Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final protocol, 16th June 2009

1. Title of the project

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

2. Name of TAR team and 'lead'

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3. Plain English Summary

The hepatitis C virus (HCV) can be acquired through coming into contact with infected blood, primarily through contaminated needles. Once caught, the virus can stay in the body in the long term with few obvious signs and symptoms of infection. Approximately one third of patients with HCV will develop significant liver disease over a number of years (sometimes decades). During this time, the virus may attack the liver causing progressive damage resulting in fibrosis and sometimes cirrhosis (scarring of the liver). If the virus is not successfully treated or a liver transplant is given, the infected person may die from liver failure and related complications such as primary liver cancer. In England and Wales it is estimated that 191,000 people aged 15-59 years carry the HCV virus.

Drug treatment is available for HCV, and usually involves taking a combination of pegylated interferon alfa (injected beneath the skin usually once a week) and ribavirin (taken orally each day) for between 6 and 12 months. The National Institute for Health and Clinical Excellence (NICE) approved the use of this drug combinant in England and Wales in 2004, and then again in 2006 specifically for people with the milder form of HCV. The licenses for the two available brands of pegylated interferon alfa have recently been extended to allow people who were not successfully treated with pegylated interferon alfa and ribavirin to undergo a second course, as well as those people who are also infected with HIV to receive treatment. The

licence changes also allow shorter courses of treatment to be given to certain people with particular sub-types of hepatitis C (known as 'genotypes'). Given these recent changes in the drug licenses it is important for NICE to update its guidance to the health service. The aim of this project is to systematically review the clinical trials to enable NICE to make evidence-informed policy recommendations for the treatment of HCV. In addition, an overall estimate of the cost per quality adjusted life year (QALY) will be made, to allow NICE to determine whether treatment represents an efficient use of health service money.

4. Decision problem

The aim of this health technology assessment is to assess the clinical-effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of moderate to severe hepatitis C was appraised by NICE in 2004 (TA75[1]) and an appraisal specifically for mild hepatitis C was carried out in 2006 (TA106[2]). Both appraisals were based on independent assessment reports conducted by SHTAC.[3,4]

Since NICE's clinical guidance was published, there have been extensions to the licences for peginterferon alfa-2a and -2b. This health technology assessment is a part-review of the current NICE guidance and will be restricted to the patient subgroups that are affected by the licence extensions for the peginterferons. This includes people who have been previously treated with peginterferon alfa and ribavirin in combination and who either did not respond or who responded but relapsed, people who meet the licensed criteria for receiving shortened courses of combination therapy and people with HCV/HIV co-infection.

4.1 Background

Hepatitis C

Hepatitis C is a slowly progressing infectious disease of the liver arising from the blood-borne hepatitis C virus. First identified in 1989, the hepatitis C virus belongs to the *Flaviviridae* family of viruses. It is a ribonucleic acid (RNA) virus and, as such, is much less stable and more prone to mutation than a deoxyribonucleic acid (DNA) virus, resulting in different genetic variations of HCV, known as genotypes.[5,6] There are six major genotypes which are indicated numerically (e.g. genotype 1, 2, 3, etc.), and several sub-types of HCV (labelled a, b, c, etc.), the prevalence of which varies considerably between countries. In England and Wales, the most prevalent genotypes are 1 and 3, representing more than 90% of all diagnosed infections.[7] Genotype 3a remains the most common with a prevalence of 39%,

followed by genotype 1a (22%).[7] Response to treatment is strongly influenced by HCV genotype. Anti-viral treatment is more effective in those with genotypes 2 and 3 (comprising more than half of those infected in England and Wales) compared to those with genotypes 1, 4, 5 and 6.

