decompensated cirrhosis	HCC
No. of observations	183	115	40	20
Outpatient visits	222 (185)	84 (82)	77 (107)	64 (86)
Inpatient days	128 (500)	445 (1801)	6722 (7405)	5883 (7861)
Investigations	150 (151)	155 (221)	309 (297)	283 (306)
Procedures	227 (350)	426 (685)	1772 (2555)	1827 (2057)
Drugs	3 (16)	29 (117)	241 (491)	69 (169)
Total	717 (1029)	1138 (2479)	9120 (9610)	8127 (8541)

with managing moderate disease were driven by the higher hospitalisation and procedure costs. For patients with decompensated disease the annual costs were higher than for either of the two previous stages. The mean annual total cost was £9120 for decompensated cases without HCC. The mean total costs for HCC were slightly lower than for decompensated cirrhosis (£8127), as some patients in this state had cirrhosis (n = 7) rather than decompensated cirrhosis (n = 13). The principal cost component for both the decompensated and HCC health states was inpatient days which, on average, accounted for over 70% of the total costs.

The mean total costs of the antiviral treatment substage for patients with moderate disease was £4910. This was much lower than the costs for the similar stage for the patients with mild disease, reflecting the shorter treatment duration. The mean cost of the SVR substage following treatment for moderate disease was £211, which was similar to the corresponding state for the patients with mild disease (mean £259).

Liver transplant costs

For patients who had a liver transplant following decompensated cirrhosis or HCC, health service costs were taken from a Department of Health study examining the costs and outcomes following liver transplantation.[92] This study was undertaken by a group of health economists at Brunel University. In brief, the costing study divided the total costs of liver transplantation into different phases, waiting list phase, assessment phase, transplant operation and follow-up (up until 2 years). This study used a similar costing methodology to the hepatitis C study, and measured the resources used on an individual patient basis. Patients with various underlying liver diseases were recruited to the study from all six UK liver transplant centres (n = 772). For this study the costs for the subsample of elective transplant patients who had a diagnosis of hepatitis C were included (n = 67). The main cost results for these cases are shown in *Table 38*.

TABLE 38 *Mean (SD) total costs (£) of liver transplant, from Longworth and colleagues*[92]

Phase	Total cost (£)
Waiting list phase	3,727 (6,338)
Assessment phase	8,413 (7,614)
Transplant stay	27,330 (23,613)
Follow-up phase (0–12 months)	9,458 (20,856)
Follow-up phase (12–24 months)	1,385 (2,906)

Results from statistical analysis

Extrapolating from the mild hepatitis C costing centres to all centres in the RCT

The results from the mild hepatitis C costing study showed that the patients included in the costing study had similar characteristics to those patients included in the RCT but excluded from the costing study. Nevertheless, it might not be accurate to assume that the costs from this subsample apply to all the patients included in the RCT. To consider this, the treatment costs for the costing subsample (n = 44) were extrapolated to the mild hepatitis C patients who were treated but excluded from the costing sample (n = 52). The aim was to provide a cost estimate for all the treated patients included in the mild hepatitis C RCT (n = 96). The focus was on treatment costs because this was likely to be an important determinant of the cost-effectiveness of antiviral therapy. Data were also collected on treatment duration for all patients randomised to the treatment arm of the RCT, which provided a basis for extrapolation. To do this extrapolation, a regression model was developed to estimate the effect of treatment duration and patient covariates on treatment costs for the cases included in the mild hepatitis C costing study. The model that fitted the data best included just treatment duration; none of the patient covariates helped to explain the variability in treatment costs. The predictive validity of the simple model was reasonable (adjusted R^2 = 0.50). Using this model to predict costs gave a mean treatment cost for the patients excluded from the costing (n = 52) of £6675, which was slightly lower than the mean costs of the original costing sample (£7141). The average treatment cost estimated across all the mild hepatitis C patients included in the RCT was £6871.

Effect of patient factors on health service costs within each disease stage

OLS regression analysis was used to estimate the effect of patient cofactors (age, gender, genotype) on the total costs of each of the main disease stages. The results showed that for the base-case analysis none of the patient factors was significantly associated with treatment costs, and the model was poor at explaining the variability in treatment costs across the patients sampled (adjusted R^2 = 0) (*Table 39*). In the base-case analysis the treatment costs are those observed in the trial. A second scenario for the treatment costs was considered, where the duration of treatment is limited to a maximum of 24 weeks for the patients with genotype non-1. If this approach is followed then patients with genotype non-1 have

TABLE 39 *Results from the regression analysis estimating the effects of patient cofactors on the costs (£) within each disease stage*

	Treatment costs (observed costs) Coefficient (95% CI)	Treatment costs (limit to 24 weeks for genotype non-1) Coefficient (95% CI)	Moderate Coefficient (95% CI)	Cirrhosis Coefficient (95% CI)
Age (years)	–19 (–120 to 81)	–43 (–132 to 45)	–2 (–14 to 10)	1 (–45 to 48)
Genotype non-1	–984 (–2,903 to 934)	–3,426 (–5,113 to –1,740)	–[a]	–
Female gender	–195 (–2,000 to 1,609)	9 (–1,578 to 1,596)	–257 (–523 to 9)	–589 (–1,645 to 469)
Constant	9,597 (4,483 to 14,669)	12,692 (8,213 to 17,170)	1,160 (551 to 1,768)	1,833 (–443 to 4,090)
Adjusted R^2	0	0.33	0	0

[a] Genotype data were not available for later disease stages.

significantly lower treatment costs than patients with genotype 1. For patients with moderate disease and cirrhosis patient cofactors were generally poor at explaining cost variability between individuals, although women had lower moderate disease costs than men ($p = 0.06$).

Between-stage comparisons of health service costs

The final aspect of the statistical analysis tested the hypothesis that health service costs increased with disease progression after adjusting for differences in patient characteristics across the disease stages. One difficulty with formulating this regression model was that covariates such as age and gender could not be used to adjust for differences in the patient characteristics across disease stages, as these variables are themselves associated with disease progression. This regression model therefore just included source of infection as a variable to adjust for differences in the characteristics of cases, alongside disease stage (*Table 40*). Nevertheless, this model explained a fair proportion of the cost variability across the disease stages (adjusted $R^2 = 0.35$). Disease stage was associated with an increase in costs after adjusting for differences in route of infection. However, as there was considerable variability about the cost estimates within each stage, the costs of moderate disease and cirrhosis were not significantly higher than those for mild disease. This considerable variability surrounding the mean costs of each disease stage will need to be captured in the cost-effectiveness model.

TABLE 40 *Effect of disease stage on total costs (£), adjusting for source of infection*

	Coefficient (95% CI)
Disease stage	
Mild disease (reference)	
Moderate disease	569 (–771 to 1909)
Cirrhosis	903 (–512 to 2,320)
Decompensated cirrhosis	8,850 (7,126 to 10,574)
HCC	7,869 (5,771 to 9967)
Source of infection	
IVDU (reference)	
Blood products	180 (–788 to 1148)
Unknown	576 (–354 to 1,506)
Constant	2 (–1,243 to 1,248)
Adjusted R^2	0.35

Sensitivity analysis

Sensitivity analysis was used to test assumptions made when estimating the unit costs. This was done by presenting other plausible assumptions about the allocation of costs, and then examining the impact of changing these assumptions on the total costs of each disease stage. Where the cost results are found to be sensitive to the assumptions made, it may be necessary to vary the cost input in the cost-effectiveness model and assess the sensitivity of the overall result to the costing assumptions made.

The assumptions tested related to the allocation of overheads and capital when estimating unit costs. These assumptions were chosen based on concerns about the assumptions made in the base-case analysis regarding the allocation of these cost components. Previous studies have shown that the way in which these cost components are allocated can have an important impact on the results[96] (Graves N, Unpublished PhD Thesis, University of London; 2002).

In the base-case analysis inpatient overheads were allocated according to the proportions specified by the finance departments in each of the centres concerned, and outpatient and procedure costs by the proportion specified in the hospital-acquired infection study.[96] To test the importance of

allocating higher and lower proportions of overheads and capital to the costs of procedures and inpatient stays, the proportions used in the base-case analysis were varied by ±30%. The results showed that for the stages related to mild and moderate disease, changing the proportion allocated to overheads and capital had little impact on the overall results (*Table 41*). This reflected the low use of these cost components by patients in these disease stages. However, varying the allocation of overheads and capital by ±30% changed the mean costs of decompensated cirrhosis and HCC by 16% and 17%, respectively. Therefore, for these disease stages it may be worth considering different levels of overhead allocation during the sensitivity analysis for the cost-effectiveness analysis.

However, even changing the proportion allocated to overheads and capital by ±30% may not fully capture the uncertainty surrounding the use of overheads and capital. In particular, considerable uncertainty surrounds the appropriateness of the allocation of inpatient overheads and capital, which relied on the allocations specified by the finance departments in each of the costing centres. To address this in the sensitivity analysis (*Table 41*; higher inpatient overheads) overheads and capital allocations for inpatient costs from the hospital-acquired infection study[96] were used. These led to higher inpatient costs, and although the costs of early disease were unchanged, the costs of later disease stages increased considerably.

The final sensitivity analysis excluded overheads and capital costs (*Table 41*). The purpose of this was to provide cost estimates that are suitable for use under a shorter time-horizon for the cost-effectiveness analysis. If the model's time-horizon was only 10 years, then overheads and capital could be regarded as fixed; their use would not alter according to changes in the resources used by hepatitis C patients. Under this scenario the costs of all the disease stages fall, but again the biggest change is for the decompensated and HCC disease stages. (Deciding on which costs are fixed and which are variable under different horizons is notoriously difficult. As Dawson[98] points out, certain staff inputs in the NHS may be regarded as fixed in the short to medium term. For the purposes of this analysis it was simply assumed that overhead and capital were fixed costs, and all other costs were regarded as variable.)

Discussion and conclusions

The aim of this section was to provide empirical estimates of the health service costs associated with each stage of hepatitis C for use in the cost-effectiveness model. The results confirm that there are substantial costs associated with antiviral treatment. This investment may be worthwhile if disease progression is prevented, as these results also show that the health service costs of later disease stages are substantial.

This study provides detailed estimates of the costs of various stages of hepatitis C for the first time. Comparison with previous estimates is problematic as previous studies have failed to provide detailed estimates of the costs associated with each disease stage. However, in an analysis for NICE, Shepherd and colleagues estimated that the monitoring costs during antiviral treatment were £1280,[48] which is much higher than the present estimates, which suggest that monitoring costs are on average £626. This reflects the generally lower resource use observed during the treatment phase than previously estimated. In addition, the unit costs,

TABLE 41 *Results from the sensitivity analysis looking at the impact of different assumptions about the allocation of overheads and capital on mean total costs (£) of each disease stage*

Stage	Base	–30% allocated costs	+30% allocated costs	Higher inpatient overheads	No overheads
Cost work-up	684	660	708	688	632
Cost controls	138	132	144	138	131
Cost treatment	7,141	7,100	7,181	7,190	7,050
Cost non-responders	118	110	144	123	115
Cost SVR	259	251	267	270	257
Moderate	730	684	776	791	660
Cirrhosis	1,138	980	1,297	1,343	901
Decompensated	9,587	8,027	11,148	11,709	7,485
HCC	8,127	6,760	9,494	10,141	6,407

for example, for outpatient visits, were much higher in the Shepherd study than in this study. For moderate disease and cirrhosis the present total cost estimates are higher than previous estimates; for example, Siebert and colleagues[42] reported the mean costs of moderate disease and cirrhosis to be only €130 and €673; however, no detail was given on the components of these estimates to assist comparability.

Apart from providing accurate estimates of mean costs, the use of specific, detailed estimates also enables the variability in the costs across the patient group to be presented and explored. The results show that there was considerable variability in resource use and hence costs across the patients sampled, with the standard deviation often approaching or exceeding the mean. This is commonly observed in cost estimates[46] and such uncertainty needs to be considered in cost-effectiveness models. By providing an estimate of statistical uncertainty alongside the mean estimates it will be possible to solve the model using an analytical method, probabilistic sensitivity analysis,[99] which recognises this sampling uncertainty. In the cost analysis some attempts were made to see whether this sampling uncertainty could be attributed to particular covariates, such as age, gender or patient genotype. The results showed that although disease stage was important in explaining total costs, patient characteristics within each disease stage did not explain much of the remaining cost variability.

Apart from considering sampling uncertainty, cost-effectiveness analysts need to recognise the uncertainty arising when generalising their results and the assumptions made when conducting unit cost estimates. In this large multicentre study 15 centres were recruited to the trial, but it was only possible to collect detailed resource-use and unit cost information in three centres. However, this improves on standard practice in most multicentre studies, which only measure costs in one centre and then generalise to all centres.[100] As part of the trial, information was collected on patient characteristics and treatment duration, which suggested that the patients recruited to these three costing centres were reasonably representative of patients recruited in general to the RCT. Nevertheless, this does not necessarily make these costs generalisable as the unit costs from these three centres may not be generally applicable. However, evidence from the UK reference cost database suggests that for key resource inputs (e.g. endoscopies), the unit costs for these three centres lie between the 25th and 75th percentiles of costs across UK centres, and may therefore be reasonably representative.

The assumptions made regarding the estimation of unit costs were clearly stated, and tested in the sensitivity analysis. Of particular importance was the allocation of certain cost items to the level of the patient bed-day, which was not done specifically for patients with hepatitis C. The sensitivity analysis suggested this was relatively unimportant for early disease stages where care was mostly provided in an outpatient setting. However, for later disease stages different ways of allocating unit costs did have an important effect on the estimates of disease costs and may need to be considered in the sensitivity analysis for the cost-effectiveness model.

The cost analysis showed that the key determinant of treatment costs was the duration of antiviral therapy, which was on average 38 weeks. This partly reflected the trial protocol, which allowed patients with genotype non-1 to have treatment beyond 24 weeks. As the results from the analysis of SVRs (Chapter 3) suggested that there was no additional benefit to patients with genotype non-1 in continuing therapy beyond 24 weeks, the model will also consider a scenario where the duration of treatment is limited to 24 weeks.

In general, the costs collected by both the mild hepatitis C RCT and the observational study were compatible with the requirements of the model. There was one area, however – the costs of treating moderate disease – where using results from the observational study as a model input would lead to inconsistencies. The costs of antiviral treatment for moderate disease were much lower than for mild disease; this reflected the much shorter treatment duration for moderate hepatitis C patients. The most likely explanation for this difference is that the patients with mild disease were treated in a trial setting, whereas the patients with moderate disease were mainly treated in a routine practice setting. The SVR rates used in the model for both patients with mild and moderate hepatitis C are those observed during the mild RCT (33% cases having an SVR). To preserve consistency between the response rates used and the costs of treatment, the costs of mild treatment will also be applied to the moderate treatment substage.

Apart from the costs of the intervention itself, this study found that important costs were incurred monitoring the intervention, and for some patients the side-effects of the intervention led to

hospital episodes. The total costs of managing the disease during the treatment phase need to be considered, together with the deterioration in HRQoL, when conducting the cost-effectiveness analysis. The results also suggested that important costs were incurred following an SVR, both in the mild hepatitis C RCT and in the observational study of the hepatitis C patients with later disease. The follow-up period for these costs was relatively short (approximately 1 year), and to assess accurately the long-term costs following an SVR further research is needed. In the meantime the model will test the implications for cost-effectiveness of making different assumptions about the continuation of costs related to previous hepatitis C, following an SVR.

To provide appropriate cost estimates for the model, various methodological challenges had to be overcome. In particular, the model cycles were over a 1-year period, which meant that annual costs were required for each disease stage. However, in the observational study, costs were available over observation periods of different lengths (e.g. 6 months, 2 years, 3 years). To provide cost estimates compatible for the model, an average annual cost for each patient was calculated by dividing each patient's observed costs by the duration of the observation period, to give an average annual cost for each individual. These individual costs were summed across all the individuals in the stage in question, and divided by the number of cases to give an average cost in each disease stage. Where the costing period was shorter than that required by the model (e.g. 6 months), this approach assumed that the intensity of the costs would be repeated over the entire year for which the costs were required; so, doubling the 6-month observed costs gave an accurate estimation of annual costs. However, the strength of this assumption may depend on a number of factors, including the reason for the censoring of the observation. Recent advances have been made in the statistical analysis of cost-effectiveness analysis, in particular looking at the best ways to analyse censored costs.[101,102] It would seem an important area of future research to investigate the appropriateness of these techniques for estimating costs that have been censored for the purposes of populating a cost-effectiveness model.

The results are presented from a health service perspective and broader societal costs have been excluded. Although recent NICE recommendations on appropriate costing methods do not require a societal perspective,[66] ignoring patient and productivity costs can lead to the costs of certain interventions and diseases being seriously underestimated. In the case of antiviral therapy for hepatitis C it would seem important to extend the analysis to include these broader costs; for example, the intervention involves frequent visits for monitoring, leading to potentially high societal costs.

Finally, the retrospective nature of the costing study for the later disease stages means that recent or future advances in the technology associated with hepatitis C management may be ignored. For example, certain procedures are now routinely done as day-case interventions which previously required an overnight stay. Consideration of the likely change in technology over time is an important issue in economic evaluation and yet is widely ignored.[103] Although preliminary results from this study suggest that conclusions about cost-effectiveness are robust to likely changes in technology (Grieve R, Roberts JA. Unpublished paper presented to the International Health Economics Association, San Francisco; 2003), further consideration of this issue would seem worthwhile.

In conclusion, this section provides detailed accurate estimates of the costs of the different stages of the disease, which are suitable for use in the cost-effectiveness model (*Table 42*). The results

TABLE 42 *Mean costs (£) for the main disease stages in the model*

Mild disease stages	Cost	Later disease stages	Cost
Work-up for mild hepatitis C	678	Monitoring moderate disease	730
Monitoring for mild hepatitis C	138	Antiviral treatment moderate disease	7,141
Treatment for mild hepatitis C	7,141	Monitoring following SVR	211
Monitoring following SVR	259	Management of cirrhosis	1,138
Monitoring following non-SVR	118	Management of decompensated disease	9,121
		Management of HCC	8,127
		Liver transplantation	27,330
		Follow-up following transplantation	9,458

showed that while the costs associated with the intervention were substantial, so are the costs associated with disease progression. The cost-effectiveness model will explore whether the costs of subsequent disease are offset by providing antiviral therapy for patients with mild hepatitis C.

As well as providing accurate mean cost estimates, the cost analysis provided measures of interpatient cost variability, which were found to be substantial. The uncertainties surrounding these cost estimates will be considered during the cost-effectiveness analysis.

Chapter 6

HRQoL for different stages of hepatitis C

Introduction

To estimate the additional cost per QALY of interferon-α and ribavirin compared with placebo for patients with mild hepatitis C, information is required on the HRQoL for patients at various stages of the disease. The life-years experienced in each health state need to be weighted by a measure of HRQoL that reflects preferences for the various health states. Previous studies in hepatitis C have used generic measures of HRQoL such as the SF-36 and demonstrated that the HRQoL for patients with hepatitis C is worse than that for the general population.[32] Indeed, the results from the mild hepatitis C RCT (Chapter 3) demonstrated that patients at this early disease stage experience important detriments to their HRQoL. The purpose of this chapter is to extend the measurement of HRQoL by using a measure that incorporates preferences for the different dimensions of HRQoL, and produces a single measure of outcome that is suitable for use in cost–utility analysis.