Acute HCV refers to the period immediately after HCV infection, whilst chronic HCV is defined as infection with the hepatitis C virus persisting for more than six months. It is categorised as mild, moderate or severe according to the extent of liver damage, based on the level of fibrosis (or scarring) that has occurred in the liver as well as the degree of necroinflammation. Symptoms in patients with chronic HCV are typically mild and non-specific and include fatigue, flu-like symptoms, anorexia, depression, sleep disturbance, right upper quadrant pain, itching and nausea.[8,9] Although the symptoms are mild, they can cause a significant decrease in quality of life for some people. Symptoms and signs of chronic HCV may occur later in the disease when scarring of the liver has progressed. A small minority of patients with chronic HCV remain asymptomatic.

Aetiology

HCV is transmitted parenterally, and is acquired primarily through exposure to contaminated blood. The most common source of HCV transmission in the UK is unsafe intravenous drug use which accounts for around 90% of cases. Other, less common, sources of infection include mother to baby transmission, occupational exposure (e.g. via needle stick injury), tattooing and body piercing. Before the introduction of blood screening in 1991, it was also spread through the use of contaminated blood products or organ transplantation. The risk of sexual transmission is thought to be low.

Epidemiology

HCV is one of the leading causes of chronic liver disease. The estimated global prevalence of HCV is around 2-3%, corresponding to about 130-170 million people.[5,10] In England & Wales, a recent report from the Health Protection Agency[7] has estimated that around 191,000 people aged 15-59 years carry the HCV virus, with 142,000 people chronically infected; a prevalence of 0.44% in this age group. Prevalence and incidence data are difficult to estimate because symptoms of HCV are frequently absent or non-specific and thus people can remain undiagnosed for many years. New infections will arise mainly from two sources - newly acquired infections in current UK residents (largely from injecting drug users (IDUs)) and inward migration of chronically infected individuals from other countries. Up to date estimates of overall incidence are not available yet, but recent studies in IDUs suggest 3-42% of susceptible injectors become infected each year.[7] HCV is more common in men and in the

25-44 years age group. Of those individuals exposed to HCV, approximately 20% will clear the virus spontaneously whilst the remaining 80% will go on to develop a chronic infection.

Progression and prognosis

Up to two thirds of people infected with HCV will not develop significant liver disease. In those who do, the rate of progression is slow and variable, over 20-50 years. Progressive liver disease is characterised by inflammation of the liver that leads to gradual fibrosis (scarring), which in its severe form produces cirrhosis. Cirrhosis can progress from a compensated state (where the liver is still functioning despite the fibrosis) to a decompensated stage (where the functioning of the liver is seriously affected). Decompensation is characterised by ascites, variceal bleeding and hepatic encephalopathy. Cirrhosis can develop rapidly, within 1-2 years of exposure, but more usually develops slowly, over 2-3 decades. About 20-30% of those initially infected develop cirrhosis within 20 years.[11] Patients with HCV-related cirrhosis are at risk of developing hepatacellular carcinoma (HCC) with an annual incidence of 1-4%.[12] Some patients with end-stage liver disease or HCC may require liver transplantation. Risk factors associated with more rapid disease progression include more advanced stage of fibrosis at baseline biopsy, age at infection >40 years, co-infection with HIV, excessive alcohol consumption and male gender.

Current treatment options

The majority of people with HCV will not clear the virus spontaneously and will need anti-viral treatment. The current NICE guidance[1,2] recommend combination therapy with ribavirin and either peginterferon alfa 2-a or peginterferon alfa 2-b for adult patients with chronic hepatitis C, regardless of disease severity. Monotherapy with peginterferon alfa 2-a or peginterferon alfa 2-b is recommended for patients who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. For those with mild HCV, the decision whether to treat immediately or adopt an approach of 'watchful waiting' is made by the patient and clinician on an individual basis. The standard duration of treatment is 24 or 48 weeks depending on the genotype, initial viral load and response to treatment. Treatment is currently restricted to:

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

4.2 Definition of the intervention

The intervention under review is combination therapy with peginterferon alfa and ribavirin (or peginterferon monotherapy for those who cannot tolerate ribavirin). The peginterferons are cytokines whose mechanism of action is to assist the immune response by inhibiting viral replication. Two forms are available: peginterferon alfa-2a (Pegasys, Roche Products) and peginterferon alfa-2b (ViraferonPeg, Schering-Plough). Ribavirin is a synthetic nucleoside analogue which is available in three forms: Copegus (Roche Products), Rebetol (Schering-Plough) and Ribavirin Teva (Teva UK Ltd.). Copegus is licensed for combination therapy only with peginterferon alfa-2a, whilst the latter two drugs are licensed for combination therapy only with peginterferon alfa-2b.

Peginterferon alfa-2a was licensed in June 2002 with extensions to the license granted in June 2007. The recommended dose is 180 mcg once per week, administered subcutaneously, for 16, 24 or 48 weeks dependent on genotype, baseline viral load and treatment response. Peginterferon alfa-2b was licensed in February 2002 with extensions to the license granted in May 2005. The recommended dose is 1.5 µg/kg bodyweight once per week, administered subcutaneously, for 24 or 48 weeks dependant on genotype, baseline viral load and treatment response.

The three forms of ribavirin (Rebetol [Schering-Plough], Copegus [Roche Products] and Ribavirin Teva [Teva UK]) were licensed in May 1999, November 2002 and March 2009 respectively. The recommended dose of ribavirin ranges from 800mg to 1400mg taken orally each day in two divided doses (200mg capsules), with the dose depending on the patient's bodyweight, and for the Roche form (Copegus) also on genotype.

For both forms of peginterferon alfa, the therapeutic indication is the treatment of adult patients with chronic hepatitis C who are positive for serum HCV-RNA, including patients with clinically stable HIV co-infection. The preferred indication is in combination with ribavirin but monotherapy is indicated in cases of intolerance or contraindication to ribavirin. Patients may be treatment naïve or may have failed previous monotherapy or combination treatment.

Full details of the indications, dosages and duration of treatment are given in the Summary of Product Characteristics.[13-17]

4.3 Place of the intervention in the treatment pathway

Treatment of chronic HCV is aimed at eradicating the virus and preventing related complications. Accordingly, the main goal of treatment is to clear HCV (defined as undetectable HCV-RNA in the serum) at least 6 months after treatment cessation (sustained virological response, SVR). The current NICE clinical guidance[1,2] recommends combination therapy with peginterferon alfa and ribavirin as first-line treatment for chronic HCV patients who are treatment naïve. The extensions to the licences for the peginterferons now include offering peginterferon combination therapy as second-line treatment to non-responders and relapsers, as well as first-line therapy to certain sub-groups of patients (see section 4.5).

4.4 Relevant comparators

The comparators for this review will vary according to the patient populations. For patients who have been previously treated with combination therapy, and for HCV/HIV co-infected patients, the comparator will be no active treatment (best supportive care, BSC), in line with current clinical practice. BSC includes monitoring of viral load and disease progression, symptomatic treatment, etc. For patients who meet the criteria for receiving shortened courses of combination therapy, the comparator will be standard-duration courses of combination therapy.

4.5 Population and relevant sub-groups

The patient populations for this review are restricted to those that are affected by the licence extensions for the peginterferons. They include people who have been previously treated with peginterferon alfa and ribavirin in combination and did not respond or who responded but relapsed, people who meet the licensed criteria for receiving shortened courses of combination therapy and people with HCV/HIV co-infection. Those with mild, moderate or severe HCV-related liver disease are included. Potential subgroups can be described according to the presence of factors associated with a sustained virological response (e.g. genotype, baseline viral load). Assessment of the effectiveness of peginterferon alfa and ribavirin for any of these subgroups will be limited by the available data and the appropriateness of subgroup analyses (defined a priori, evidence that is statistically powered) within any identified trials.

5. Report methods for synthesis of evidence of clinical-effectiveness

A review of the evidence for clinical-effectiveness and cost-effectiveness will be undertaken systematically following the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care.[18]

5.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (i) clinical-effectiveness studies reporting on comparisons between peginterferon and ribavirin combination therapy (or peginterferon monotherapy for those who cannot tolerate ribavirin) and BSC or standard-duration courses of peginterferon/ribavirin (as described in section 5.2); (ii) studies reporting on the cost-effectiveness of peginterferon and ribavirin, and the relative comparisons. The search strategy will also identify studies reporting resource use and costs, epidemiology and natural history.