Previous cost–utility analyses in hepatitis C have relied on using expert opinion to estimate HRQoL rather than empirical estimates derived from questionnaires completed by patients.[6,7,43–45,48–50,64,65] However, HRQoL estimates derived from healthcare professionals differ from those based on patients' descriptions of their own HRQoL, and may be an inaccurate proxy for HRQoL. One recent cost-effectiveness analysis did estimate HRQoL for German hepatitis C cases using preference-based techniques;[42] however, few details were provided on the methodologies used and it is uncertain whether the results are applicable to the UK.

An important aim of this study was therefore to collect estimates of HRQoL for UK hepatitis C cases using a preference-based measure. The health states included in the model and requiring estimates of HRQoL are listed in *Table 43*.

Information on HRQoL associated with the mild hepatitis C health states was collected as part of the mild hepatitis C RCT, and a separate observational study was designed to collect data for the moderate, cirrhotic and decompensated cirrhosis health states. It was not possible to collect HRQoL data on all of these substates as part of this study. Data from a large UK transplantation study were therefore used for the remaining health states.[104]

Methods

The HRQoL for patients at each relevant disease stage was estimated using the EuroQol 5 Dimensions (EQ-5D) questionnaire. This instrument was chosen as it provides a preference-based measure of HRQoL and has been widely used in cost–utility analysis. To estimate HRQoL using the EQ-5D tariff, patients were first asked to describe their own HRQoL. The questionnaire for this is self-administered and covers five dimensions of health, with each dimension having three levels of response. The descriptions of each patient's health status are then translated into an estimate of HRQoL using a reference set of preference weights derived from a representative sample of the UK general population.[105] These weights were derived using the time trade-off technique.[106] Combining these preference weights with the health states described by each patient gives a measure of HRQoL for each patient on a scale from 0 (death) to 1 (perfect health).

HRQoL: mild disease

To estimate the HRQoL for cases with mild disease, the EQ-5D was completed by each patient

TABLE 43 *Health states included in the model and requiring HRQoL estimates*

Mild disease	Treatment for mild disease	Mild disease SVR
Moderate disease	Treatment for moderate disease	Moderate disease SVR
Cirrhosis	Decompensated cirrhosis	
Hepatocellular carcinoma	Post-liver transplantation	

included in the mild hepatitis C RCT. At each visit during the trial (baseline, treatment weeks 12, 24 and 48, and follow-up weeks 12, 24 and 48) patients completed the questionnaires in the clinic before seeing the healthcare professional and without knowing their current disease status. The questionnaires were self-administered and reviewed for completeness by a local investigator. The data from all cases attending the baseline visit were used to estimate the HRQoL associated with mild disease. This was the most appropriate data point as it used the maximum amount of data, and was applied before patients had suffered any detrimental effects to their HRQoL from being in the trial.

The data at weeks 24 and 48 post-treatment were used to estimate the effect of having an SVR on HRQoL. For the treatment group, the effect of antiviral treatment on HRQoL was estimated using the data from weeks 12 and 24, when most cases were still taking antiviral treatment.

HRQoL: moderate disease and cirrhosis

To estimate the HRQoL associated with moderate disease, cirrhosis and decompensated cirrhosis, a separate observational study was conducted using cases recruited to the costing study (see Chapter 5). Of the 355 patients included in the costing study, 53 had either died or had a liver transplant before the start of the HRQoL study and were therefore excluded. Each of the remaining 302 patients was included in the study, and in June 2002 a postal questionnaire including the EQ-5D was sent to each patient. Information about the study was also enclosed, and each patient was asked to give written consent and return the questionnaire. Patients who did not reply were sent reminders after 1 and 2 months. Clinical and virological databases at each centre were accessed to find out whether patients were on antiviral therapy or had had an SVR at the time of questionnaire completion.

HRQoL: post-transplantation

The model also required HRQoL estimates for the post-liver transplantation stage. The estimates available were from the Department of Health-funded liver transplantation study, which estimated utility for 455 patients assessed for liver transplantation during the period January 1996 to December 1998.[104] This study included 46 patients with hepatitis C-related cirrhosis and eight with HCC. This study also measured HRQoL using the EQ-5D. Patients were asked to complete the EQ-5D at transplant listing and at 3, 6, 12 and 24 months post-transplantation. These descriptive measures were then valued using the same national estimates based on the time trade-off method.[105]

Data analysis

The mean HRQoL scores were calculated for all cases with mild hepatitis C who completed the EQ-5D at the baseline visit. To estimate the effect of treatment on HRQoL, EQ-5D data had to be available at 24 or 48 weeks post-treatment (or control), otherwise the follow-up HRQoL was defined as missing and the case was excluded from the main analysis. (Follow-up HRQoL was defined by the HRQoL from post-week 48 if available, otherwise post-week 24.) For the cases with complete data the mean HRQoL at follow-up was compared between the treatment and control groups. To adjust for baseline differences between the groups the change in HRQoL between the treatment and control groups was compared using *t*-tests to estimate confidence intervals around the differences in means. ANCOVA was conducted, which adjusted for any baseline differences between the groups by estimating a linear regression model relating baseline to follow-up HRQoL for each group.[107] This regression model was then used to predict HRQoL at follow-up for those patients missing follow-up data. Similarly, the short-term effect of antiviral treatment on HRQoL was estimated using ANCOVA to compare the HRQoL at the 12- or 24-week visits between the treatment and control groups. (Treatment HRQoL was defined by the HRQoL at week 12 if available, otherwise the result at week 24 was used.)

The baseline HRQoL for the mild hepatitis C patients was compared with the HRQoL for those with moderate disease or cirrhosis. OLS regression analysis was used to estimate the effect of disease stage on HRQoL, adjusting for differences in patient characteristics between cases at different stages of the disease.

Results

HRQoL following antiviral treatment for mild hepatitis C

Of the 196 cases (98 treatment, 98 controls) included in the mild hepatitis C RCT, 14 patients did not complete a baseline EQ-5D questionnaire (three treatment, 11 controls) and were excluded from the analysis. The mean (SD) baseline HRQoL for the 182 patients included in the study was 0.77(0.22). A total of 130 patients completed a follow-up EQ-5D questionnaire at 24 or 48 weeks

post-treatment (or control). The response rate was higher for the treatment (73%) than for the control group (67%). The HRQoL at follow-up was higher in the treatment compared with the control group, although the difference was small and not statistically significant (*Table 44*). Simply comparing the follow-up HRQoL ignores the difference in baseline HRQoL. The ANCOVA model which adjusted for the baseline differences therefore found slightly greater (although still non-significant) differences in HRQoL between the treatment and control groups.

The comparison of HRQoL between controls, treated patients who did not have an SVR and those who did have an SVR showed that the mean HRQoL at baseline was higher for those who had an SVR (*Table 45*). Although the mean HRQoL at follow-up, after adjusting for baseline differences, was higher for the SVR group than for the control group, this difference was small and non-significant. There did not appear to be any gains in HRQoL following treatment for those who did not have an SVR.

The ANCOVA model with treatment group and baseline measure as covariates provided a reasonable fit to the data and was used to predict HRQoL for each patient with missing follow-up data. The predicted values for the controls with missing data were lower than for those with complete data, so including these patients reduced the estimate of mean HRQoL for the control group, whereas for the treatment groups imputing HRQoL estimates for those missing data had little impact on the results (*Table 46*).

TABLE 44 *Comparison of mean HRQoL (EQ-5D) for treatment versus control groups at follow-up (24/48 weeks post-treatment)*

Visit	Mean (SD) EQ-5D score		Difference in means (95% CI)	*p*-Value
	Control (*n* = 61)	Treatment (*n* = 69)		
Baseline	0.79 (0.19)	0.76 (0.19)	–0.03 (–0.10 to 0.06)	0.53
Follow-up	0.76 (0.22)	0.77 (0.30)	0.02 (–0.08 to 0.10)	0.73
Change	–0.03 (0.23)	0.01 (0.22)	0.04 (–0.05 to 0.03)	0.28
ANCOVA			0.03 (–0.04 to 0.11)	0.36

TABLE 45 *Comparison of mean HRQoL at follow-up for control group, versus treatment non-SVRs and treatment SVRs*

Visit	Mean (SD) EQ-5D score			Difference between means (95% CI)	
	Control (*n* = 61)	Treatment Non-SVR (*n* = 45)	Treatment SVR (*n* = 24)	Non-SVR-Control	SVR-Control
Baseline	0.79 (0.19)	0.75 (0.30)	0.80 (0.22)	–0.04 (–0.14 to 0.05)	0.01 (–0.09 to 0.10)
Follow-up	0.76 (0.22)	0.75 (0.34)	0.82 (0.21)	–0.01 (–0.11 to 0.10)	0.06 (–0.05 to 0.17)
Change	–0.03 (0.23)	0 (0.20)	0.02 (0.27)	0.03 (–0.05 to 0.12)	0.06 (–0.06 to 0.17)
ANCOVA				0.02 (–0.06 to 0.11)	0.06 (–0.05 to 0.16)

TABLE 46 *Predicted mean HRQoL (EQ-5D) at follow-up for controls, treatment non-SVRs and treatment SVRs for patients with complete and missing data*

	Complete data		Imputations for missing data		All cases	
	n	Mean	*n*	Mean	*n*	Mean (95% CI)
Control	61	0.76	29	0.68	90	0.73 (0.70 to 0.76)
Treatment non-SVR	45	0.75	19	0.80	64	0.76 (0.72 to 0.81)
Treatment SVR	24	0.82	7	0.82	31	0.82 (0.77 to 0.87)

TABLE 47 *Comparison of mean (SD) HRQoL (EQ-5D) results for treatment versus control groups at 12/24 weeks post-randomisation*

Visit	Mean (SD) EQ-5D score		Difference between means (95% CI)	*p*-Value
	Control (n = 64)	Treatment (n = 80)		
Baseline	0.75 (0.23)	0.79 (0.26)	0.03 (–0.04 to 0.11)	0.41
12 or 24 weeks[a]	0.75 (0.30)	0.66 (0.32)	–0.09 (–0.20 to 0.1)	0.06
Change	0 (0.21)	–0.13 (0.24)	–0.13 (–0.20 to –0.05)	<0.01
ANCOVA			–0.12 (–0.19 to –0.05)	<0.01

[a] Where utility data were available after 12 weeks these were used, otherwise utility data from week 24 were used.

TABLE 48 *Predicted mean HRQoL at weeks 12/24*

	Complete data		Imputations for missing data		All cases	
	n	Mean	*n*	Mean	*n*	Mean (95% CI)
Control	64	0.75	26	0.75	90	0.75 (0.71 to 0.79)
Treatment	80	0.66	15	0.60	95	0.65 (0.61 to 0.69)

HRQoL during treatment

HRQoL data following 12 or 24 weeks of treatment were available for 144 patients in the mild hepatitis C RCT (71% of the control group and 84% of the treatment group). Once again, the mean baseline HRQoL score was worse in the control than in the treatment group, so ANCOVA was used to adjust for baseline differences between the groups. Once the baseline differences were adjusted for, HRQoL at 12 or 24 weeks was significantly worse for the treatment than for the control group (*Table 47*).

The ANCOVA model was used to predict HRQoL scores at week 12 or 24. The predictions suggested that the mean differences between the treatment and control groups were similar whether or not the patients with missing data were included in the analysis (*Table 48*).

Estimates of HRQoL for mild disease, moderate disease and cirrhosis

The mean (SD) EQ-5D for all the 185 patients with mild disease who attended the baseline trial visit was 0.77 (0.23). The HRQoL estimates for moderate and cirrhotic cases were taken from the observational study. Of the 302 patients included, the overall response rate in the observational study was 56%, 60% for patients with moderate disease, 54% for those with cirrhosis and 28% for patients with decompensated cirrhosis. The low response rate for the group with decompensated cirrhosis meant that there were insufficient data to provide a robust estimate of HRQoL for this group, who were therefore excluded from the analysis. At the time of questionnaire completion six patients were having antiviral treatment and 31 patients had had an SVR. The results for the remaining patients with moderate disease (n = 71) or cirrhosis (n = 40) were analysed alongside the baseline data for the patients in the mild hepatitis C trial (n = 185). The patient characteristics for those patients in the observational study who responded to the questionnaire were slightly different to those who did not. In particular, those who responded to the questionnaire were generally less likely to have IVDU as their route of infection (32%) compared with the non-responders (68%). In the cirrhosis group the average age of patients who completed the questionnaire was similar to those who did not, whereas in the moderate group those who completed the questionnaire were on average older than those who did not (mean age 43.7 versus 37.7 years). Consideration was given to using a regression model to impute data for those with missing values. However, none of the patient characteristics measured (age, gender, route of infection, duration of infection) was significantly associated with HRQoL, and hence the predictive validity of the regression model was low. The mean values for those patients who responded to the questionnaire were therefore assumed to be representative of the larger patient sample from which they were drawn.

TABLE 49 *Patient characteristics for each disease stage for patients completing the HRQoL (EQ-5D) questionnaire*

	Mild (*n* = 185)	**Moderate (*n* = 71)**	**Cirrhotic (*n* = 40)**
Age (years), mean (SD)	39.8 (8.1)	43.8 (10.4)	47 (8.40)
Men, *n* (%)	97 (52%)	42 (59%)	29 (73%)
Source of infection			
IVDU	54%	39%	33%
Blood products	16%	36%	25%
Other	30%	24%	43%
Duration of infection (years),[a] mean (SD)	16.5 (8.4)	16.4 (9.3)	22.4 (9.8)

[a] *n* = 130, 56, 28. Date of infection was not available for all cases.

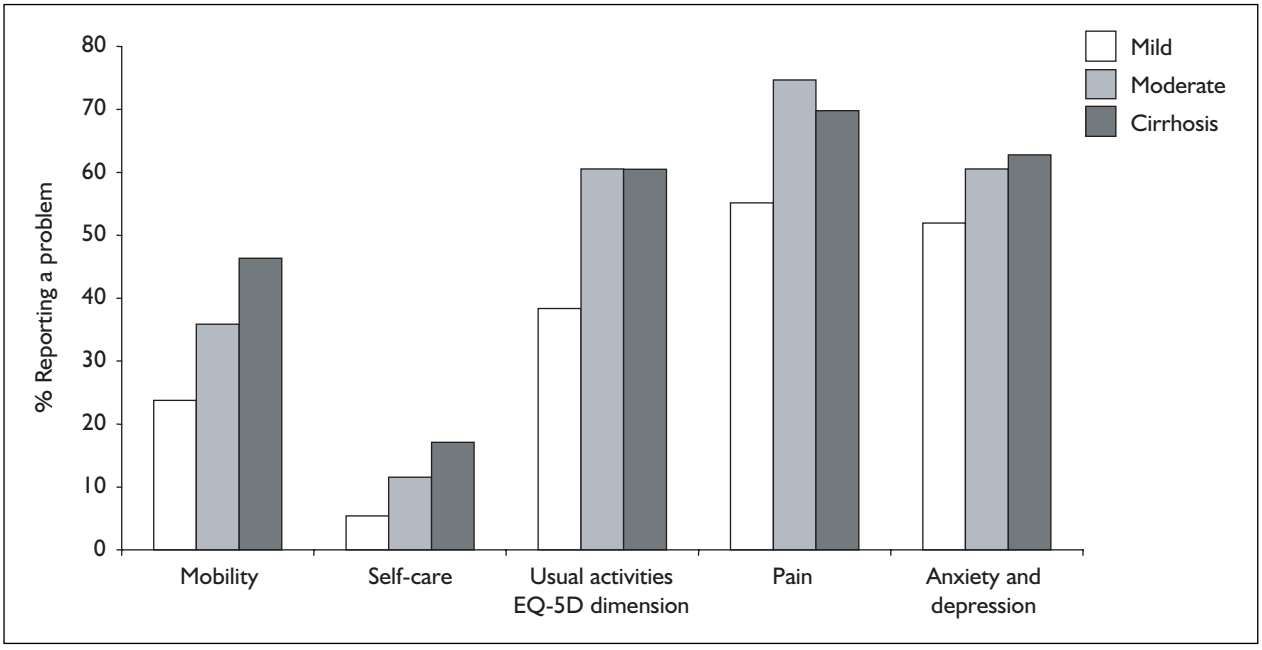

FIGURE 13 *Proportion of cases in each disease stage reporting problems for each dimension of the EQ-5D*

The comparison of patient characteristics across the disease stages for the patients who completed the HRQoL questionnaire shows that patients with mild hepatitis C were more likely to have contracted the disease through IVDU than were the patients with moderate disease or cirrhosis. The patients in these later disease stages were on average older, and the cirrhotic group had had the infection for longer (*Table 49*).

The results from the EQ-5D health state descriptions showed that a higher proportion of the moderate and cirrhotic patients reported some or severe problems for each of the five dimensions covered by the questionnaire. For example, the proportion of cases reporting problems with mobility was 24% for patients with mild disease, 36% for moderate cases and 46% for cirrhotics (*Figure 13*). The cirrhotic group tended to have the highest proportion of patients reporting severe problems, for example, the proportion of patients reporting severe problems with performing their usual activities was 12% for patients with cirrhosis, compared with 3% for patients with moderate disease and 2% for patients with mild disease.

The mean HRQoL was higher in the group with mild disease than in those with moderate disease or cirrhosis (*Table 50*). The linear regression results suggested that HRQoL for mild disease was significantly higher than for either moderate disease or cirrhosis (*Table 50*). The mean differences remained the same when the regression analysis adjusted for differences in patient characteristics across the groups (*Table 50*).

TABLE 50 *HRQoL (EQ-5D) comparison across disease stages: difference between the groups estimated using OLS regression analysis to adjust for differences in patient characteristics*

Stage	*n*	Mean (SD)	Difference (95% CI)
Mild (all cases, baseline)	185	0.77 (0.22)	
Moderate	71	0.66 (0.25)	
Cirrhotic	40	0.55 (0.34)	
Moderate–mild			–0.11 (–0.18 to –0.04)
Cirrhotic–mild			–0.21 (–0.30 to –0.13)
Cirrhotic–moderate			–0.11 (–0.20 to –0.01)

TABLE 51 *Mean HRQoL for each disease stage*

Mild disease: 0.77	Treatment for mild disease: 0.65	SVR after mild disease: 0.82
Moderate disease: 0.66	Treatment for moderate disease: 0.55	SVR after moderate disease: 0.72
Cirrhosis: 0.55	Decompensated cirrhosis: 0.45	
HCC: 0.45	Post-liver transplantation: 0.67	

Estimating the HRQoL associated with SVR following antiviral treatment for moderate disease, and during treatment for moderate disease

A total of 21 patients included in the study had had an SVR following moderate disease; the mean HRQoL estimate from these patients was 0.72 (95% CI 0.61 to 0.83).

There were insufficient patients to estimate directly the short-term effect of antiviral treatment on HRQoL for patients with moderate disease. Instead, the coefficient from the ANCOVA model estimating the treatment effect for mild disease was used, substituting the mean estimated HRQoL for moderate disease (0.66) as the baseline value. This model predicted that for those patients with moderate disease the mean HRQoL during treatment was 0.55. The analysis was repeated using the 95% confidence intervals for the baseline value for moderate disease; these gave predicted values of the HRQoL for treatment for moderate disease ranging from 0.50 to 0.60.

HRQoL estimates for stages where empirical data were unavailable

As there were insufficient data available from the observational study on HRQoL for patients with decompensated cirrhosis or HCC these estimates were taken from the Brunel transplantation study.[104] In this study patients were included with a range of conditions that warranted liver transplantation, including HCC and decompensated cirrhosis related to hepatitis C (n = 64). The mean HRQoL score at transplant listing across all these hepatitis C patients was 0.45; this was used to approximate the HRQoL for patients with decompensated cirrhosis or HCC. (The estimate used was the one that adjusted for informative dropout.) The HRQoL post-transplantation was taken as 0.67; this was the mean score at 1-year post-transplantation.

Discussion

The aim of this aspect of the study was to estimate HRQoL for each disease stage included in the model (*Table 51*). The main result was that the HRQoL associated with moderate disease and cirrhosis was significantly lower than for mild disease. If antiviral therapy (interferon-α and ribavirin) prevents disease progression for some cases with mild hepatitis C, this would avoid the reduction in HRQoL associated with disease progression and lead to a gain in QALYs. These results also showed a considerable reduction in HRQoL during antiviral therapy. Any gains in QALYs associated with preventing disease progression would therefore need to be compared to the reduction in HRQoL during treatment.

These results suggest that the HRQoL associated with mild hepatitis C could be much lower than previously estimated by healthcare professionals.[6,7,43,45,49,50,65] For example, Stein and colleagues[49] used estimates for the HRQoL of mild hepatitis C of 0.98, compared with the present estimate of 0.77. Using the empirical estimate presented here in a model predicting QALYs will

lead to fewer QALYs being predicted for the no-treatment group. The results also suggested that moderate disease and cirrhosis were both associated with much lower values of HRQoL than previously estimated. Stein and colleagues[49] suggested that the average HRQoL was 0.92 for moderate disease and 0.82 for cirrhosis, compared with the HRQoL estimates of 0.66 and 0.55 in this study. Studies in other disease areas have suggested that if healthcare professionals are asked to derive estimates of HRQoL they may ignore detriments in certain dimensions of health status such as anxiety and depression or pain and discomfort, which patients regard as highly important.[108] Indeed, in the current study over 60% of moderate patients reported problems with either pain and discomfort or anxiety and depression. Using the empirical estimates presented here in a model estimating the cost-effectiveness of antiviral treatment would therefore increase the QALYs gained from treatment, compared with relying on literature-based estimates.

This study did not find any statistically significant gains in HRQoL associated with having an SVR. This could be because the follow-up time was insufficient for any impact on HRQoL to be detected. Alternatively, as the EQ-5D has only five dimensions and three levels, it could have lacked the sensitivity required to detect changes in HRQoL. However, the results from the SF-36 survey (see Chapter 3) found non-significant gains in HRQoL, which suggests that the choice of instrument may not be a problem. In another study of liver disease the EQ-5D was found to be more sensitive to change than the SF-6D, the subsection of the SF-36 questionnaire used to derive utilities.[109] The most likely explanation for the absence of a significant difference is that the study was powered to detect differences in virological status between the treatment and control groups, and therefore insufficient cases were included in the study to detect differences in HRQoL. In two large antiviral therapy trials in hepatitis C, SVR was associated with a significant increase in HRQoL.[34,110]

The implications of the positive but non-significant increase in HRQoL for the model are that while a higher mean value for HRQoL will be used following an SVR compared with being in the mild hepatitis C health state, these mean input values will be surrounded by wide confidence intervals. This will mean that the uncertainty in these parameters will be incorporated into the model's analysis and the estimate of the cost per QALY gained of antiviral therapy.

These preference weighted estimates of HRQoL also suggest that the patients most likely to have an SVR are those who have a higher HRQoL to start with. Those cases with lower HRQoL, who for example are already anxious and depressed, may find the side-effects of antiviral therapy intolerable and stop treatment, which makes them much less likely to have an SVR. Identifying the patients most likely to respond to treatment would increase the overall QALYs gained from the treatment, as gains in HRQoL would be achieved for those having an SVR while avoiding the detriment in HRQoL during treatment for the non-responders. This study suggested that there were no gains in HRQoL for patients who were treated but did not have an SVR.

Methodological issues

Although these estimates are an improvement on previous estimates of HRQoL they still need to be treated with some caution. In particular, the estimates for the mild hepatitis C patients came from the patients entered into the RCT, whereas the estimates for the moderate and cirrhotic disease stages came from an observational study. This could lead to an overestimate of the differences in HRQoL if the HRQoL estimates reported for patients enrolled into the mild hepatitis C RCT were higher than for the more general mild hepatitis C population. To assess this the characteristics of patients included in the mild hepatitis C RCT were compared with those cases at later disease stages included in the observational study. Certain characteristics are associated with progression and are more likely to be prevalent in later disease stages, irrespective of the study setting (observational study versus RCT). For example, patients in the later disease stages were older, and more likely to be men; age and male gender are both associated with disease progression.[5,6] Other differences, between the observational and RCT groups, for example in the proportion of ex-intravenous drug users, may not reflect progression and may instead have reflected biases in the way in which the study samples were recruited. However, source of infection and other differences in patient characteristics were not found to be associated with HRQoL. Although these factors were adjusted for in the regression analyses comparing HRQoL across disease stages, they did not reduce the observed reduction in HRQoL associated with progression.

Another potential explanation for the differences in HRQoL across disease stages was how the questionnaire was administered. The patients in the mild hepatitis C RCT completed the

questionnaire in the hospital setting before attending a liver clinic, whereas those with moderate disease or cirrhosis received a postal questionnaire. Previous research has shown that the mode of questionnaire administration (self-completion versus interview) can lead to different results, with the results from the SF-36 being higher if administered during an interview rather than through a postal questionnaire.[111] However, although the questionnaire was completed in different places, each patient self-administered the questionnaire. There is no evidence to suggest that self-completing the EQ-5D in a hospital setting leads to higher HRQoL values compared with completing it in the patient's home.

Differences in the place of administration could, however, explain why the completion rates were much higher in the mild hepatitis C study than in the observational study. For the mild hepatitis C patients it was possible to develop a robust model for imputing the missing values for the mild cases with missing follow-up data using their baseline results. For the more severe cases the overall response rate was lower (56%), although it compared reasonably well with the response rate for the hepatitis C patients included in the Brunel transplantation study (61%). If the non-responders in the moderate and cirrhotic groups had much better HRQoL than the responders then this could explain some of the differences in the mean HRQoL between these patients and those with mild hepatitis C. However, differences in patient characteristics were generally small and in characteristics not associated with HRQoL.

The mean HRQoL for each sample was therefore assumed to apply to each of the disease stages of interest.

The uncertainties arising from the sampling variation caused by the relatively small number of cases in each disease stage and the possible biases mentioned will need to be incorporated into a full sensitivity analysis as part of the cost–utility analysis. The use of these empirical estimates represents an improvement on previous approaches. Further research to estimate HRQoL more precisely, particularly following an SVR, could be useful. The results suggest that the EQ-5D is sensitive to change and may therefore be an appropriate instrument for providing preference-weighted measures of HRQoL for use in cost–utility analysis of new interventions for hepatitis C.

In conclusion, to estimate the cost-effectiveness of new interventions in hepatitis C, HRQoL data for each relevant disease stage are required. The only estimates available from the literature used expert opinion to derive HRQoL. This study elicited responses from patients to estimate HRQoL for the main disease stages included in the model. These estimates suggest that HRQoL deteriorates as the disease progresses. Antiviral therapy that delays or prevents disease progression may therefore lead to gains in QALYs. These gains will need to be balanced against the short-term reduction in HRQoL associated with the intervention.

Chapter 7

Results of the cost-effectiveness analysis

Introduction

This chapter presents the results of the cost-effectiveness analysis. The analysis uses as model inputs the efficacy data presented in Chapter 3, the transition probabilities from Chapter 4, and the health service costs and HRQoL estimates given in Chapters 5 and 6. As well as reporting mean estimates for each model input, by collecting empirical data it was possible to report the sampling variation for each parameter. The sampling variation surrounding some of these model inputs was large, for example for the cost parameters, the SD often exceeded the mean. The recent literature on the analysis of cost-effectiveness models has emphasised the importance of considering the uncertainty surrounding the model inputs when analysing cost-effectiveness models, and suggested the use of probabilistic sensitivity analysis for this purpose.[99,112] Briggs[99] highlighted that in addition to variation in parameter values that may be defined as random variation, parameters may vary across defined patient subgroups (e.g. different ages) and parameter uncertainty may arise according to different methodological assumptions made. All of these forms of uncertainty may contribute to the overall uncertainty surrounding the results. In the analysis of this cost-effectiveness model each of these different forms of uncertainty is considered in turn.

This chapter presents the cost-effectiveness results. The first section outlines the assumptions made in the base-case analysis and describes the probabilistic sensitivity analysis. The next section presents the base-case cost-effectiveness results, followed by an examination of the cost-effectiveness for different patient subgroups. The following section tests the importance of some of the methodological assumptions made and the final section considers the use of pegylated interferon-α.

Base-case cost-effectiveness: definition and analytical method

Summary of assumptions made in the base-case analysis

The base-case estimates of relative cost-effectiveness for interferon-α plus ribavirin are presented for a patient with the average characteristics of a patient entered into the mild hepatitis C trial (*Table 52*). The base-case analysis used the recently recommended discount rate for economic evaluations in the UK of 3.5% on costs and benefits,[113] and estimated cost-effectiveness over the lifetime. The analysis compared the mild hepatitis C antiviral treatment group with a no-treatment group. This group was defined by a policy of monitoring or watchful waiting at a mild stage, but then once patients reached moderate disease they were assumed to receive interferon-α and ribavirin, as previously recommended by NICE (*Table 52*).[15]

Method used for analysing cost-effectiveness: probabilistic sensitivity analysis

In total, 1000 cases with the characteristics listed (*Table 52*) were entered into the treatment and no-

TABLE 52 *Summary of assumptions made in the base-case analysis*

Methodological assumptions
Comparison groups:
Treatment group: interferon-α plus ribavirin for mild disease, no treatment for moderate disease
No-treatment group: no treatment for mild disease, interferon-α plus ribavirin for moderate disease
Discount rate: 3.5% (costs and benefits)
Analysis period: lifetime
Patient characteristics
60% men, 40% women
50% genotype 1, 50% non-1
Average age at infection: 25; average age at model entry: 40 years
Efficacy
33% SVR for cases with mild or moderate hepatitis C

treatment model cohorts. The model was analysed using probabilistic sensitivity analysis. Under probabilistic analysis, rather than taking an average value for each parameter input, the value is drawn from a distribution.[114] Monte Carlo simulation is then used to sample randomly from this distribution, to construct a probability distribution for the costs and QALYs associated with each treatment option.[114] The probability distribution for each of the input variables is constructed using sample data to provide estimates of the mean value and standard error. The beta distribution is appropriate for transition probabilities as it is bounded by zero and one, whereas the gamma distribution is more appropriate for cost estimates.[99]

The techniques above were applied to the model using the means, standard errors and appropriate distributions for each input variable (see Appendix 5). Monte Carlo simulation randomly sampled from each of these input distributions simultaneously for 1000 runs of the model. For each run the following model outputs were estimated for the treatment and the no-treatment groups: the number of liver deaths, the number of life-years and total costs in each disease stage, the total lifetime costs and QALYs. For each of these model outputs an average was calculated over the 1000 runs for the treatment and no-treatment groups.

The incremental cost-effectiveness ratio (ICER) was defined as:

$$\frac{\text{ATC}_{\text{treatment}} - \text{ATC}_{\text{notreatment}}}{\text{AverageQALYs}_{\text{treatment}} - \text{AverageQALY}_{\text{notreatment}}}$$

where ATC refers to the average total health service costs over the lifetime for either group, and average QALYs refers to the lifetime QALYs for each group. The ICER was estimated for the 'average' group with the characteristics outlined: the base case.

To summarise the uncertainty surrounding the cost-effectiveness result, cost-effectiveness acceptability curves (CEACs) were drawn.[115] To do this the incremental net benefit (INB) associated with the intervention was calculated. The net benefits approach requires either the difference in costs or effects to be rescaled using the ceiling ratio (R_c).[116] The ceiling ratio is the amount that the decision-maker or society is prepared to pay for a unit of health gain. A commonly used threshold for cost-effectiveness analyses in the UK is £30,000 per QALY.[117] The mean INB on the cost scale is defined as:

$$\overline{INB} = R_c\Delta\bar{E} - \Delta\bar{C}$$

where $\Delta\bar{E}$ is the difference in average effects between the groups (in this case average lifetime QALYs) and $\Delta\bar{C}$ is the difference in the average lifetime costs between the groups. Where the mean INB is positive, the intervention may be said to be cost-effective for the given ceiling ratio, that is, the benefits, valued in monetary terms, exceed the costs.

The mean INB of the intervention was calculated for each run of the model, and this was repeated 1000 times for a given ceiling ratio. The ceiling ratio was varied from £0 per QALY to £100,000 per QALY. The proportion of runs where there was a positive mean INB was taken to give the probability that the intervention was cost-effective for each ceiling ratio. The CEAC plotted the probability that the intervention was cost-effective against the ceiling ratio. Thus, the CEAC summarised the uncertainty in the INB that emanated from random variation about the parameter estimates, for different ceiling ratios.

Base-case cost-effectiveness results

The results of the base-case analysis (*Table 53*) showed that over 1000 patients there were four fewer deaths from liver disease in the mild treatment group, which led to an average gain of 0.03 life-years (discounted). The mean number of life-years experienced during each disease stage differed between the groups. On average, the patients in the mild treatment cohort had 6 years in the post-SVR health state, which meant that they had fewer years with mild disease where the HRQoL was lower. Patients in the no-treatment cohort had more life-years with mild disease, and slightly more years in the moderate disease state, where some were treated and had an SVR leading to an average of 1.47 life-years in the SVR state following moderate disease. There were fewer life-years with cirrhosis for the mild treatment group compared with the mild no-treatment group (0.75 versus 0.82 life-years). The QALYs gained from clearing the virus in the mild treatment group more than offset the HRQoL lost during antiviral therapy; the net average lifetime gain in QALYs for treatment at a mild rather than a moderate stage was 0.38.

TABLE 53 *Base-case estimates from probabilistic sensitivity analysis (all results are means per patient unless stated otherwise)*

	Treatment	No treatment	Difference
Outcomes			
Total liver deaths (over 1000 cases)	85.20	92.44	–7.24
Average life-years (over all health states)	20.47	20.44	0.03
Lifetime QALYs	15.47	15.09	0.38
Average life-years in each health state			
SVR following mild disease	6.46	0.00	6.46
Mild disease	10.55	15.20	–4.66
Moderate disease	2.52	2.73	–0.21
SVR following moderate disease	0.00	1.47	–1.47
Cirrhosis	0.75	0.82	–0.07
Postcirrhotic health states	0.19	0.21	–0.02
Average total lifetime cost (£)	**13,199**	**9,552**	**3,647**
Lifetime costs, by disease stage (£)			
SVR following mild disease	2,640	0	2,640
Mild disease	6,235	2,748	3,487
Moderate disease	1,839	3,984	–2,145
SVR following moderate disease	0	95	–95
Cirrhosis	857	939	–82
Postcirrhotic health states	1,628	1,785	–157
Lifetime ICER: cost per QALY (£)			**9,535**

The costs of antiviral treatment led to higher lifetime costs for the treatment cohort where all cases were treated, compared with the no-treatment cohort, where only those cases reaching moderate disease were treated (53%). The additional costs experienced during the mild disease states were partly offset by preventing some patients progressing to moderate disease; the incremental lifetime costs of treatment at a mild stage were £3647. The ICER combining the additional average QALYs of early treatment with the additional costs gave an overall cost per QALY gained of £9535.

The CEAC (*Figure 14*) showed that if the ceiling ratio was £30,000 per QALY then the probability of treatment at a mild stage compared with treatment at a moderate stage being cost-effective was 0.78, that is, it is more likely than not to be cost-effective. The CEAC also showed that the probability of the intervention being cost-effective varied from 0.06 if the ceiling ratio is 0 (this reflects the probability of the costs being lower in the treatment cohort) to 0.85 if the ceiling ratio is £80,000. This indicates that even at this ceiling ratio there is a reasonable probability ($p = 0.26$) that the intervention is not cost-effective. This reflects the variability about the mean estimates of efficacy and HRQoL. There were some runs of the model where the values used for these input variables resulted in a worse QALY outcome for the treatment compared with the no-treatment group.

Parameter uncertainty due to different patient characteristics

Although the probabilistic analysis provided an estimate of the effect of parameter uncertainty, all of the variation was attributed to random variation. Variation in parameter values may not be completely random; it may reflect particular patient characteristics that are associated with efficacy, transition probabilities, costs or HRQoL. The results from previous chapters suggested that viral genotype was associated with efficacy, and that age and gender were associated with disease progression. To consider these, the probabilistic sensitivity analysis was repeated for patients with different characteristics, to examine the cost-effectiveness of the intervention for various subgroups. From the results of the previous chapters, the main subgroups of interest were defined as genotype 1 versus non-1, men versus women and older (aged 65 years at study entry) versus younger patients (aged 20 years at study entry). The probabilistic analysis was rerun for each of the subgroups of interest using mean input values and accompanying standard errors appropriate for the subgroup in question.

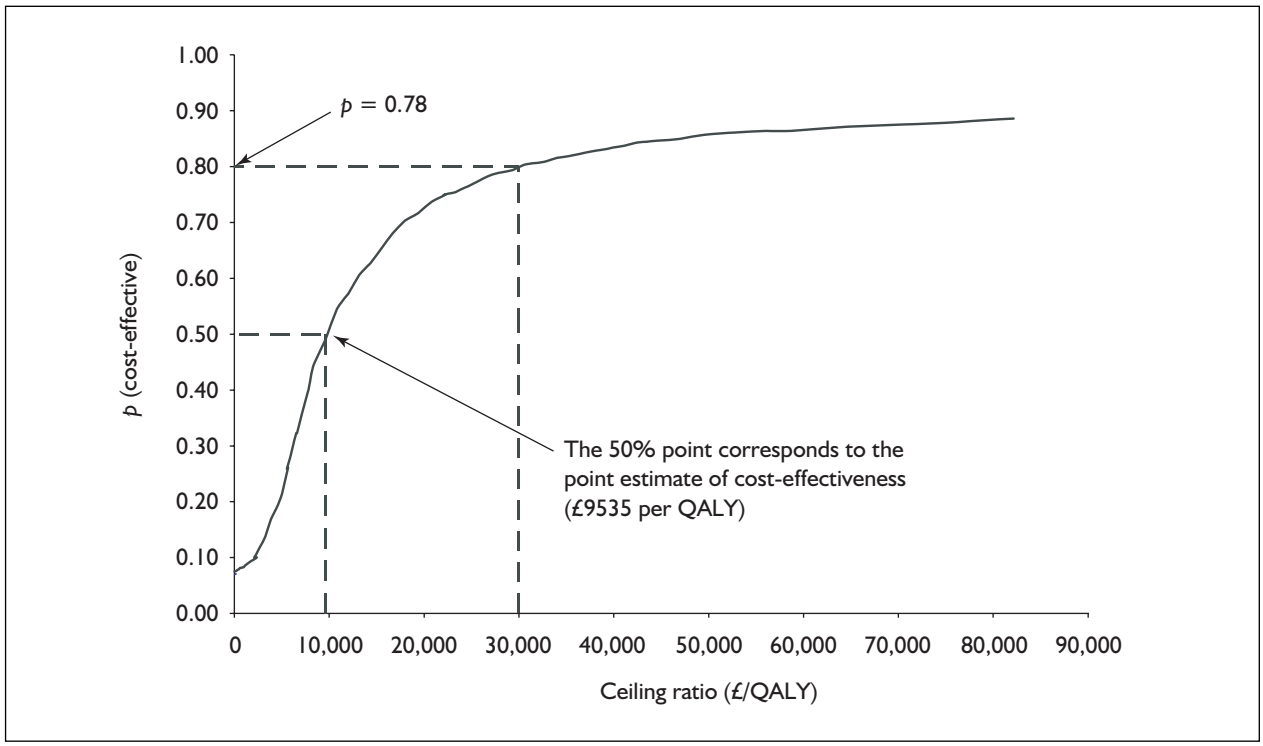

FIGURE 14 *CEAC: base case*

Subgroup results: by genotype

To estimate the effect of genotype on the cost per QALY, the model inputs were changed to reflect the mean values for the genotype in question. For example, the subgroup analysis from the trial was used which reported that 18% of cases with genotype 1 and 49% of cases with genotype non-1 had an SVR. The probabilistic results showed that for patients with genotype non-1 the probability of treatment for mild hepatitis C being cost-effective at a threshold of £30,000 per QALY was 0.86, and the mean cost per QALY was £4535. For patients with genotype 1, treatment at a mild stage was associated with an increase in QALYs of 0.17 and a cost per QALY gained of £25,188. At a threshold of £30,000 per QALY the probability that antiviral treatment at a mild stage was cost-effective was 0.52 for patients with genotype 1 (*Figure 15*). The main reason for the higher costs per QALY for patients with genotype 1 was the lower proportion of these patients having an SVR. In addition, more of the genotype 1 patients had antiviral treatment for 1 year, so the incremental costs of treatment for mild disease were higher, and the intervention was therefore less likely to be cost-effective. However, the results still suggest that provided a decision-maker is willing to pay £30,000 for each QALY gained, the intervention may be regarded as relatively cost-effective for patients in either genotype group.