The following electronic databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); PreMedline In-Process & Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) & Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); NIHR-Clinical Research Network Portfolio; Clinical Trials.gov and Current Controlled Trials. Relevant hepatitis C symposia will also be searched. The draft search strategy for Medline is shown in Appendix 10.1. This will be adapted for other databases.

Bibliographies of related papers will be assessed for relevant studies where possible. The manufacturers' submissions to NICE will be assessed for any additional studies that meet the inclusion criteria. Experts will be contacted to identify additional published and unpublished evidence.

Literature searches will be carried out from April 2007 (the date the most recent search was conducted[19]) to the present and will be limited to randomised controlled trials (RCTs) and the English language (NB. the search will incorporate the references identified in our previous technology assessment reports[3,4] in which literature searching extended back to the year 2000. These references will be re-screened according to the inclusion criteria for the current

assessment). For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see section 6.2) and may include a wider range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report.

5.2 Inclusion and exclusion criteria

The following criteria are those stipulated in the final scope issued by NICE.[20]

5.2.1 Population

Adults with chronic hepatitis C infection, restricted to:

- people who have been previously treated with peginterferon alfa and ribavirin in combination but who relapsed / did not respond
- people who meet the criteria within the marketing authorisation for receiving shortened courses of peginterferon alfa and ribavirin in combination, namely:
  - patients with genotype 2 or 3 with a low viral load at the start of treatment and a rapid viral response (defined as HCV RNA undetectable by week 4);*
  - patients with genotype 1 with a low viral load and a rapid viral response (defined as HCV RNA undetectable by week 4 and at week 24);
  - patients with genotype 4 and a rapid viral response
- people with HCV/HIV co-infection.

The subgroups are not mutually exclusive.

(*Applies only to peginterferon alfa-2a).

5.2.2 Intervention

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

5.2.3 Comparators

For patients who have been previously treated with combination therapy, and for HCV/HIV co-infected patients:

- Best supportive care (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy)

For patients who meet the criteria for receiving shortened courses of combination therapy:

- Standard-duration courses of peginterferon alfa/ribavirin combination therapy (up to 24 or 48 weeks as appropriate)

5.2.4 Outcomes

Studies must report sustained virological response (SVR, defined as undetectable HCV RNA at least 6 months after treatment cessation). Studies may also include one or more of the following outcomes:

- virological response (e.g. during treatment, end of treatment)
- biochemical response (e.g. ALT levels)
- histological improvement (fibrosis and inflammation)
- survival
- adverse effects of treatment
- health-related quality of life
- cost-effectiveness (incremental cost per QALY)

5.2.5 Types of studies

- Fully published RCTs will be included.
- Studies published as abstracts or conference presentations from 2007 onwards will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations (cost-effectiveness analyses (reporting cost per life year gained), cost-utility analyses or cost-benefit analyses).
- Systematic reviews will only be used as a source of references.
- Case series, case studies, narrative reviews, editorials and opinions will not be included.
- Non-English language studies will be excluded.

5.3 Screening and data extraction process

5.3.1 Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed by one reviewer. Full papers of studies that appear potentially relevant will be requested for further assessment, and these will be screened by one reviewer and checked by

a second. Any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

5.3.2 Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 10.2). Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

5.4 Quality assessment strategy

The quality of the clinical-effectiveness studies will be assessed according to criteria based on that used by the CRD (University of York)[18] Economic evaluations will be assessed using criteria recommended by Drummond and colleagues[21] (see Appendix 10.3), and/or the format recommended and applied in the CRD NHS Economic Evaluation Database (using principles outlined in the NHS EED Handbook[22]). For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues[23]). Published studies carried out from the UK NHS and PSS perspective will be examined in more detail.

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus, and if necessary a third reviewer will be consulted.