Subgroup results: by gender

Men were found to be more likely to progress through the earlier stages of hepatitis C than women. The cost analysis showed that for both moderate disease and cirrhosis the mean costs of the disease were lower for women than for men. The probabilistic analysis was repeated for both genders, but with higher transition probabilities and total costs for men compared with women. For example, the mild–moderate transition was taken to be 0.031 for men compared with 0.021 for women with genotype non-1. The results are summarised using the CEAC for patients with genotype non-1 (*Figure 16*). This shows that the intervention was slightly more cost-effective for men than for women.

Subgroup results: by age

The only input variables found to vary with age were the early transition probabilities, which were found to vary with age at infection. However, when changing the age at entry to the model, the duration of the model analysis also changed, which in itself had an impact on the results. To illustrate the effect of age, the probabilistic model was run for patients aged 20 and 65 years at model entry. The models were run for patients with both genotype 1 and non-1.

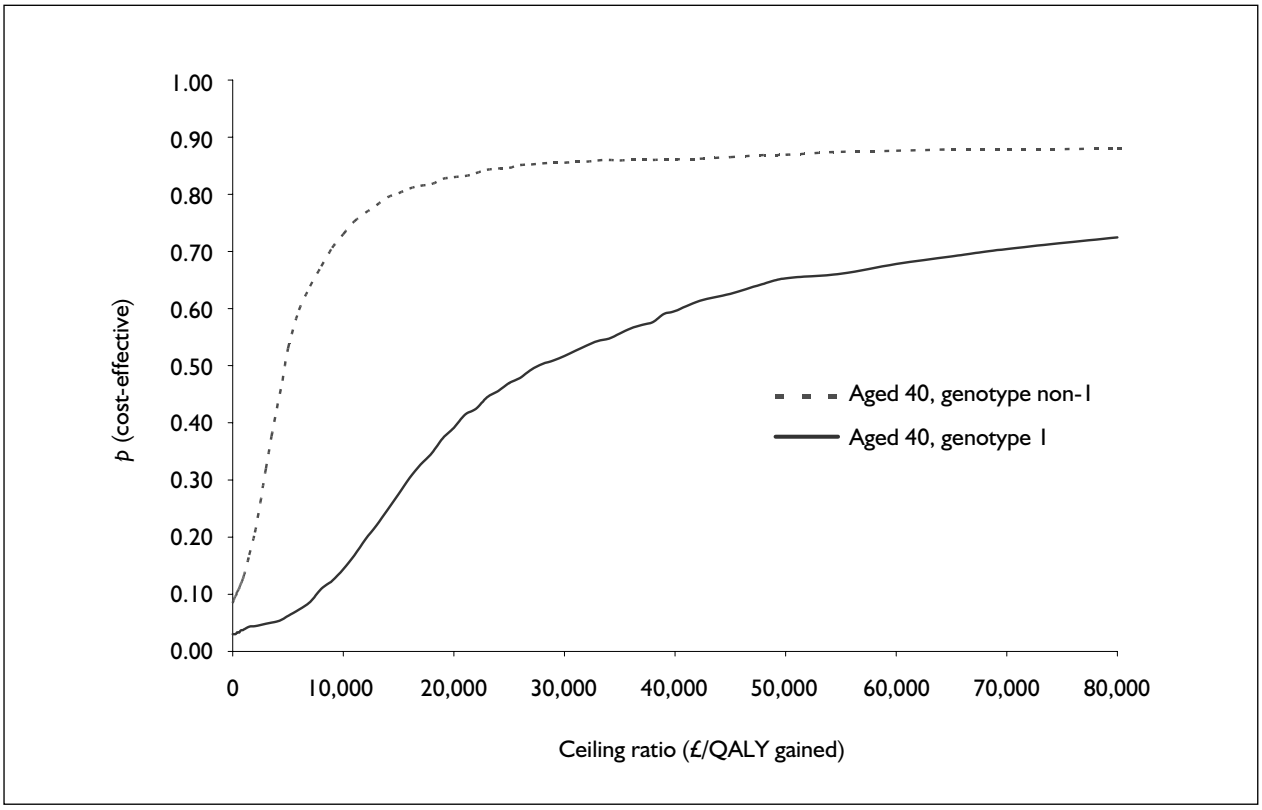

FIGURE 15 *CEAC of interferon-α and ribavirin versus no treatment for patients with mild chronic hepatitis C: by genotype*

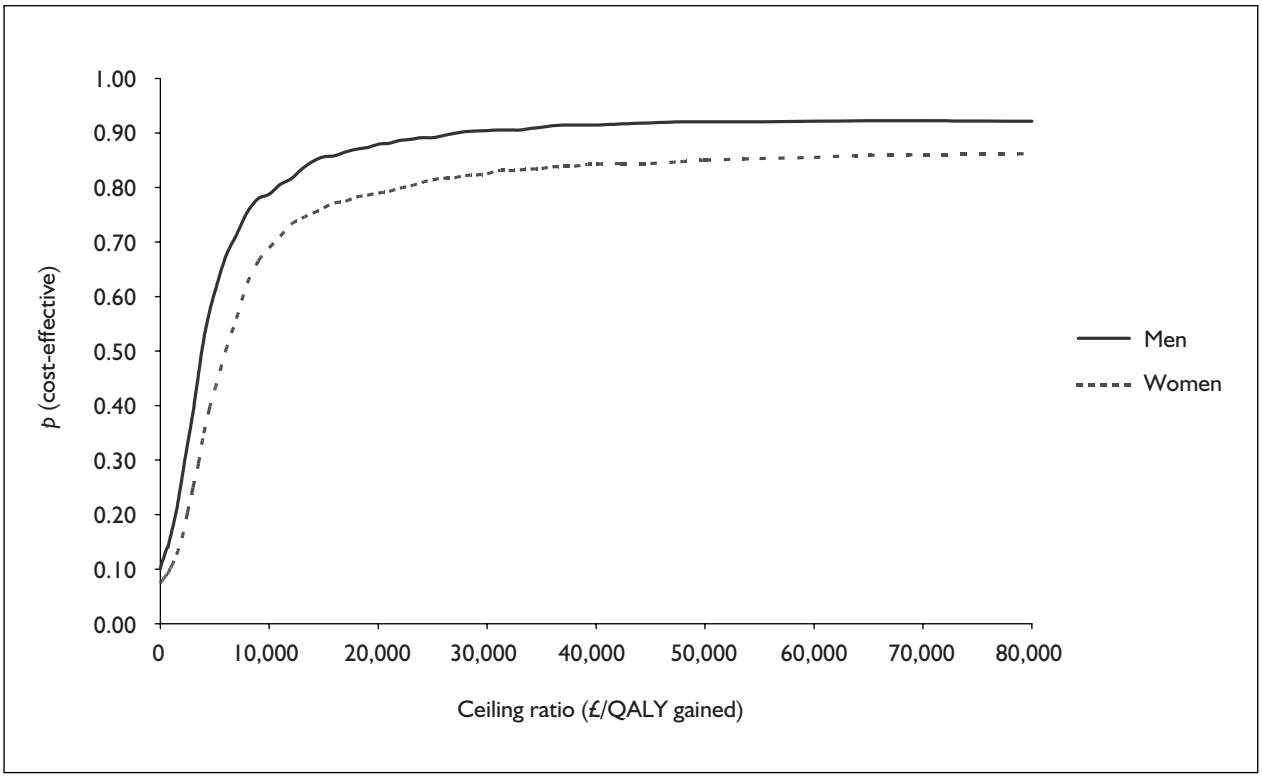

FIGURE 16 *CEAC of antiviral therapy, by gender (genotype non-1)*

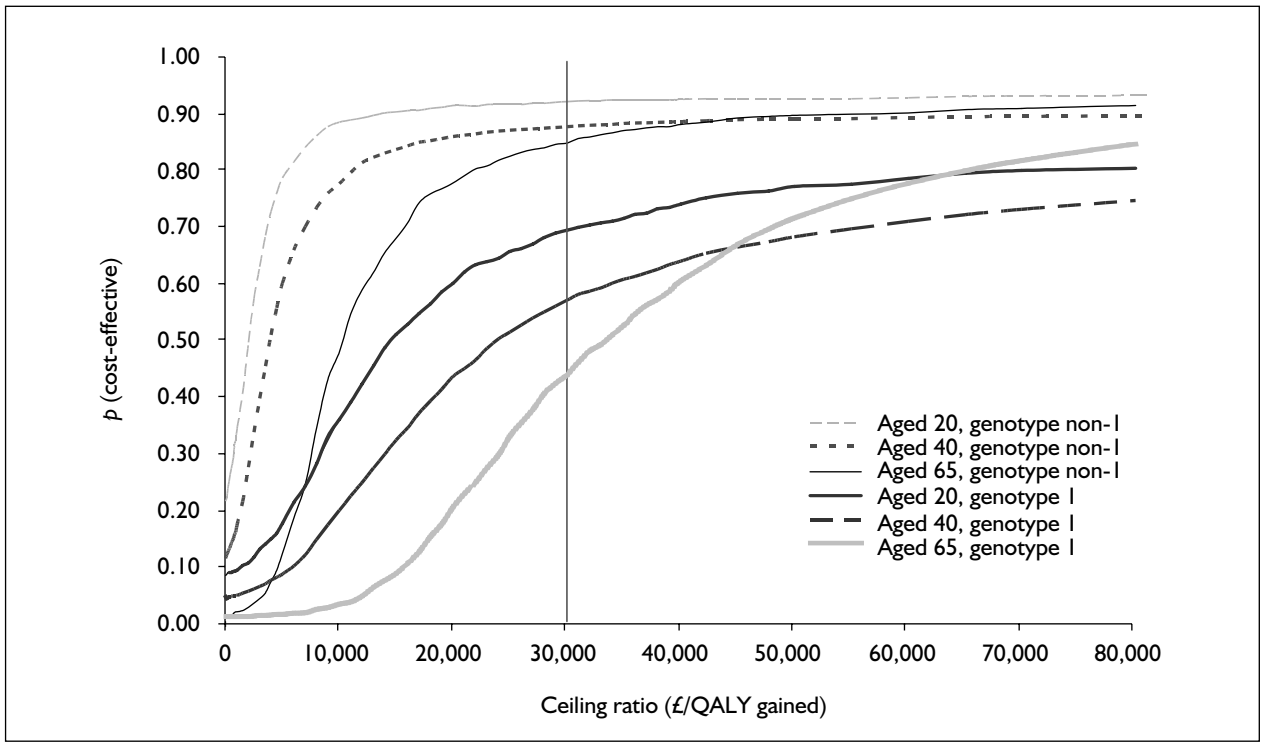

FIGURE 17 *CEAC of interferon-α and ribavirin versus no treatment, by genotype and age*

Although patients aged 65 or over had faster rates of disease progression, their shorter remaining life expectancy meant they generally gained fewer QALYs from antiviral treatment at a mild stage. For patients aged 65 with genotype 1, treatment with interferon α-2b and ribavirin at a mild stage was not cost-effective. For these cases the cost per QALY gained for interferon α-2b and ribavirin was £53,017 per QALY and the probability that the intervention was cost-effective at £30,000 per QALY was 0.28 (*Figure 17*).

For patients aged 20, although the probabilities of progressing to cirrhosis were lower compared to the base case, patients had more remaining life expectancy during which they could gain QALYs from early treatment. For this age group the probability that the intervention was cost-effective exceeded 0.5 at £30,000 per QALY for both genotype groups (*Figure 17*).

Uncertainty surrounding methodological assumptions

The methodological assumptions made in the base-case analysis have been made explicit, and the analysis will now consider how making different methodological assumptions may change the results. This will be important to facilitate comparisons with other studies that may have taken different methodological standpoints. Different methodological scenarios will therefore be given, with the base-case ICER recalculated for each scenario again using probabilistic sensitivity analysis. The use of different methodological scenarios will also test the robustness of the main conclusion from the preceding analysis, that if the willingness to pay for a QALY gained is £30,000 per QALY then antiviral treatment for mild disease is relatively cost-effective. The results for each of the scenarios will be compared with the base-case analysis.

Assumptions about gain in HRQoL following SVR

In the base-case analysis it was assumed that there was a gain in HRQoL of 0.05 units following a SVR. While this gain was based on data collected alongside the RCT, the numbers of patients who had an SVR and completed the EQ-5D was relatively small, and hence the results were uncertain. To test whether the study's conclusions are robust to the assumption that there was a gain in HRQoL following an SVR, the analysis was repeated assuming no gain in HRQoL following an SVR. The results showed that if there was no gain in HRQoL, then the costs per QALY for patients with genotype 1 rose to nearly £100,000

per QALY and the intervention could no longer be regarded as cost-effective (*Table 54*). If it was assumed that there was a small gain in HRQoL of 0.01 units, then the cost per QALY for patients with genotype 1 was nearly £60,000 per QALY (*Table 54*). For patients with genotype non-1 the results were relatively insensitive to the gain in HRQoL following an SVR.

Time horizon of the analysis

In the base-case analysis a lifetime perspective was taken; for a patient aged 40 years at entry to the model, this meant that costs and effects were measured over a 50-year period. However, it may be that decision-makers prefer to adopt a shorter time-horizon. Previous studies have taken a 30-year time-horizon;[45,48] therefore, the model was reanalysed using a 30 year time-horizon. The results showed that for patients with genotype non-1, while the cost per QALY rose compared to the base case, it was still below £10,000 per QALY. For patients with genotype 1, the costs per QALY gained rose to £34,392 (*Table 54*).

Treatment duration

Rather than using treatment costs based on the costs observed in the trial, it may be more realistic to assume that patients with genotype non-1 would only have 6 months of treatment. For these cases the results from the RCT showed that there were no improvements in the SVRs from prolonging treatment beyond 6 months (Chapter 3). If treatment for patients with genotype non-1 was stopped at 6 months and the proportion of cases having an SVR remained at 49%, then the cost per QALY falls to £1480 per QALY.

Use of viral kinetics

Results from the mild hepatitis C RCT (Chapter 3) showed that viral kinetic data could be used to predict those treated patients most likely to have an SVR. The viral load data at 12 weeks after the start of therapy predicted that certain patients would not respond to the intervention, and for these patients treatment could be stopped early. A preliminary attempt was made to incorporate the use of viral kinetic data into the cost-effectiveness model. Using the viral kinetic data at 12 weeks meant there was no need to adjust the effectiveness data, as none of those patients predicted by the viral load data to fail treatment went on to have an SVR. The only parameters in the model that were changed were the costs of treatment and the HRQoL during the treatment year. These parameters were adjusted for patients with both mild and moderate disease.

For patients with genotype non-1 the viral kinetic data suggested that at week 12, 20% of patients could be identified as non-responders and treatment stopped at 12 weeks. Doing this would reduce the incremental costs of treatment to £926 for patients with genotype non-1, and £3244 for patients with genotype 1 (*Table 54*). In addition, using the viral kinetic data meant that it was no longer assumed (as in the base case) that HRQoL was lowered for 12 months during treatment. For those patients whose viral load data suggested that treatment should be stopped early it was assumed that HRQoL only fell during the 12 weeks of treatment. Using the viral kinetic data therefore led to a greater gain in QALYs and lower incremental costs per QALY for treatment at a mild stage for patients in both genotype groups.

Pegylated interferon-α and ribavirin

In keeping with the objectives of the study, the cost-effectiveness model has focused on comparing interferon-α and ribavirin for mild hepatitis C (*Table 55*, strategy A), with no treatment for mild disease, and interferon-α and ribavirin for those patients predicted to progress to moderate hepatitis C (*Table 55*, strategy B). However, pegylated interferon-α and ribavirin has been shown to be more effective than interferon-α and ribavirin.[23,24] It was therefore desirable to estimate the costs and effects of two further strategies: treatment with pegylated interferon-α and ribavirin for mild hepatitis C (*Table 55*, strategy C), and no treatment for mild disease followed by treatment with pegylated interferon-α and ribavirin for those progressing to moderate disease (*Table 55*, strategy D). Most of the parameters such as the HRQoL and costs associated with later disease stages can be left unchanged; in addition, it was assumed that the HRQoL associated with treatment and SVR was the same as for standard interferon-α and ribavirin.

To estimate the costs and effects associated with pegylated interferon-α and ribavirin it was necessary to use an efficacy measure from the RCTs of pegylated interferon-α and ribavirin for patients with chronic hepatitis C. However, the results from these trials may not be directly applicable to patients with mild or moderate hepatitis C treated in an NHS setting (see Chapter 8). Therefore, to provide an estimate of the likely effectiveness of pegylated interferon-α and ribavirin for patients with mild hepatitis C in an NHS setting, an extrapolation was needed. Manns and colleagues[23]

TABLE 54 *Sensitivity analyses looking at the impact of different methodological assumptions on the mean cost per QALY*

	Genotype 1			Genotype non-1		
	QALYs gained	**Incremental cost (£)**	**Incremental cost per QALY gained (£)**	**QALYs gained**	**incremental cost (£)**	**Incremental cost per QALY gained (£)**
Base	0.17	4,361	25,188	0.61	2,782	4,535
No gain in HRQoL	0.04	4,340	98,227	0.26	2,732	10,569
Small gain in HRQoL	0.07	4,267	57,195	0.33	2,842	8,538
30-year time horizon	0.13	4,484	34,392	0.52	3,011	5,742
24 weeks of treatment	0.17	4,361	25,188	0.67	989	1,480
Viral kinetics	0.19	3,244	17,031	0.65	926	1,425

A 'small' gain in HRQoL was taken to be 0.01 units on the EQ-5D scale. The probabilistic sensitivity analysis was re-run for each scenario, thus even when the mean values of the input values were left unchanged there were still small variations in the model's outputs between the simulations. For example, in the scenario where it was assumed there was no gain in HRQoL, although the costs of each disease stage were left unchanged, there was still a small difference in the incremental costs of treatment compared to the base case.

TABLE 55 *Mean lifetime QALY and mean lifetime costs (£) for different treatment strategies for patients with mild chronic hepatitis C aged 40 years*

	Genotype 1		Genotype non-1	
	Mean QALYs	**Mean lifetime costs**	**Mean QALYs**	**Mean lifetime costs**
A. No treatment for mild disease, Interferon-α and ribavirin for moderate disease	14.99	10,472	15.18	8,561
B. Interferon-α and ribavirin for mild disease No treatment for moderate disease	15.17	14,883	15.79	11,343
C. No treatment for mild disease Pegylated interferon-α and ribavirin for moderate disease	15.03	11,581	15.21	9,630
D. Pegylated interferon-α and ribavirin for mild disease No treatment for moderate disease	15.29	18,897	15.91	15,084

found that the odds ratios of an SVR for pegylated interferon-α and ribavirin compared with interferon-α and ribavirin were 1.25 (95% CI from 0.70 to 2.24) for patients with genotype non-1 and 1.43 (1.05 to 1.96) for patients with genotype 1. Based on these odds ratios and the proportions of patients having SVRs in the mild hepatitis C RCT, the SVRs for pegylated interferon-α and ribavirin in an NHS setting were estimated to be 55% for patients with genotype non-1 and 24% for patients with genotype 1. Manns and colleagues[23] did not find significant differences in SVR according to the patients' histology (i.e. mild versus moderate disease), so these SVRs were applied to patients in the model treated at a mild or a moderate disease stage.

The results presented showed that in general it was cost-effective to provide antiviral treatment, either pegylated interferon α-2b or interferon α-2b combined with ribavirin, at a mild rather than a moderate stage (*Table 55*). Although treatment with pegylated interferon α-2b and ribavirin at a mild stage (strategy D) led to higher costs, it also had the most QALYs, compared to any other treatment option (*Table 55*). The cost per QALY gained from providing pegylated interferon α-2b and ribavirin at a mild (strategy D) rather than a moderate stage (strategy C) was £7821 for patients with genotype non-1 and £28,409 for patients with genotype 1.

The assessment of which early treatment option (pegylated interferon α-2b or interferon α-2b with ribavirin), was the most cost-effective depended on the genotype group and the cost per QALY threshold. For patients with mild hepatitis C and genotype non-1, providing pegylated interferon α-2b (strategy D) rather than interferon α-2b with ribavirin (strategy B), led to a gain of 0.12 QALYs and an additional cost of £3741, an incremental cost per QALY gained of £32,226. For patients with genotype 1, providing pegylated interferon α-2b (D) rather than interferon α-2b (B) with ribavirin led to a gain of 0.12 QALYs, incremental costs of £4064, and an additional cost per QALY gained of £32,896. At a cost per QALY threshold of £30,000 per QALY, the probability that pegylated interferon α-2b was cost-effective was 0.50 for patients with genotype non-1 and 0.49 for patients with genotype 1.

Summary of findings

To summarise, the main finding was that the intervention was on average cost-effective at levels of cost per QALY at which NHS policy makers routinely consider an intervention to be cost-effective. However, this average result concealed important variations and uncertainties (see summary in *Table 56*). In general, interferon-α and ribavirin was cost-effective at a mild stage

TABLE 56 *Summary of cost-effectiveness results comparing interferon-α and ribavirin for mild hepatitis C with no treatment, for a 40-year-old patient unless otherwise stated*

	Mean cost (£)/QALY	Cost-effective?
Overall	9,535	Yes
Genotype 1	25,188	Yes
Genotype non-1	4,535	Yes
Genotype 1		
Age 20 years	28,515	Yes
Age 65 years	53,017	No
Genotype non-1		
Age 20 years	5,182	Yes
Age 65 years	8,668	Yes
No gain in HRQoL		
Genotype 1	98,227	No
Genotype non-1	10,569	Yes
30-year perspective		
Genotype 1	34,392	No
Genotype non-1	5,742	Yes
Up to 24 weeks if viral load drops sufficiently, 12 weeks if it does not		
Genotype 1	17,051	Yes
Genotype non-1	1,425	Yes

The intervention was judged 'cost-effective' if the mean cost per QALY gained was below £30,000 per QALY.

for patients aged 40 years or younger in either genotype group. The results suggested that for patients aged 65 or over, the intervention was not cost-effective for patients with genotype 1. The most critical assumption in the analysis was that clearing the virus led to long-term gains in HRQoL. Assuming no or small gains in long-term HRQoL pushed the cost per QALY gained for genotype 1 patients above £50,000 per QALY. Based on extrapolated data, the model's results also suggested that it was more cost-effective to provide pegylated interferon-α and ribavirin at a mild rather than a moderate stage.

Chapter 8
Discussion

Introduction

This study consisted of an RCT of the efficacy of combined treatment with interferon-α and ribavirin for patients with mild hepatitis C, and a cost-effectiveness model to assess the cost-effectiveness of the intervention over the patients' lifetime. The study was conducted within an NHS framework. Treatment for patients at each centre was based on treatment protocols that are already routinely used for antiviral treatment for patients with moderate hepatitis C. Each participating centre managed patients in the trial like any other patient with hepatitis C. There were no visits from representatives of the sponsors and no prescreening or selection of patients likely to comply. The results of this study represent those that could be expected in an NHS setting.

In this chapter the RCT is discussed first, beginning with consideration of the management and methods used, the initial response rate and dropout rate of patients, and the adverse clinical events associated with treatment. It proceeds to discuss the SVRs, viral kinetics and the HRQoL measured using the SF-36. The cost-effectiveness model is then scrutinised, indicating areas where the model has made significant advances on previous work and the limitations of the model. The results derived from the model and the results from previous studies are then discussed.

Methodological and management issues encountered in the trial

Patients lost to follow-up

One of the most important management issues encountered in conducting the trial was that of maintaining recruits in the trial to minimise the numbers lost to follow-up. This was an important problem for the trial for a number of reasons. The patient population was highly mobile and many patients simply moved away without leaving a forwarding address. Three moved abroad, at least two of the controls enrolled in other trials of hepatitis C therapy outside this study and were therefore ineligible for follow up, and two patients who were prisoners were lost to follow-up on release from prison. The loss to follow-up was particularly a problem among the control group patients. Many of the controls were unhappy not to be receiving any active therapy and 11 failed to participate after receiving their randomisation designation at the baseline visit. Although the nature of the randomised trial was explained to them when they gave their consent to participate, many stated that their participation in the trial was viewed solely as an opportunity to receive therapy. Consequently, when randomised to the control group some patients defaulted. Although patients were not supposed to know their randomisation state before their baseline visit, the fact that six of those randomised to the control group compared with two randomised to treatment did not attend baseline suggests a leakage of information.

This high dropout rate in the control group appears to reflect the dissatisfaction felt because the group was not receiving treatment. It indicates a perceived need for treatment that is not met by current guidelines.[15–17,47] For patients with hepatitis C, the disease means more than just the state of their liver histology. They are also concerned about whether they might infect others and uncertain about what will happen to them in the future. They are also anxious about the multiple symptoms that they attribute to the virus. The combination of these factors together with, in some cases, a history of intravenous drug use or, in others, previous major illness leads to a decreased HRQoL compared with the general population.[32–35,39]

Previous trials of interferon-α and ribavirin have demonstrated considerable proportions of patients unable to complete the trial protocol.[20–22] In the treatment arm of this trial, which took place under standard NHS conditions, the rate of therapy discontinuation was higher than expected and this had an adverse impact on SVR. In the trial by McHutchison and colleagues[20] 92% of patients in the interferon-α and ribavirin arm were able to complete 24 weeks of therapy and 79% completed all 48 weeks. By comparison, in the UK mild hepatitis C trial only 79% completed 24 weeks and only 63% completed more than 36 weeks of treatment. There are several possible reasons for the high rate of early cessation of therapy in the

treatment group of the study. There was a considerable burden of adverse effects, which required dose reductions and resulted in hospital admissions for a number of patients. Given these adverse events, patients with mild disease may feel less committed to therapy than patients with more severe histology on liver biopsy. Moreover, before this study some patients had been told many times by their physicians that their disease was mild and did not require treatment. In the protocol, patients were blind to their current PCR status. A number of patients who dropped out of treatment early were, at the time of the final treatment sample, PCR negative. Possibly, knowledge that they were responding would have improved their compliance.

There were no baseline demographic factors associated with poor compliance or attendance. In particular and of importance, there was no difference between those infected via the IVDU route and those infected by blood products. When comparing those patients on treatment who took the drugs for less than 12 weeks with those who managed more than 36 weeks there was evidence of worse HRQoL at baseline in the former. It may be that if baseline HRQoL is severely impaired the side-effects become harder to bear.

All patients knew that their liver histology was mild. The poorer compliance compared with other published trials of this regimen may be due to the patients' knowledge of their disease severity and their willingness to tolerate side-effects to cure it.

Certain initiatives were taken to maximise the number of patients followed up, including a £100 reward for patients if they attended the final visit and a £50 bounty for nurses for final visits. This approach met with considerable success, enabling data capture on 25 patients who would otherwise have been lost to follow-up. To track patients who were no longer contactable via their trial centres, GPs were asked for help in tracing them. Six patients were traced in this way and had final blood samples taken in the GPs' surgeries.

Maximum retention of study participants is part of good practice in clinical trials, regardless of adherence to study protocol. A considerable number of patients in the control group was lost to follow-up in this trial despite the above approach. The planned analysis was by ITT, which is the definitive analysis for a randomised clinical trial and preserves the validity of comparisons between groups established by randomisation.

There are several alternative methods established for analysing incomplete data. A 'completers analysis' is popular and includes only those patients who completed follow-up or those who took a majority of the drug doses.[41] There is a risk of bias if attrition rates differ between treatment subgroups. During therapy, as in this trial, patients often require encouragement to carry on and for this reason the virological response rates (primary end-point) for those who complete therapy are also shown.

Another approach is to use the 'last value carried forward' method, with the last PCR value for an individual included in the final analysis. This is inappropriate for this trial as patients who initially respond to therapy may subsequently relapse. The results of the analysis are discussed below.

Results of the RCT

Primary end-point

The primary end-point analysis demonstrated a 44% EOTR and a 32% SVR. For genotype 1, EOTR was 30% and SVR was 18%. For genotype non-1, EOTR was 60% and SVR was 49%.

Analysis of other baseline variables and their effect on outcome did not demonstrate any significant difference between genders, age, ALT or baseline viral load. The trial was powered to detect the primary end-point and the genotype 1/non-1 dichotomy, but may have been underpowered for the other baseline factors, which may explain the difference between this trial and that of Poynard and colleagues.[21] Logistic regression analysis on the subgroup of patients who took at least 24 weeks of therapy also failed to show significance for baseline factors other than viral genotype.

In comparison to the two major studies of interferon-α and ribavirin,[20,21] in which no distinction based on histology was made, there was no significant difference in SVR (*Figure 18*).

Duration of treatment, as expected, is crucial in determining outcome. Those patients with genotype 1 infection who took between 36 and 48 weeks of therapy had a higher SVR than those who took it for between 24 and 36 weeks (25% versus 14%). For genotype non-1, maximal SVR was obtained after 24 weeks and was not improved by extending treatment. Protocol deviation in some centres resulted in responders' treatment being stopped after 24 weeks if genotype non-1. Compared with these results, SVR appeared to fall

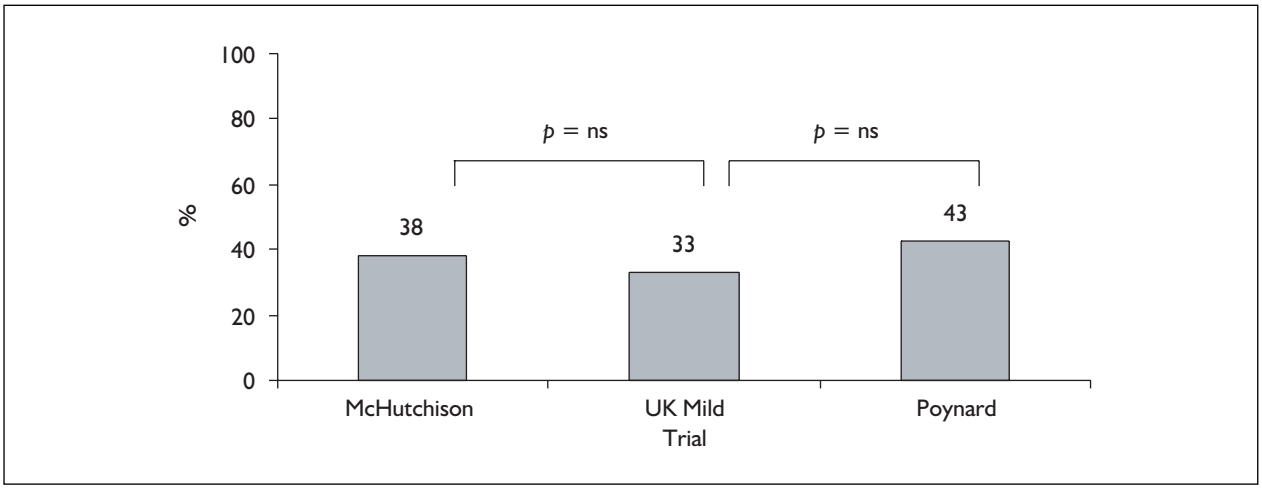

FIGURE 18 *SVR in patients assigned to 48 weeks of therapy: comparison of UK mild hepatitis C trial with other large trials of standard interferon-α and ribavirin. ns, not significant.*

in those who were treated for more than 36 weeks. Non-responders by 24 weeks who continued therapy in these centres experienced a fall in SVR with longer treatment.

When those patients who had therapy for more than 24 weeks are considered separately, the overall response of 42% compares much more favourably with previous trials.

One of the hypotheses underlying the potential benefits of treating mild hepatitis C was that SVR rates may fall as fibrosis progresses and therefore treating mild cases would give better virological results. A number of smaller studies suggested that higher SVRs could be obtained when treating mild disease.[30,31] Treatment of patients (mainly exposed healthcare workers) with acute HCV results in SVR rates in excess of 95%,[27] while treatment following cirrhosis results in lower SVRs compared with those with less severe histology.[21,29]

These observations were not confirmed by the results of this trial. The high rate of dropout in the treatment arm may contribute to this. However, even in the subgroup of patients who were able to tolerate 24 weeks or more of therapy, the overall rate of SVR was 42% (23% genotype 1 and 65% genotype non-1), which is not significantly better than the trials of all comers.[20,21] Moreover, this trial probably most accurately represents the results to be expected in a UK healthcare setting and these are the figures taken forward in the cost-effectiveness model.

It is important to differentiate between early infection and mild infection when thinking about mechanisms involved in clearance. Patients with acute self-limiting infections develop an early, vigorous and multispecific CD4 response with a Th1 cytokine profile. If this response is too weak or too short lived, or if a Th2 profile dominates, viral persistence occurs.[118,119] Treatment in the first few months may augment this immune response, facilitating clearance. During acute infection with HCV the host interferon response is inhibited. Exogenous interferon therefore avoids this viral mechanism of resistance to host defence. Early treatment may also 'remove' the virus before it becomes embedded in certain sanctuary sites such as the brain and lymphoid tissues. Once infection is established (mean duration in these patients was 15 years) it is difficult to see a mechanism by which fibrosis (short of cirrhosis) could have an impact on treatment outcome.

Viral kinetics

Data on viral load were collected for a subgroup of the patients at baseline, day 3, day 7, day 10, day 14 and week 12. The aim of this component of the project was to predict, early in the course of treatment, those patients who were destined to respond and those in whom treatment could be discontinued.

In responsive patients treated with interferon-α there is a rapid first phase decline in viraemia during the first day of treatment, and a slower decline thereafter (second phase).[120] The slope of this second phase decline has been shown to predict SVR[52] and may represent a means by which treatment destined to be unsuccessful can be terminated very early on.

An approach using the degree of fall in viral load at the time-points indicated and subsequent

outcome was used in preference to the more complex biostatistic approach described above, as it is likely to be more easily applicable to the clinical setting. Serial early measurements are required every few hours in the first few days to obtain the curves described by Zeuzem and colleagues.[52] This is impractical in settings involving large numbers of patients undergoing routine treatment, such as in an NHS setting.

Although a 2-log drop in viral load at day 10 performed best in terms of predicting SVR (Chapter 4), stopping treatment at this point would exclude 18% of people who could be cured. No patient failing to achieve at least a 2-log drop at 12 weeks went on to achieve SVR. This is in keeping with evidence from trials of pegylated interferon-α and ribavirin.[24] Discontinuing treatment at this point would allow a considerable reduction in costs and avoidance of side-effects for an ultimately futile intervention. Those patients responding at these time-points could be encouraged and helped on through side-effects by knowledge of a greater likelihood of a cure (*Figure 19*). The proportion of patients achieving a 2-log drop at this time-point (84%) is nearly identical to those treated with pegylated interferon and ribavirin in the paper by Fried and colleagues.[24]

Stopping patients at week 12 if they had not responded by this point would save 9 months of therapy for those with genotype 1 and 3 months of therapy for those with genotype non-1.

HRQoL

Using histology alone to determine management is insufficient. Clinicians who care for hepatitis C-infected patients will have observed the disparity between the degree of hepatic histological abnormality and the patients' symptoms. Disabling symptoms such as fatigue, malaise, bodily pain, joint symptoms, cognitive symptoms and depression are common and severely reduce HRQoL in afflicted individuals. These symptoms are also present in patients without cirrhosis and are at least partly independent of how the patient acquired the infection.