5.5 Methods of data analysis/synthesis of clinical-effectiveness data

Clinical-effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using Cochrane Review Manager (RevMan 5) software. Where data allows, clinical- and cost-effectiveness will be assessed according to patient sub-groups (e.g. by genotype, baseline viral load).

6. Methods for synthesising evidence of cost-effectiveness

6.1 Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations. Any economic evaluation included in

sponsor submissions to NICE will be assessed using the same quality criteria as for published economic evaluations, but will be reported separately.

6.2 Economic Modelling

Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one using best available evidence. The Markov model developed by SHTAC for a previous NICE assessment of treatment for mild chronic hepatitis C[4] will be reviewed to assess its applicability to the patient sub-groups within the scope of the current review. If the model structure is considered appropriate, the model will be further reviewed to determine whether updated parameter estimates for disease progression, health state utility or resource use/ cost are required. All updated parameter estimates will be derived from the best available published literature, NHS sources (including Finance Department at Southampton University Hospitals Trust) and industry submissions, where applicable.

The perspective for the analysis will be that of the NHS and Personal Social Services. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per QALY gained, as well as the cost per life year gained if data permit. Both cost and outcomes will be discounted at 3.5%.

Parameter values for the model will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or experts' clinical opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

The simulated population will be defined on the basis of the published evidence about the characteristics of UK chronic hepatitis C patients, within the scope of the current review, and the populations for which good quality clinical effectiveness is available. The base case results will be presented separately for the sub-groups of patients:

- who have been previously treated with peginterferon alfa and ribavirin in combination and did not respond or responded but relapsed;

- who meet the licensed criteria for receiving shortened courses of combination therapy;
- with HCV/HIV co-infection.

The time horizon for our analysis will initially be governed by the outcomes reported, and the follow-up data available from included clinical trials - we will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

6.2.1 Methods for estimating quality of life

Where presented, QOL information as well as incidence of adverse events and side effects of treatment will be extracted from included RCTs. Adverse effects of treatment that are likely to have a substantial impact on patients' quality of life, will be included in estimates of health state utility while on treatment. Where QOL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. Ideally utility values will be taken from studies that have been based on "public" (as opposed to patient or clinician) preferences elicited using a choice-based method (in accordance with NICE methodological guidance).[24]

6.2.2 Analysis of uncertainty

Analysis of uncertainty will focus on cost-utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

7. Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the TAR team no later than 27/08/09. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's guidance on presentation,[24] will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Methods adopted, and incremental cost effectiveness ratios (ICERs) estimated from models supporting the company submission will be compared with published economic evaluations of peginterferon and ribavirin included in the assessment report and with the results from the

Assessment Group's analysis. Reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'academic in confidence' data or 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report.

8. Competing interests of authors

There are no competing interests..

9. References

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10. Appendices

10.1. *Draft search strategy (Medline)*

1 (hepatitis c or HCV).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Hepatitis C/
3 Hepatitis C, Chronic/
4 Hepacivirus/
5 1 or 2 or 3 or 4
6 (peginterferon$ or peg-ifn or peg-interferon$ or (pegylat$ adj3 interferon$) or peg$ or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or Pegasys).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 exp interferon type i, recombinant/ or exp interferon-alpha/ or exp interferon alfa-2a/ or exp interferon alfa-2b/ or exp interferon alfa-2c/
8 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab.
9 6 or 7 or 8
10 9 and 5
11 limit 10 to (english language and yr="2007- ")
12 meta-analysis/
13 (meta analysis or metaanalysis).ab,pt,ti.
14 (systematic$ adj2 (review$ or overview$)).ti,ab.
15 or/12-14
16 (letter or editorial or comment).pt.
17 15 not 16
18 17 and 11
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomized controlled trials/
22 random allocation/
23 double-blind method/
24 single-blind method/
25 exp evaluation studies/
26 exp clinical trials/
27 clinical trial.pt.
28 (clin$ adj5 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
29 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
31 exp placebos/
32 placebo$.tw.
33 random$.tw.
34 exp research design/
35 30 or 31 or 32 or 33 or 34
36 29 or 35
37 36 and 11