HRQoL is clearly important during treatment as it reflects the side-effects of therapy. After treatment it represents an end-point: does treatment make people feel better? It has been postulated that the diagnosis of a chronic disease can have HRQoL implications as a result of labelling and stigmatisation. A recent study from Australia found that patients followed up 20–25 years after an episode of non-A non-B hepatitis (which was subsequently determined to be HCV) reported decreased HRQoL compared with normal controls. Those who were aware of their HCV status at the time of the questionnaire reported greater impairments than those who were unaware. Foster and colleagues[32] were able to show that having chronic hepatitis C gave significant symptoms regardless of underlying histology. Perhaps equally as important, HCV-positive patients in this study were also compared with

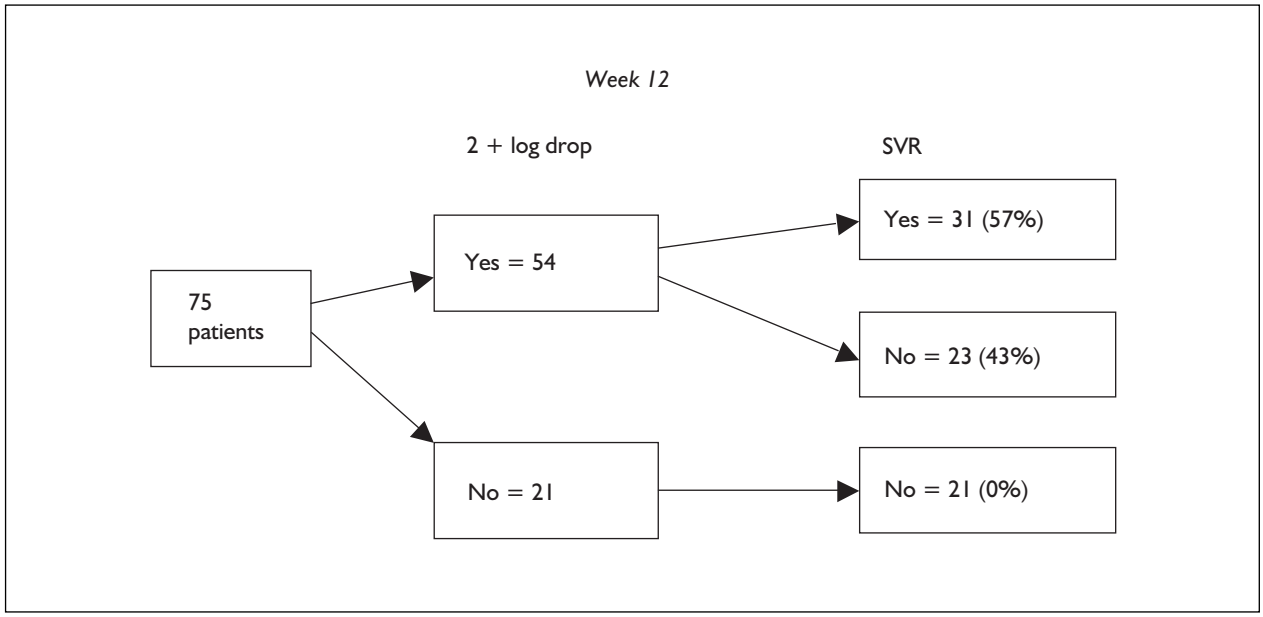

FIGURE 19 *Prognostic value of 2-log drop at week 12 of treatment*

matched patients with hepatitis B and were found to have significantly worse scores, making the effect of a 'chronic hepatitis diagnosis' unlikely to be the sole explanation. Early data suggest that HCV may replicate in the brain and has measurable deleterious effects on psychomotor functioning.[37–39] Clearance of the virus improves HRQoL measured using either the SF-36 or the EQ-5D.

If a treatment is poorly tolerated, compliance will be low and those offered treatment would not be cured regardless of its potency. Side-effects during treatment with interferon-α can be physical, psychological, economic and social. They are well described and their impact on HRQoL measured by the SF-36 has already been established in a large trial.[34]

Compared with UK population norms as recorded in the Oxford Healthy Life survey,[58] patients enrolled in the trial had significantly worse HRQoL on all eight scales of the SF-36. The impairments were equivalent to those previously reported in non-cirrhotic individuals. There were no significant differences between the treatment and control groups at baseline (according to the protocol, patients were asked to fill in the forms before learning of their randomisation designation). There were also no significant differences in HRQoL when mode of acquisition of HCV, intravenous drug-related or otherwise, was assessed. As expected, there was a decrease in HRQoL in all eight parameters of the SF-36 questionnaire in those on treatment compared with controls. Each parameter returned slowly to baseline, or to a level slightly above baseline, during the 6 months post-treatment.

There was a clear trend between low HRQoL at baseline and subsequent inability to complete treatment. It may be that for some individuals other interventions such as antidepressant therapy and social interventions to maximise the chances of completion are necessary before treatment is started.

There was considerable variation in the effect of treatment on HRQoL at 24 weeks post-therapy. An improvement in physical health (PCS) was reported in 61% of the successfully treated patients. However, of equal importance, 39% reported a deterioration. In those patients who had an SVR, the mean change in seven out of eight of the SF-36 subscales was an improvement, although this effect was modest and not statistically different from patients who were treated but who did not have an SVR. Overall, the improvements were most pronounced in the physical health scores, with significant changes in the physical health subscales and in PCS compared with the controls. Treated patients who did not achieve an SVR also reported an improvement in physical health (PCS), although this was a non-significant trend compared with the controls. The control group reported deteriorations in all subscales. This suggests that, over the course of 18 months of follow-up, there were true deteriorations in well-being in the control patients.

Despite clear trends towards improvement with successful treatment, very few changes in the parameters of the SF-36 score reached statistical significance. In addition, the EQ-5D data collected for the cost-effectiveness model suggested that having an SVR was associated with non-significant gains in HRQoL. There are several possible explanations for this:

- The study did not have the power to detect differences in HRQoL. The trial was powered for the primary end-point and the effects on HRQoL were smaller than anticipated, with fewer people than expected (around 60%) completing the questionnaires. The magnitude of improvement, where present, was small. This is an important point, as many patients with HCV attribute all of their quality of life-impairing symptoms to the virus. Clearly, treatment that is successful in clearing the virus does not completely remove these symptoms and it would be wrong to encourage patients to expect this.
- The treated patients who did not have an SVR also showed significant improvements in HRQoL measured using the SF-36 (Chapter 3). This effect has not been reported before, although studies to date have included patients at all stages of chronic hepatitis.[34] This surprising result is not easily explained, and was not supported by the EQ-5D data, which showed no gains in HRQoL for patients not having an SVR (Chapter 6). It could be speculated that, in patients with histologically mild hepatitis C, different mechanisms are responsible for the impairments in HRQoL compared with patients with more advanced liver disease, and that these respond differently to antiviral therapy, regardless of virological outcome.
- It is possible that 24 weeks of follow-up after treatment is insufficient for a virological response to lead to an improvement in HRQoL.

Although Bonkovsky and Woolley[34] were able to show benefit at 24 weeks post-treatment, their cohort had more advanced liver disease. Equally, the side-effects of treatment with interferon-α, such as CNS effects, may not have completely resolved by the 24th week of follow-up.

- Although the baseline data show significant impairments compared with a normal population, a proportion of the study group had normal or near normal baseline HRQoL. This group might be considered to have 'asymptomatic' disease. There was a marked relationship between baseline scores and response to treatment in all treated patients, with improvements in those with low baseline scores, who managed to tolerate therapy, and negligible improvements or deteriorations in the 'asymptomatic' group. Thus, the baseline status may be an equally important or more important factor than virological response in predicting improvements in HRQoL and may be significant in the future with regard to patient selection for therapy.
- Finally, and most importantly, there are multiple determinants of HRQoL. The benefits of an SVR and the knowledge thereof may be outweighed by other personal factors, unknown to the study. The study design should in theory control for this, but the relatively small numbers studied may not have allowed this.

Adverse events

Two patients were admitted to hospital with self-poisoning. Both had previous psychiatric histories, one undisclosed. It is well known that there is potential psychiatric morbidity associated with these treatments. This, plus the trend noted between baseline HRQoL and subsequent duration of treatment, suggests that some patients should not be offered treatment. The argument that HCV impairs HRQoL, and that this is reason enough for treatment, is at odds with this. The decreased HRQoL compared with population norms, the trend towards worsening in control patients over the course of the trial and the high levels of adverse events in the control group (not a placebo side-effect as no placebo was used) all support treatment despite these problems.

Clearly (as is current practice), patients with depression who are put forward for treatment should be managed appropriately and closely monitored. Antidepressant therapy should probably be started before treatment.

Histopathology

This study was known to be underpowered to detect a significant difference in histological change between the treatment and control group. Recent work has suggested that serial biopsies only a few years apart are too insensitive to detect the anticipated change.[5] In this patient group in particular, where many patients have little or no fibrosis at baseline, the chances of any meaningful data being obtained were minimal. For this reason, and in view of possible associated mortality and morbidity, repeat liver biopsy was not pursued.

Conclusions and recommendations associated with the RCT will be summarised in Chapter 9. The results of the cost-effectiveness model are now considered.

The cost-effectiveness model

The aim of the cost-effectiveness study was to compare the cost-effectiveness of interferon-α and ribavirin at a mild stage with waiting until the patient reached moderate disease before providing treatment. Previous cost-effectiveness analyses were limited by lack of data on efficacy, disease transition probabilities, health service costs and HRQoL. This cost-effectiveness model improved on previous approaches by being populated with empirical data. The way in which this allowed the cost-effectiveness assessment to improve on previous attempts is reviewed briefly below.

Methodological improvements

Use of mild efficacy data collected in an NHS setting

Previous cost-effectiveness analyses in hepatitis C[42,48–50] have used efficacy data from multinational clinical trials.[20,21,23] These trials may not generate results that can be replicated in an NHS setting. As the results from Chapter 3 showed, a high proportion of patients in the mild trial who were treated in routine NHS clinical settings did not comply with the trial protocol. They did not complete their treatment regimen and this was reflected in the proportion of patients treated who had an SVR. By basing the cost-effectiveness analysis on relevant efficacy data, this report provides a realistic assessment of the value of the intervention to the NHS.

Another advantage of conducting the assessment alongside the trial was that efficacy data were specifically available for the main population of interest: patients with mild hepatitis C. Previous

studies of the cost-effectiveness of mild hepatitis C have been based on models that used efficacy data collected from patients with hepatitis C with a range of histological severity.[43,64,65]

Empirical estimates of transition probabilities

This study estimated the transition probabilities of moving from mild to moderate disease and from moderate disease to cirrhosis, using a UK observational database. Compared with previous cost-effectiveness studies that relied on literature-based estimates, less restrictive assumptions were made about disease progression. In addition, previous cost-effectiveness analyses have used the same transition probabilities for different patient subgroups.[6,7,44,45,48–50] In this study multivariate analysis was used to predict transition probabilities for different patient subgroups.

Subgroup analysis

As empirical data were available for each of the main input variables, it was possible to estimate cost-effectiveness results for each of the subgroups of interest. Previous studies have only been able to adjust the efficacy data for different patient characteristics, and have generally used common input parameters across all patient subgroups. The present results therefore provide more accurate estimates of the effect of gender, age and genotype on the cost-effectiveness of treatment.

Empirical estimates of costs and HRQoL

Previous studies have used clinical protocols and expert opinion to estimate costs and HRQoL.[6,7,44,45,48–50] The present results suggest that this may have led to inaccurate estimates of cost-effectiveness. In particular, the patients' estimates of their HRQoL following an SVR were lower than suggested by expert opinion. In addition, the use of empirical estimation allowed for the variability of costs and HRQoL to be made transparent. This variability informed the probabilistic sensitivity analysis and the patient subgroup analysis.

Probabilistic sensitivity analysis

The analysis of the transition probabilities, costs, efficacy and HRQoL showed that there was considerable variability surrounding the mean estimates of these input parameters. By analysing the cost-effectiveness model using probabilistic sensitivity analysis, it was possible to reflect these variations in the input parameters when reporting cost-effectiveness. The results were summarised by CEACs which present a summary of the sampling uncertainty that surrounds the central estimates of cost-effectiveness.[115] The use of this technique is growing in the general economic evaluation literature, but has not previously been used in hepatitis C.

Limitations

The main limitations of the cost-effectiveness analysis are discussed below.

High variability surrounding key variables

The RCT was powered to detect differences in SVR between treatment and control groups. It was not powered to examine differences in HRQoL or costs between patient groups. The variability in the costs and HRQoL for the early disease stages was high which, together with the relatively small numbers of patients, meant there was considerable uncertainty surrounding the values of these parameters. The one-way sensitivity analysis suggested that changing the values of the HRQoL estimates had an important bearing on the final measure of cost-effectiveness. The probabilistic sensitivity analysis took account of all the variability in the input parameters simultaneously, and the results suggested that on average the intervention was relatively cost-effective for patients with genotype non-1. It is this average measure of cost-effectiveness that decision-makers should use when deciding whether it is worthwhile funding a new healthcare intervention.[121] However, reporting the level of uncertainty surrounding the results can highlight the need for further research, in this case on the HRQoL following an SVR.

Correlation between variables

While the probabilistic sensitivity analysis provided a good estimate of the importance of sampling uncertainty, it could be developed further. The analysis presently assumes that there is no correlation between the input values. This assumption is widely used in probabilistic sensitivity analysis, and often analysts do not have data available on model inputs to test this assumption. In this instance, empirical data are available on input variables that make it possible to test whether there are important correlations, for example between treatment costs and outcomes or between early and later transition probabilities, that should be incorporated into the model. Estimating these correlations and using these estimates in the analysis of the model could improve the accuracy of the model's predictions.

Markovian assumption

There was a lack of evidence about disease progression over time and so the Markovian assumption was made that the probability of

progression for any case depended only on being in a particular disease state. Longitudinal data are being collected by groups such as the Trent HCV study group and there should eventually be sufficient follow-up data to test this assumption.[122]

Assumption about efficacy data for moderate disease

To compare treatment at a mild stage with treatment for those who reach moderate disease, efficacy data were required for patients with moderate disease. There were no UK trial data available from the literature for this subpopulation. The only efficacy data available were from multinational trials of interferon-α and ribavirin for patients with chronic hepatitis C. These trials reported a slightly higher rate of SVR compared with the mild hepatitis C trial. It was assumed that this was because the multinational trials were highly regulated pharmaceutical sponsored RCTs, rather than pragmatic trials delivered in an NHS setting. There is evidence to suggest that antiviral therapy is at least as successful for patients with histologically milder disease.[23] The efficacy data from the mild hepatitis C RCT were therefore applied to patients in the model who progressed to moderate disease and had antiviral treatment.

No efficacy data on pegylated interferon-α and ribavirin

As pegylated interferon-α and ribavirin has now been recommended in England and Wales for patients with moderate hepatitis C and cirrhosis,[47] an important question is whether it is cost-effective to provide this treatment for patients with mild hepatitis C. There are, however, no efficacy data available from an RCT on the efficacy of this intervention for patients with mild hepatitis C. In light of this, the present model has extrapolated the efficacy data available, to project the likely cost-effectiveness of pegylated interferon-α and ribavirin for patients with mild hepatitis C. The results mirrored those for standard interferon-α and ribavirin: that the intervention is only cost-effective for patients with genotype non-1. Although cost-effectiveness models require sound data on efficacy to reach definitive conclusions, the benefits from a trial on pegylated interferon-α and ribavirin for patients with mild hepatitis C may not justify the costs.

Main results of the cost-effectiveness analysis

The overall results suggested that, on average, the gains in QALYs from early treatment offset the HRQoL lost during treatment, at a small additional cost. The average ICER of early treatment was approximately £10,000 per QALY. Although the threshold for interventions provided by the NHS is uncertain, it appears that this intervention compares reasonably favourably with other therapies that have been judged to be cost-effective.[117]

The average result concealed important variation by genotype: the intervention was less cost-effective for patients with genotype 1, but was highly cost-effective for patients with genotype non-1 (£5000 per QALY). The cost-effectiveness improved further if treatment was limited to 24 weeks, as is usual practice,[20] and to 12 weeks for patients whose viral load data predicted that they were unlikely to respond. Pegylated interferon-α and ribavirin also appeared cost-effective if provided at a mild rather than a moderate stage.

As empirical data were available for each of the main input variables, it was possible to estimate cost-effectiveness results for each of the subgroups of interest. Previous studies have been able to adjust the efficacy data by patient characteristics, but have generally used common input parameters across all patient subgroups. The results of this study, therefore, provided more accurate estimates of the effect of gender, age and genotype on the cost-effectiveness of treatment. In general, the subgroup analysis showed that men were more cost-effective to treat than women, although the differences were relatively small. Treatment at a mild stage was less cost-effective for older patients; and for patients aged 65 or over with genotype 1, the intervention was not cost-effective.

Previous studies comparing interferon-α and ribavirin with no treatment for patients with chronic hepatitis C have generally concluded that the intervention was cost-effective.[7,48,49,64] For example, Shepherd and colleagues found that the cost per QALY of interferon-α and ribavirin compared with no treatment was £7579.[48] For the same comparison, Stein and colleagues found that the overall cost per QALY gained was £3791, with the lowest cost per QALY for chronic hepatitis C patients with genotype non-1 (£2848).[49] Even for patients with genotype 1, Stein and colleagues[49] found the intervention was reasonably cost-effective (£6330 per QALY), and interferon-α and ribavirin was previously recommended for patients with moderate hepatitis C irrespective of their genotype. These studies reported results for patients with chronic disease, rather than specifically for those with mild disease. The only cost-effectiveness analysis in the literature focusing

on patients with mild hepatitis C compared interferon-α monotherapy with no treatment, and concluded that the intervention was cost-effective with a cost per QALY of US$1900 for patients aged 35 years at treatment.[43]

There are several reasons why the costs per QALY reported in this study are higher than for previous cost-effectiveness analyses of antiviral therapy in hepatitis C. In particular, the comparison group in this study was not 'no treatment' per se. In line with previous NICE recommendations,[15] patients reaching moderate disease were assumed to have treatment with interferon-α and ribavirin therapy. This meant that the gains in QALYs from the intervention were smaller and there were no gains in life expectancy, only gains in HRQoL. Another important factor was that as the patients were at an early stage of liver disease, the probabilities of death from liver disease within a 10- or 20-year time-horizon were very low, as cases had to progress through moderate disease and cirrhosis before they faced a chance of dying from liver disease. The progression rates used were much lower than those used in previous models.[6,7,42,44,48–50] Finally, the efficacy data were based on an NHS trial and the SVR rates were much lower than those used to populate previous models.

Although on average antiviral treatment at a mild stage may be effective and cost-effective, there were important uncertainties surrounding this result. This discussion section has outlined the key methodological advances made by this cost-effectiveness analysis, highlighted some study limitations and discussed the results in the context of previous studies. The final chapter will report the overall conclusions for the study and the areas for further research.

Chapter 9
Conclusions

The SVR following interferon-α and ribavirin therapy for patients with histologically mild liver disease was similar to that reported for patients across all stages of hepatitis C who were included in previous trials.[20,21,24] This multicentre study was conducted in clinical NHS units without pharmaceutical industry involvement and therefore the SVR rates are likely to reflect those that can be achieved in day-to-day NHS practice. For patients with genotype non-1 (i.e. genotype 2 or 3) the SVR was 49%, and was equally good after only 24 weeks of therapy. For patients with genotype 1 the SVR was only 18% and these patients required treatment for up to 48 weeks.

Failure to achieve a 2-log drop in viral load by 12 weeks of therapy is associated with subsequent failure to respond and enables the drugs to be stopped prematurely, with improvements in the cost-effectiveness, regardless of viral genotype. The patients in this trial demonstrated similar impairments in baseline HRQoL and similar behaviour in terms of early viral kinetics to those with more severe disease.

Successful treatment led to modest improvements in HRQoL, measured by both the SF-36 and the EQ-5D. Statistical significance was not reached, but this was probably due to a lack of statistical power. The magnitude of the improvement, however, was small and a note of caution should be sounded before informing patients that clearance of HCV will remove all of their symptoms. It may be that longer follow-up will be required to detect a lasting benefit in HRQoL after successful therapy. Where improvement occurred it was in those who were symptomatic before treatment. There was a documented decline in HRQoL for those patients who were asymptomatic before treatment.

Considerable adverse events were documented and this led many patients to discontinue therapy, despite encouragement. Although treatment should not be restricted based on histology, the usual contraindications remain.

The cost-effectiveness model showed that providing interferon-α and ribavirin at a mild stage is relatively cost-effective at the levels of cost per QALY at which policy makers in the NHS consider interventions to be cost-effective. The intervention becomes more cost-effective if viral load data are used to identify those patients most likely to respond. The intervention is less cost-effective for older patients; in particular for patients aged 65 or over with genotype 1, the intervention is not cost-effective.

Previous cost-effectiveness analyses of interventions for mild hepatitis C have largely relied on expert opinion to estimate costs and HRQoL. This study improved on previous cost-effectiveness models by using empirical data on efficacy, transition probabilities, HRQoL and health service costs. The sensitivity analysis suggested that the finding that the intervention was cost-effective for patients with genotype non-1 was robust to different methodological assumptions. However, the finding that antiviral therapy is cost-effective for patients with genotype 1 relies on there being the HRQoL improvement following an SVR that was observed during the RCT. This improvement was only measured over 6–12 months, on a relatively small number of patients. It should be noted though that previous studies that have recruited more patients and followed them for longer suggest that the improvement in HRQoL may be greater than that observed in this trial.[34,112] The cost-effectiveness estimates as presented are therefore likely to be conservative.

Recommendations for further research

The findings of the study suggest that it is most effective to treat patients who are infected with genotypes 2 and 3. It is also more cost-effective to treat these patients while they still have mild disease rather than using liver biopsies to monitor these patients and only treating those cases who have progressed to moderate disease. It may therefore no longer be justified to insist that patients with genotype 2 and 3 have a liver biopsy before treatment.

For patients with genotype 1, the relatively low proportion of cases who had an SVR meant that

the costs per QALY gained from antiviral treatment at a mild rather than a moderate stage were generally higher than for those cases with genotype non-1. However, for younger patients (aged 40 or less), with genotype 1, provided that the willingness to pay for a QALY gained was £30,000 per QALY, the intervention was still relatively cost-effective, and for these patients a liver biopsy prior to treatment may not be justified.

The implications of treating patients without a liver biopsy should therefore be considered in further research, comparing the costs and outcomes of a strategy of liver biopsy before treatment with no liver biopsy prior to treatment for all patients with genotypes 2 and 3 and younger patients with genotype 1.

It should be recognised that the RCT had a relatively short follow-up time, and the HRQoL following SVR was only measured on a small number of patients. The HRQoL following an SVR was found to be a sensitive parameter in the cost-effectiveness model. It would be useful to conduct a study to ascertain the long-term effect of an SVR for patients with mild hepatitis C and genotype 1.

The RCT showed the value of viral kinetics in predicting SVR. When these estimates were used in the cost-effectiveness model, the cost-effectiveness of the intervention improved. The use of predictive tests based on pharmacogenomics to target therapy to those most likely to respond should now be developed.

The cost-effectiveness model can be adapted to estimate the cost-effectiveness of new technologies in hepatitis C, including pegylated interferon-α. The estimates presented suggest that, based on extrapolated data on efficacy, treatment with pegylated interferon-α and ribavirin is likely to be cost-effective for patients if provided at a mild rather than a moderate stage. These results suggest that a trial in this area may not be worthwhile. However, an observational study that measures HRQoL, costs and the proportion of patients having an SVR, and therefore reduces the uncertainties surrounding the cost-effectiveness assessment, would seem justified.

This study was a multicentre RCT that included 15 centres across the UK, and the results relating to the mild disease stage would therefore seem generalisable, at least to patients who meet the criteria for treatment specified by the trial protocol. If, however, the intervention were to be rolled out to patient groups excluded from the trial (e.g. those with co-morbidities such as HIV or haemophilia), the results would be unlikely to be generalisable. The effectiveness and HRQoL associated with antiviral treatment may well differ for these groups. Further research is required to assess how the key parameters can be adjusted to make the results applicable to patients excluded from the RCT.

While the cost-effectiveness analysis benefited greatly from empirical estimates of transition probabilities, these were generated from patients recruited to one tertiary referral centre. Further research is currently being undertaken to produce more general estimates of disease transition.

A retrospective cohort study estimated the costs of later disease stages. The observation period differed across the patients included in this study, as patients were censored for different reasons (e.g death or disease progression). To deal with the problem of censored costs, advanced statistical techniques have been applied to trial-based cost-effectiveness analyses.[101,102] These techniques have yet to be used for estimating the long-term costs required by cost-effectiveness models; this would seem to be an area worthy of further methodological research.

Cost-effectiveness models can be adapted to evaluate new interventions as they become available. However, analysts seldom consider the accompanying changes in the ways in which patients are managed, which may have an important bearing on cost-effectiveness. Hepatitis C, with its slowly progressive nature requiring cost-effectiveness to be estimated over 50 years, would provide an excellent case study for investigating the effect of incorporating technological change into the health technology assessment. For example, in the future new therapies will be developed, liver biopsies may no longer be required and other procedures may be done on an inpatient rather than a day-case basis. Preliminary work has suggested that incorporating these changes over the model's projection period could have an important impact on the cost-effectiveness of therapies preventing disease progression (Grieve R, Roberts JA. Unpublished paper presented to the International Health Economics Association, San Francisco; 2003).

To conclude, this study found that it was relatively cost-effective to treat patients with hepatitis C who had genotype non-1 (i.e. genotype 2 or 3). For

patients with genotype 1 aged 40 or less, antiviral treatment at a mild stage was cost-effective at the cost per QALY threshold previously used by NHS decision-makers (£30,000 per QALY). For older patients (aged 65 or over) with genotype 1, intervention at a mild stage was not cost-effective. These results were based on empirical estimates of efficacy, health service costs and HRQoL all estimated using UK data and analysed specifically for this cost-effectiveness assessment. Further research, in particular on the long-term HRQoL following the clearance of HCV for patients with genotype 1, would assist future management of the disease.

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Mild Hepatitis C Trial Investigators

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Steering Committee

Professor Patrick Sissons (Chairman), Professor Margaret Bassendine, Professor Chris Bulpitt, Dr Janice Main, Professor Humphrey Hodgson, Professor Jenny Roberts, Professor Peter Sever and Professor Howard Thomas.

Data and Safety Monitoring Committee

Dr Douglas Maxwell (Chairman), Professor Janet Darbyshire, Professor Nick Bosaenquet and Professor Roger Williams.

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Contribution of authors

Mark Wright (Research Fellow) was responsible for coordination of the trial, analysis of the trial data and the writing of the final report. Richard Grieve (Lecturer in Health Economics) and Jenny Roberts (Professor of Economics and Public Health) designed the economic evaluation, analysed the economics data and helped to write the report. Howard Thomas (Professor of Medicine) and Janice Main (Reader in Infectious Diseases) instigated the study, designed the protocol and were the principal investigators.

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Appendix 1

HRQoL data

TABLE 57 *Comparison of baseline SF-36 data from mild hepatitis C patients with a standard UK population*

Parameter	Z-score (SDs from mean)	Range
Physical functioning	–0.24	–4.4 to 0.64
Role – physical function	–0.63	–2.9 to 0.47
Bodily pain	–0.68	–3.8 to 0.85
General health	–0.33	–3.7 to 1.3
Vitality	–0.45	–3.1 to 2
Social functioning	–1	–4.5 to 0.6
Role – emotional function	–0.51	–5.7 to 0.54
Mental health	–0.55	–4.28 to 1.5

TABLE 58 *SF-36 scores at week 12*

Parameter	Treatment group	Control group	*p*
Physical functioning			
Number	78	57	0.004
Mean (SD)	72.5 (28.4)	85.1 (21.7)	
Role – physical function			
Number	76	56	0.0003
Mean (SD)	38.5 (43.1)	66.5 (42.2)	
Bodily pain			
Number	75	56	0.116
Mean (SD)	60.5 (29.6)	68.6 (28.4)	
General health			
Number	76	56	0.691
Mean (SD)	53.7 (24.3)	55.4 (24.1)	
Vitality			
Number	78	57	0.004
Mean (SD)	41.7 (23)	53 (21.2)	
Social functioning			
Number	78	57	0.0001
Mean (SD)	50.7 (30.8)	71.7 (28.9)	
Role – emotional function			
Number	76	54	0.039
Mean (SD)	53.5 (43.6)	69.1 (39.8)	
Mental health			
Number	78	57	0.085
Mean (SD)	57.8 (23.4)	64.5 (20.3)	

TABLE 59 *SF-36 scores at week 24*

Parameter	Treatment group	Control group	*p*
Physical functioning			
Number	66	60	0.0003
Mean (SD)	69.2 (28.4)	85.2 (18.6)	
Role – physical function			
Number	63	56	0.0001
Mean (SD)	37.7 (39.1)	67 (41.6)	
Bodily pain			
Number	63	58	0.036
Mean (SD)	59.7 (30)	71 (28.3)	
General health			
Number	66	58	0.056
Mean (SD)	49.4 (23.7)	57.4 (22)	
Vitality			
Number	65	60	0.009
Mean (SD)	37.4 (24.5)	48.5 (22.3)	
Social functioning			
Number	65	60	0.006
Mean (SD)	49.9 (35.7)	66.9 (31.5)	
Role – emotional function			
Number	63	58	0.004
Mean (SD)	40.7 (41.7)	64.8 (45.8)	
Mental health			
Number	66	60	0.103
Mean (SD)	55.2 (25.7)	62.4 (23.6)	

TABLE 60 *SF-36 scores at week 48*

Parameter	Treatment group	Control group	*p*
Physical functioning			
Number	65	51	0.106
Mean (SD)	76.4 (24.2)	83.24 (20)	
Role – physical function			
Number	63	47	0.009
Mean (SD)	45.6 (43.2)	67.6 (41.7)	
Bodily pain			
Number	63	50	0.409
Mean (SD)	61.8 (31.5)	66.6 (30.2)	
General health			
Number	65	50	0.814
Mean (SD)	57.4 (21.8)	58.4 (24.9)	
Vitality			
Number	65	51	0.148
Mean (SD)	43.5 (25.8)	50.1 (21.7)	
Social functioning			
Number	65	50	0.001
Mean (SD)	53.4 (31.4)	73.1 (30.6)	
Role – emotional function			
Number	63	49	0.019
Mean (SD)	51.3 (43.9)	70.8 (41.2)	
Mental health			
Number	65	51	0.561
Mean (SD)	59.6 (21.3)	62.04 (23)	

TABLE 61 *SF-36 scores at post-week 24*

Parameter		Treatment group	Control group	*p*
Physical functioning	Number	71	62	0.79
	Mean (SD)	84.2 (23)	85.2 (20.7)	
Role – physical function	Number	69	60	0.774
	Mean (SD)	72.5 (38.1)	70.42 (42.6)	
Bodily pain	Number	70	61	0.027
	Mean (SD)	76.7 (26.5)	65.9 (29.03)	
General health	Number	71	61	0.517
	Mean (SD)	60.5 (22.9)	57.8 (23.5)	
Vitality	Number	72	62	0.413
	Mean (SD)	55 (24.2)	51.6 (23.7)	
Social functioning	Number	72	61	0.883
	Mean (SD)	72.2 (30)	71.4 (31.8)	
Role – emotional function	Number	71	61	0.545
	Mean (SD)	73.2 (40.1)	68.9 (43)	
Mental health	Number	72	62	0.283
	Mean (SD)	66.9 (20.8)	62.84 (23.2)	

TABLE 62 *HRQoL by treatment outcome (post-week 24)*

Parameter	Treatment group		Control group	*p* (ANOVA)
	SVR	No SVR		
Physical functioning				0.183[a]
Number	24	46	62	0.577[b]
Mean (SD)	90 (15.6)	80.1 (25.7)	85.2 (20.7)	0.557[c]
Role – physical function				0.472[a]
Number	23	45	60	0.571[b]
Mean (SD)	80.4 (32.8)	68.3 (40.7)	70.4 (42.6)	0.963[c]
Bodily pain				0.881[a]
Number	24	45	61	0.120[b]
Mean (SD)	78 (26.3)	75.6 (26.9)	65.9 (29)	0.180[c]
General health				0.661[a]
Number	23	47	61	0.534[b]
Mean (SD)	63 (25.1)	58.7 (21.9)	57.8 (23.5)	0.977[c]
Vitality				0.364[a]
Number	24	47	62	0.278[b]
Mean (SD)	59.2 (21.6)	52.2 (25.2)	51.6 (23.7)	0.990[c]
Social functioning				0.586[a]
Number	24	47	61	0.716[b]
Mean (SD)	79.2 (26.3)	69.6 (31.2)	71.4 (31.8)	0.950[c]
Role – emotional function				0.713[a]
Number	24	46	61	0.996[b]
Mean (SD)	66.7 (42.8)	76.1 (38.9)	68.9 (43)	0.645[c]
Mental health				0.708[a]
Number	24	47	62	0.379[b]
Mean (SD)	69.3 (19.9)	65.4 (21.6)	62.8 (23.2)	0.813[c]

[a] SVR versus no SVR.
[b] SVR versus control.
[c] No SVR versus control.

TABLE 63 *HRQoL at baseline compared with at post-week 24, for patients achieving an SVR*

Parameter	Patients achieving SVR		*p* (paired samples *t*-test)
	Baseline	Post-week 24	
Physical functioning			
Number	23		
Mean (SD)	90.9 (12.7)	89.6 (16.1)	0.661
Role – physical function			
Number	22		
Mean (SD)	76.1 (34.1)	79.6 (33.3)	0.589
Bodily pain			
Number	23		
Mean (SD)	69 (28.62)	78.2 (26.8)	0.117
General health			
Number	22		
Mean (SD)	60.1 (25.8)	63.8 (25.35)	0.348
Vitality			
Number	23		
Mean (SD)	55.2 (20.36)	58.5 (21.8)	0.353
Social functioning			
Number	23		
Mean (SD)	74.5 (21.5)	78.3 (26.5)	0.486
Role – emotional function			
Number	23		
Mean (SD)	76.8 (36.8)	65.2 (43.2)	0.057
Mental health			
Number	23		
Mean (SD)	70.1 (16.8)	68.9 (20.2)	0.715

TABLE 64 *HRQoL at baseline compared with at post-week 24, for patients achieving an SVR*

Parameter	Patients achieving SVR		*p* (paired samples *t*-test)
	Baseline	Post-week 24	
Physical component summary score			
Number	24	24	
Mean (SD)	48.1 (5.2)	49.2 (4.97)	0.185
Mental component summary score			
Number	24	24	
Mean (SD)	49.6 (2.78)	49.7 (3.0)	0.729

TABLE 65 *HRQoL at baseline compared with at post-week 24, for patients failing to achieve an SVR*

Parameter	Patients failing to achieve SVR		*p* (paired samples *t*-test)
	Baseline	Post-week 24	
Physical functioning			
Number	43		
Mean (SD)	82.1 (26)	81.7 (25.7)	0.915
Role – physical function			
Number	40		
Mean (SD)	61.3 (44.2)	73.1 (38.6)	0.052
Bodily pain			
Number	42		
Mean (SD)	69 (28.5)	78.2 (25)	0.035
General health			
Number	44		
Mean (SD)	59.4 (23.1)	59.6 (22.1)	0.945
Vitality			
Number	44		
Mean (SD)	51.3 (25.2)	53 (25.3)	0.652
Social functioning			
Number	44		
Mean (SD)	72.1 (31.4)	71.4 (30.8)	0.887
Role – emotional function			
Number	43		
Mean (SD)	64.3 (41.4)	78.3 (38.4)	0.03
Mental health			
Number	44		
Mean (SD)	68.7 (22.2)	66.4 (21.1)	0.421

TABLE 66 *HRQoL at baseline compared with at post-week 24, for patients failing to achieve an SVR*

Parameter	Patients failing to achieve SVR		*p* (paired samples *t*-test)
	Baseline	Post-week 24	
Physical component summary score			
Number	44	44	
Mean (SD)	46.8 (6.8)	47.5 (6.6)	0.39
Mental component summary score			
Number	44	44	
Mean (SD)	49.5 (3)	50 (2.9)	0.38

TABLE 67 *HRQoL at baseline compared with at post-week 24 for control patients*

Parameter	Control patients		*p* (paired samples *t*-test)
	Baseline	Post-week 24	
Physical functioning			
Number	58		
Mean (SD)	86.6 (20.3)	86.2 (17.9)	0.892
Role – physical function			
Number	56		
Mean (SD)	76.8 (33.7)	71 (42.6)	0.229
Bodily pain			
Number	58		
Mean (SD)	71.8 (27.3)	65.8 (29.1)	0.111
General health			
Number	56		
Mean (SD)	62.5 (21.9)	58.6 (23.5)	0.069
Vitality			
Number	58		
Mean (SD)	57.2 (21.2)	51.4 (22.8)	0.006
Social functioning			
Number	57		
Mean (SD)	71.7 (26.8)	70.7 (32.4)	0.807
Role – emotional function			
Number	57		
Mean (SD)	73.1 (39.1)	69 (43.1)	0.478
Mental health			
Number	58		
Mean (SD)	65 (19.4)	63.3 (23.2)	0.445

TABLE 68 *HRQoL at baseline compared with at post-week 24 for control patients*

Parameter	Control patients		*p* (paired samples *t*-test)
	Baseline	Post-week 24	
Physical component summary score			
Number	58	58	
Mean (SD)	48.5 (4.64)	47.5 (5.86)	0.09
Mental component summary score			
Number	58	58	
Mean (SD)	49.5 (2.73)	49.5 (2.84)	0.86

TABLE 69 *Route of infection and baseline SF-36 score*

Parameter	IVDU	Blood product	*p*
Physical functioning			
Number	98	29	0.37
Mean	85.5	82	
Role – physical function			
Number	94	27	0.52
Mean	68	73	
Bodily pain			
Number	98	29	0.88
Mean	66	65	
General health			
Number	98	29	0.34
Mean	56	61	
Vitality			
Number	98	29	0.81
Mean	52	54	
Social functioning			
Number	98	29	0.97
Mean	68	68	
Role – emotional function			
Number	95	28	0.16
Mean	65	78	
Mental health			
Number	98	29	0.08
Mean	61	69	