10.2. *Draft data extraction form*

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Ref ID: **Author:** **Year:** **Study design**: **Number of centres:** **Country**: **Sponsor**:	**Intervention 1:** n = Drug 1 Dose: Duration: Drug 2 Dose: Duration: **Intervention 2:** n = Drug 1 Dose: Duration: Drug 2 Dose: Duration: **Intervention 3:** n = Drug 1 Dose: Duration: Drug 2 Dose: Duration:	**Total numbers involved**: total and number per treatment group **Eligibility**: **Treatment naïve:** **Previous treatment:** **HCV/HIV co-infection:** **Recruitment**:: **Inclusion/exclusion criteria**: **Baseline measurements**: **Viral load**: **Serum ALT:** **Histology**: Classification system used: Fibrosis score, mean (±SD): F1 (%): F2 (%): F3 (%): F4 (%): Necroinflammatory score, mean (±SD): Timing of liver biopsy: **Genotypes, no. (%)**: 1: 2 or 3: 4, 5 or 6: **Gender, no. (%)**: **Age (mean & range)**: **Ethnic groups, no. (%)**: **Mode of infection, no. (%)**: Injection drug use: Transfusion: Other: **Losses to follow up**: **Compliance**:	**Primary outcomes**: **Secondary outcomes**: **Length of follow up**:

Outcome	**Intervention 1**	**Intervention 2**	**Intervention 3**
Viral Response, % (n/N) 4 wk			

12 wk End of treatment End of follow-up (SVR) SVR by genotype, % (n/N) SVR by baseline viral load Other viral response outcomes			
Biochemical response, % (n/N) End of treatment End of follow-up			
Histology (proportion with improvement) Inflammation mean change Fibrosis mean change			
Adverse Events dose discontinuation for any adverse event dose reduction for any adverse event anaemia neutropenia Specific adverse events			
Additional Results (e.g., early response factors, adverse events comparisons, quality of life): **Methodological comments**: • Allocation to treatment groups: • Allocation concealment: • Blinding: • Analysis by intention to treat: • Comparability of treatment groups at baseline: • Method of data analysis: • Sample size/power analysis: • Attrition/drop-out: **General comments** • Generalisability: • Conflict of interests: • Other: • Definitions:			

Quality criteria for assessment

1. Was the method used to generate random allocations adequate?	
2. Was the allocation adequately concealed?	
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	
4. Were outcome assessors blinded to the treatment allocation?	
5. Was the care provider blinded?	
6. Was the patient blinded?	
7. Were there any unexpected imbalances in drop-outs between groups? If so,	

were they explained or adjusted for?	
8. Is there any evidence to suggest that the authors measured more outcomes than they reported?	
9. Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	

10.3 *Drummond et. al. check-list for assessing economic evaluations*[21]

1. Was a well-defined question posed in answerable form?
1.1. Did the study examine both costs and effects of the service(s) or programme(s)?
1.2. Did the study involve a comparison of alternatives?
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?
2.1. Were there any important alternatives omitted?
2.2. Was (should) a do-nothing alternative be considered?
3. Was the effectiveness of the programme or services established?
3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
3.2. Was effectiveness established through an overview of clinical studies?
3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?
4. Were all the important and relevant costs and consequences for each alternative identified?
4.1. Was the range wide enough for the research question at hand?
4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
4.3. Were the capital costs, as well as operating costs, included?
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?
5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?
6. Were the cost and consequences valued credibly?
6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)
6.2. Were market values employed for changes involving resources gained or depleted?
6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?
7. Were costs and consequences adjusted for differential timing?
7.1. Were costs and consequences that occur in the future 'discounted' to their present values?
7.2. Was there any justification given for the discount rate used?
8. Was an incremental analysis of costs and consequences of alternatives performed?
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?
9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?
9.3. Were the study results sensitive to changes in the values (within the assumed range for

sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10. Did the presentation and discussion of study results include all issues of concern to users?

10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?

10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?

10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?

10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?

10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?