Appendix 2

Quantitative virology

TABLE 70 *Viral load values*

Study code	Date of birth	Hospital	Sample date	Day	HCV (IU ml^{-1})	Log (IU ml^{-1})
2	18/08/51	St Mary's	04/01/99	0	228,871	5.36
2	18/08/51	St Mary's	06/01/99	3	114,871	5.06
2	18/08/51	St Mary's	11/01/99	7	443,623	5.65
2	18/08/51	St Mary's	14/01/99	10	240,838	5.38
2	18/08/51	St Mary's	18/01/99	14	978,719	5.99
2	18/08/51	St Mary's	29/03/99	84	807,330	5.91
3	08/01/66	St Mary's	02/12/98	0	2,160,000	6.33
3	08/01/66	St Mary's	04/12/98	3	1,420,000	6.15
3	08/01/66	St Mary's	07/12/98	7	2,000,000	6.30
3	08/01/66	St Mary's	11/12/98	10	266,911	5.43
3	08/01/66	St Mary's	15/12/98	14	2,030,000	6.31
3	08/01/66	St Mary's	22/02/99	84	2,140,000	6.33
4	05/08/61	St Mary's	28/06/99	0	243,905	5.39
4	05/08/61	St Mary's	01/07/99	3	462	2.67
4	05/08/61	St Mary's	05/07/99	7	6,081	3.78
4	05/08/61	St Mary's	08/07/99	10	236	2.37
4	05/08/61	St Mary's	12/07/99	14	176	2.25
4	05/08/61	St Mary's	17/09/99	84	149	2.17
6	29/10/52	St Mary's	29/01/99	0	98,752	4.99
6	29/10/52	St Mary's	01/02/99	3	652	2.81
6	29/10/52	St Mary's	12/02/99	14	0	0.00
6	29/10/52	St Mary's	23/04/99	84	0	0.00
7	05/07/50	St Mary's	25/11/98	0	1,130,000	6.05
7	05/07/50	St Mary's	12/02/99	3	120,691	5.08
7	05/07/50	St Mary's	15/02/99	7	98.516	4.99
7	05/07/50	St Mary's	19/02/99	10	24,007	4.38
7	05/07/50	St Mary's	22/02/99	14	33,288	4.52
7	05/07/50	St Mary's	05/05/99	84	23	1.36
9	06/06/49	St Mary's	19/04/99	0	610,848	5.79
9	06/06/49	St Mary's	22/04/99	3	54,067	4.73
9	06/06/49	St Mary's	26/04/99	7	124,204	5.09
9	06/06/49	St Mary's	29/04/99	10	26,868	4.43
9	06/06/49	St Mary's	04/05/99	14	45,082	4.65
9	06/06/49	St Mary's	09/07/99	84	0	0.00
10	07/04/50	St Mary's	13/04/99	0	3,770,000	6.58
10	07/04/50	St Mary's	16/04/99	3	192,594	5.28
10	07/04/50	St Mary's	20/04/99	7	70,812	4.85
10	07/04/50	St Mary's	23/04/99	10	65,367	4.82
10	07/04/50	St Mary's	27/04/99	14	111,332	5.05
10	07/04/50	St Mary's	06/07/99	84	43	1.63
11	06/04/52	St Mary's	16/04/99	0	5,398	3.73
11	06/04/52	St Mary's	19/04/99	3	1,207	3.08
11	06/04/52	St Mary's	23/04/99	7	2,699	3.43
11	06/04/52	St Mary's	26/04/99	10	2,868	3.46
11	06/04/52	St Mary's	30/04/99	14	1,903	3.28
11	06/04/52	St Mary's	09/07/99	84	17,286	4.24
12	13/07/63	St Mary's	26/04/99	0	334,271	5.52
12	13/07/63	St Mary's	29/04/99	3	63,959	4.81

continued

TABLE 70 *Viral load values (cont'd)*

Study code	Date of birth	Hospital	Sample date	Day	HCV (IU ml^{-1})	Log (IU ml^{-1})
12	13/07/63	St Mary's	06/05/99	10	55,663	4.75
12	13/07/63	St Mary's	10/05/99	14	87,609	4.94
12	13/07/63	St Mary's	19/07/99	84	0	0.00
21	17/03/72	Leeds	16/05/01	0	378,718	5.58
21	17/03/72	Leeds	18/05/01	3	81,486	4.91
21	17/03/72	Leeds	23/05/01	7	21,805	4.34
21	17/03/72	Leeds	25/05/01	10	14,591	4.16
21	17/03/72	Leeds	01/06/01	14	8,025	3.90
21	17/03/72	Leeds	11/07/01	56		0.00
24	24/08/74	Leeds	17/01/01	0	244,382	5.39
24	24/08/74	Leeds	22/01/01	3	14,303	4.16
24	24/08/74	Leeds	24/01/01	7	254	2.41
24	24/08/74	Leeds	26/01/01	10	45	1.66
24	24/08/74	Leeds	31/01/01	14	0	0.00
24	24/08/74	Leeds	04/04/01	84	0	0.00
29	29/09/59	Leeds	12/06/00	0	24,691	4.39
29	29/09/59	Leeds	16/06/00	3	62,141	4.79
29	29/09/59	Leeds	20/06/00	7	105,828	5.02
29	29/09/59	Leeds	23/06/00	10	19,073	4.28
29	29/09/59	Leeds	28/06/00	14	15,188	4.18
29	29/09/59	Leeds	15/09/00	84	48,287	4.68
33	31/07/57	Leeds	09/09/99	0	2,120,000	6.33
33	31/07/57	Leeds	13/09/99	3	79,540	4.90
33	31/07/57	Leeds	17/09/99	7	2,326	3.37
33	31/07/57	Leeds	21/09/99	10	3,963	3.60
33	31/07/57	Leeds	24/09/99	14	388	2.59
33	31/07/57	Leeds	01/12/99	84	0	0.00
44	29/01/60	UCH	06/04/99	0	17,397	4.24
44	29/01/60	UCH	13/04/99	7	952	2.98
44	29/01/60	UCH	20/04/99	14	192	2.28
44	29/01/60	UCH	29/06/99	84	0	0.00
45	29/11/58	UCH	20/07/99	0	771,362	5.89
45	29/11/58	UCH	22/07/99	3	416,816	5.62
45	29/11/58	UCH	27/07/99	7	542,035	5.73
45	29/11/58	UCH	29/07/99	10	956,334	5.98
45	29/11/58	UCH	03/08/99	14	530,877	5.72
45	29/11/58	UCH	12/10/99	84	107,841	5.03
46	09/09/46	UCH	08/06/99	0	192,0000	6.28
46	09/09/46	UCH	15/06/99	7	5,775	3.76
46	09/09/46	UCH	22/06/99	14	355	2.55
46	09/09/46	UCH	31/08/99	84	0	0.00
47	22/06/53	UCH	21/09/99	0	61,903	4.79
47	22/06/53	UCH	23/09/99	3	2,186	3.34
47	22/06/53	UCH	28/09/99	7	556	2.74
47	22/06/53	UCH	30/09/99	10	241	2.38
47	22/06/53	UCH	05/10/99	14	1,052	3.02
47	22/06/53	UCH	14/12/99	84	0	0.00
48	19/12/64	UCH	11/01/00	0	237,896	5.38
48	19/12/64	UCH	13/01/00	3	71,432	4.85
48	19/12/64	UCH	18/01/00	7	214,442	5.33
48	19/12/64	UCH	20/01/00	10	92,529	4.97
48	19/12/64	UCH	25/01/00	14	84,434	4.93
48	19/12/64	UCH	04/04/00	84	711	2.85
49	14/09/58	UCH	23/11/99	0	978,600	5.99
49	14/09/58	UCH	25/11/99	3	55,169	4.74
49	14/09/58	UCH	30/11/99	7	5,016	3.70

continued

TABLE 70 *Viral load values (cont'd)*

Study code	Date of birth	Hospital	Sample date	Day	HCV (IU ml^{-1})	Log (IU ml^{-1})
49	14/09/58	UCH	02/12/99	10	3,783	3.58
49	14/09/58	UCH	07/12/99	14	738	2.87
49	14/09/58	UCH	15/02/00	84	0	0.00
50	07/09/46	UCH	13/01/00	0	3,500,000	6.54
50	07/09/46	UCH	18/01/00	3	2,900,000	6.46
50	07/09/46	UCH	20/01/00	7	1,750,000	6.24
50	07/09/46	UCH	25/01/00	10	1,970,000	6.29
50	07/09/46	UCH	27/01/00	14	1,160,000	6.06
50	07/09/46	UCH	04/04/00	84	293,874	5.47
54	24/11/60	UCH	21/03/00	0	13,6661	5.14
54	24/11/60	UCH	23/03/00	3	6,772	3.83
54	24/11/60	UCH	28/03/00	7	72,921	4.86
54	24/11/60	UCH	04/04/00	14	2,192	3.34
56	02/02/71	UCH	18/07/00	0	688,524	5.84
56	02/02/71	UCH	20/07/00	3	42,608	4.63
56	02/02/71	UCH	25/07/00	7	2,947	3.47
56	02/02/71	UCH	27/07/00	10	63	1.80
56	02/02/71	UCH	01/08/00	14	14	1.14
56	02/02/71	UCH	10/10/00	84		0.00
59	24/09/75	UCH	28/06/01	0	2,062	3.31
59	24/09/75	UCH	05/07/01	7	0	0.00
59	24/09/75	UCH	16/07/01	14	0	0.00
59	24/09/75	UCH	18/09/01	84	0	0.00
64	09/02/67	Southampton	01/10/99	0	223,479	5.35
64	09/02/67	Southampton	08/10/99	7	7,100	3.85
64	09/02/67	Southampton	14/10/99	14	3,328	3.52
64	09/02/67	Southampton	20/12/99	84	0	0.00
86	01/03/58	Royal Free	15/09/00	0	142,534	5.15
86	01/03/58	Royal Free	18/09/00	3	41,455	4.62
86	01/03/58	Royal Free	21/09/00	7	12,242	4.09
86	01/03/58	Royal Free	26/09/00	14	8,825	3.95
86	01/03/58	Royal Free	08/11/00	56	0	0.00
101	17/07/72	Glasgow	30/03/99	0	62,176	4.79
101	17/07/72	Glasgow	02/04/99	3	106,736	5.03
101	17/07/72	Glasgow	06/04/99	7	203,411	5.31
101	17/07/72	Glasgow	09/04/99	10	89,121	4.95
101	17/07/72	Glasgow	13/04/99	14	682,386	5.83
101	17/07/72	Glasgow	24/06/99	84	328,505	5.52
102	24/06/65	Glasgow	30/03/99	0	1,220,000	6.09
102	24/06/65	Glasgow	02/04/99	3	1,340,000	6.13
102	24/06/65	Glasgow	06/04/99	7	528,599	5.72
102	24/06/65	Glasgow	09/04/99	10	1,510,000	6.18
102	24/06/65	Glasgow	13/04/99	14	1,540,000	6.19
102	24/06/65	Glasgow	21/06/99	84	1,580,000	6.20
112	18/10/65	Glasgow	11/01/00	0	2,690,000	6.43
112	18/10/65	Glasgow	14/01/00	3	2,140,000	6.33
112	18/10/65	Glasgow	18/01/00	7	2,030,000	6.31
112	18/10/65	Glasgow	21/01/00	10	1,970,000	6.29
112	18/10/65	Glasgow	25/01/00	14	2,390,000	6.38
112	18/10/65	Glasgow	04/04/00	84	1,730,000	6.24
113	22/04/58	Glasgow	22/02/00	0	65,146	4.81
113	22/04/58	Glasgow	25/02/00	3	163,210	5.21
113	22/04/58	Glasgow	29/02/00	7	72,209	4.86
113	22/04/58	Glasgow	03/03/00	10	60,775	4.78
113	22/04/58	Glasgow	08/03/00	14	33,022	4.52
113	22/04/58	Glasgow	17/05/00	84	608	2.78

continued

TABLE 70 *Viral load values (cont'd)*

Study code	Date of birth	Hospital	Sample date	Day	HCV (IU ml^{-1})	Log (IU ml^{-1})
115	18/09/70	Glasgow	22/02/00	0	52,938	4.72
115	18/09/70	Glasgow	25/02/00	3	9,725	3.99
115	18/09/70	Glasgow	29/02/00	7	2,404	3.38
115	18/09/70	Glasgow	03/03/00	10	893	2.95
115	18/09/70	Glasgow	07/03/00	14	213	2.33
115	18/09/70	Glasgow	10/05/00	84		0.00
118	23/07/53	Glasgow	07/03/00	0	938,760	5.97
118	23/07/53	Glasgow	10/03/00	3	23,617	4.37
118	23/07/53	Glasgow	14/03/00	7	24,499	4.39
118	23/07/53	Glasgow	17/03/00	10	8,178	3.91
118	23/07/53	Glasgow	16/03/00	14	11,706	4.07
118	23/07/53	Glasgow	30/05/00	84	833	2.92

Appendix 3

Statistical methods for estimation of transition rates

The transition intensities (λ_{rs}) were estimated through maximum likelihood estimation using information on the states occupied at various times. For instance, if states r and s are occupied at times t and u, respectively, then the observed transition from r to s in the interval of length $u - t$ will contribute $p_{rs}(u - t)$ to the likelihood function. The full likelihood is the product of all these contributions. Multivariate analysis was used to estimate the effect of covariates (age at infection, gender, genotype, alcohol consumption) on transition intensity. A package of functions named msm written for the free statistical software R was used to fit the models (see Jackson and colleagues[123] for more details).

Model selection

Covariates were first entered into the model to test for association with fibrosis rate in a univariate analysis. The variables considered were age at infection, gender, genotype, ethnic origin, alcohol consumption and past (or present) hepatitis B infection. Likelihood ratio statistics were used to test the significance of each covariate at the 5% level. A multivariate analysis was then performed on the variables shown to be associated with fibrosis progression in the univariate analysis. Covariate effects were constrained to be equal for both transition intensities (e.g. $\beta_{12,\,\text{gender}} = \beta_{23,\text{gender}}$), apart from age at infection, where it was thought that the effect of age at infection on the mild–moderate transition intensity might differ from the effect on the moderate-cirrhosis intensity.

Model assessment and validation

In addition to the final multivariate model, a similar model was estimated using two-thirds of the patients in the cohort. The observed biopsy scores were compared with those predicted by the model at the observation times to assess goodness of fit.

The analysis was conducted on patients enrolled in the St Mary's HCV cohort with an estimated date of infection and at least one scored biopsy, without intervening treatment.

Appendix 4

Unit costs used in the cost analysis

TABLE 71 *Unit costs (£) of hospital services for each centre (2002/03 prices)*

	London	Newcastle	Southampton
Inpatient care: costs per day			
ITU	1151	1131	NA
HDU	278	367	NA
Liver unit	246	228	119
General medical ward	141	138	130
Admission ward	194	NA	175
Day-case unit	194	NA	NA
Other	141	138	130
Private	246	228	119
Outpatient services: costs per visit			
Outpatient	19	20	15
Nurse	16	19	14
A&E	68	77	81

A&E, accident and emergency; NA, not applicable (not provided in this centre).

TABLE 72 *Unit costs (£) of procedures for each centre (2002/03 prices)*

	London	Newcastle	Southampton
Colonoscopy	110	122	140
Endoscopy: diagnostic	98	124	108
Endoscopy: therapeutic injection	150	193	150
Endoscopy: therapeutic banding	259	289	242
ERCP + sphincterectomy	371	361	366
Liver biopsy	243	233	271
Ultrasound-guided liver biopsy	277	247	285
Transjugular liver biopsy	540	668	796
Inpatient liver biopsy	184	205	203
Gastric biopsy[a]	141	141	141
Diagnostic/therapeutic paracentesis	130	130	130
Barium swallow	94	38	35
Coeliac angiogram	518	555	235
Hepatic angiography	300	315	351
CT portogram	374	NA	419
Lung scan	245	245	245
TIPPS	2192	2213	2542
Post-TIPPS venogram	225	224	330
Post-TIPPS venogram + angioplasty	NA	NA	1102
Alcohol injection liver (tumour)	363	370	378
Laser ablation liver	4437	NA	NA
Radiofrequency ablation	NA	700	767
Bone scan	94	50	76
Liver aspiration	65	71	68

[a] Unit cost assumed to be the same across all three centres.
ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography.

TABLE 73 *Unit costs (£) of radiological investigations for each centre (2002/03 prices)*

	London	Newcastle	Southampton
Abdomen X-ray	34	14	14
Abdomen/liver ultrasound	66	38	108
Chest X-ray	32	14	14
CT abdomen	111	136	111
CT brain	95	114	73
ECG	20	20	33
Echocardiogram[a]	43	43	43
Isotope liver scan	174	103	NA
Liver ultrasound	44	62	108
MRI brain	240	180	185
MRI liver	240	193	185
Portal vein Doppler	66	38	108
Ultrasound-guided ascitic tap[a]	100	100	100
X-ray hip	41	14	18

[a] Unit cost assumed to be the same across all three centres.
MRI, magnetic resonance imaging.

TABLE 74 *Unit costs (£) of blood tests for each centre (2002/03 prices)*

	London	Newcastle	Southampton
α_1-Antitrypsin	8.3	5.9	5.2
α-Fetoprotein	5.3	4.5	8.3
Anti-HCV	30.4	9.6	10.9
Anti-hepatitis A antibody	29.4	10.1	9.7
Anti-hepatitis B antibody	25.7	16.2	16.9
Anti-liver, kidney and microsomal	4.1	8.0	5.1
Antinuclear antibody	8.5	8.0	5.1
Anti-smooth muscle antibody	4.1	8.0	5.1
Antithyroid microsomal antibodies	NA	8.0	5.1
Autoantibody screen	NA	13.1	5.1
Autoimmune profile	16.6	8.5	5.1
Vitamin B_{12}	5.1	4.7	6.4
Bleeding time	9.4	10.4	21.2
Blood ethanol	8.9	5.5	8.1
Bone profile	3.2	2.5	3.4
C-reactive protein	2.9	4.5	2.5
Caeruloplasmin	7.7	2.5	6.3
Cholesterol and triglycerides	3.4	2.2	4.8
Clotting	1.5	2.8	2.3
Cryglobulins	8.2	2.5	4.7
Cryoprecipitate	2.6	2.5	NA
Erythrocyte sedimentation rate	2.1	1.8	2.5
Ferritin	6.5	3.5	19.6
Full blood count	2.6	1.6	2.1
γ-Glutamyltransferase	2.9	1.3	2.4
Glucose	4.8	0.9	2.4
Group and save	2.6	6.7	9.1
Haemoglobin electrophoresis	12.6	3.2	NA
HCV (RNA)	62.7	36.0	69.3
Hepatitis ABC	62.8	27.0	27.0
HIV	17.2	5.1	6.4
Immunoglobulins	6.9	16.4	11.2
Liver function tests	3.5	3.5	3.4
Microscopy culture and sensitivity	11.4	8.2	5.0
Thyroid function tests	5.9	3.5	3.4
Urate	3.0	1.3	3.4
Urea and electrolytes	3.5	2.5	6.8
Viral genotype	113.5	80.0	88.0

TABLE 75 *Unit costs (£) of blood tests for each centre (2002/03 prices)*

	London	Newcastle	Southampton
20% salt poor albumin unit	33	34	34
4% Albumin bags	32	34	32
Cyroprecipitate bags	29	22	26
Fresh-frozen plasma bags (300 ml)[a]	44	44	44
Packed red cells bags	70	70	70
Platelets bags	150	142	146
TPN bags (days)[a]	67	67	67
Venesection	14	14	15
Whole blood bags[a]	65	65	65

[a] Unit cost assumed to be the same across all three centres.
TPN, total parenteral nutrition.

Appendix 5

Parameters for probabilistic model

TABLE 76 *Mean, standard error and distribution for each parameter*

Parameter	Mean	SE	Distribution
Transition probabilities			
Mild–moderate	0.025	0.004	Beta
Moderate–cirrhosis	0.037	0.007	Beta
Cirrhosis–decompensated cirrhosis	0.039	0.01	Beta
Efficacy (% SVR)			
Mild and moderate disease	0.33	0.05	Beta
HRQoL estimates			
Mild SVR	0.82	0.04	Beta
Mild	0.77	0.02	Beta
Mild treatment	0.66	0.04	Beta
Moderate disease	0.66	0.03	Beta
Moderate treatment	0.55	0.04	Beta
Moderate SVR	0.72	0.05	Beta
Cirrhosis	0.44	0.05	Beta
Costs (£)			
Mild disease	138	115	Gamma
Mild/moderate treatment	6805	493	Gamma
Mild SVR	259	48	Gamma
Mild non-responders	118	26	Gamma
Moderate disease	730	64	Gamma
Cirrhosis	1138	224	Gamma
Decompensated cirrhosis	9121	1519	Gamma

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Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

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The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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