TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

Final version to NCCHTA (10/12/02)

Pegylated interferon alpha 2a and alpha 2b in the treatment of chronic hepatitis C

A. This protocol is provisional and subject to change

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B. Full title of research question

Clinical-effectiveness and cost-utility of pegylated interferon alpha 2a and alpha 2b in combination with ribavirin in the treatment of chronic hepatitis C.

C. Clarification of research question and scope

C.1 Burden of disease

Hepatitis C is a viral disease of the liver. It frequently causes few or no symptoms at first infection, but has a high probability of becoming an insidious chronic disease. Only about around 20% of those infected manage to clear the virus. Around 30% of those with chronic infection will develop cirrhosis of the liver over the next 20-30 years, and a small proportion will go on to develop cancer of the liver. Hepatitis C is one of the main reasons for liver transplantation.

The prevalence in the United Kingdom is uncertain, but estimated to be between 0.1% and 1%. The largest group known to be infected are injecting drug users. Infected blood had been the source of infection via clotting factors used in haemophilia and blood transfusions, until these were rendered safe in 1985 and 1991 respectively.

C.2 Treatment options

Until several years ago, patients with moderate to severe chronic hepatitis C were treated with interferon alpha via subcutaneous injection around three times a week, but only around 17% of patients achieved a sustained virological response[1]. Dual therapy consisting of interferon alpha 2b with the oral anti-viral drug ribavirin ("Rebetol", Schering-Plough; "Virazole", ICN) licensed in May 1999 led to sustained response rates of 41% in patients not previously treated with interferon[2]; and 49% in those who had relapsed following previous interferon treatment[3].

In October 2000 NICE issued guidance regarding treatment for chronic hepatitis C, based on an appraisal[4], recommending dual therapy with interferon alpha and ribavirin for the treatment of moderate to severe hepatitis C (defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation), at standard doses for patients over the age of 18 years[5]. For patients not previously treated with interferon ('treatment naïve' patients) and those who have relapsed following previous therapy, duration of treatment should be six months. A further six months therapy is recommended only for patients infected with genotype 1 of the virus who have had an initial response by six months. Dual therapy has thus surpassed interferon alpha monotherapy as the gold standard treatment.

Since the guidance was issued there has been increasing interest in the use of 'pegylated' interferon[6]. "Pegylation" involves the addition of polyethylene glycol (PEG) molecules to the interferon alpha active molecule via either linear or branched chains. It is a method for ensuring slow release of the drug, thus prolonging action, necessitating fewer doses and resulting in greater efficacy. Pegylated interferon can therefore be given (by subcutaneous injection) once a week rather than three times a week as for interferon alpha, thus being more convenient for the patient and potentially lessening the likelihood of non-compliance. Products have been developed by Roche (2a "Pegasys") and by Schering-Plough (2b "ViraferonPeg"). The indication is for the treatment of adult patients (both those who are interferon naïve, and those who have relapsed following previous treatment) with histologically proven chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti HCV. Pegylated interferon can be combined with ribavirin, or as monotherapy if ribavirin is contra-indicated[7] (see Appendix C).

Dose ranging studies have established 180 micrograms (mcg) weekly as being the optimum dose for pegylated interferon 2a (Pegasys)[8] and 1.5 mcg/kg weekly the recommended dose for pegylated interferon 2b. It has been shown that adjusting the dose of 2b according to body weight optimises sustained virological response rates[9].

Attention has turned to the combination of pegylated interferon and ribavirin as a potential replacement for dual therapy with interferon alpha and ribavirin. Evidence from RCTs identified so far suggests that pegylated interferon has superior efficacy to interferon alpha, both as monotherapy

[8;10;11]and in combination with ribavarin[12-14]. It also appears that pegylated interferon has a similar safety profile[10;12].

However, pegylated interferon is more expensive. A 24 week course of interferon alpha costs between £1166 (3 x 3 Million units MU per week) and £2332 (3 x 6 MU per week), compared with £3408 (180mcg once weekly – Pegasys) and £3888 (1.5 microgram/kg once weekly – ViraferonPeg) for pegylated interferon. There may be some off-setting savings both in the shorter term (from the reduced frequency of injections) and in the longer term.

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

Cost-utility will be estimated in terms of Quality Adjusted Life Years gained (QALYs), when moving from one treatment option to another (e.g. moving from monotherapy for 12 months with interferon alpha to monotherapy for 12 months with pegylated interferon).

A number of favourable factors have been identified which are associated with a sustained virological response, including: genotypes 2 and 3, baseline viral load less than 2 million copies/ml, no or only portal fibrosis, female gender, and age younger than 40 years. Clinical-effectiveness and cost-utility will be estimated for sub-groups of patients in whom these factors are present, where data are available.

Guidance from NICE should ensure consistent uptake across the NHS if the new treatments are shown to be clinically and cost-effective. Evidence for the clinical-effectiveness and cost-utility of treatment for hepatitis C will form part of a wider Department of Health strategy for improving the surveillance, prevention, and treatment of hepatitis C[15].

C.3 Re-treatment of non-responders to interferon alpha monotherapy

Another issue to be investigated is the re-treatment of patients who have failed to respond to interferon alpha monotherapy. Thirteen of the 19 RCTs identified in the original assessment report included such patients, who had subsequently been re-treated with dual therapy. The pooled sustained virological response rate for dual therapy was 15% (95% Confidence Interval 11% - 18%), in comparison to 0.8% (95% CI 0.16% – 2.36%) for monotherapy. However, the cost-effectiveness analysis presented was only for patients not previously treated with interferon, or who had relapsed following a previous course. The guidance therefore does not cover re-treatment of patients who have failed to respond to interferon alpha monotherapy. Two recent meta-analyses have been published, which include many, but not all, of the 13 RCTs identified in the assessment report. They confirm the results of the report with sustained virologic response rates of 14% (95% CI 11% - 17%)[16] and 13.2% (95% CI 8.6% – 15.3%)[17] for dual therapy in comparison to 2% (95% CI 1%-4%) and 1.5% (95% CI % 0.56 – 3.34 %) for monotherapy, respectively.

Although these results indicate that re-treatment with dual therapy is more effective than re-treatment with interferon alpha monotherapy, the response rates are still somewhat disappointing. Another option, however, is the re-treatment of such patients with pegylated interferon dual therapy. A trial is in progress in the United States whereby non-responders to interferon alpha monotherapy as well as non-responders/relapsers to dual therapy (interferon alpha and ribavirin) are re-treated with pegylated interferon dual therapy[18]. Only around 13% of the 210 patients currently enrolled have completed 24 weeks of therapy and the results to date are available only as a conference abstract identified through preliminary searching. However, there may be other similar trials which have completed that may inform this issue.

The TAR will therefore examine the clinical-effectiveness and cost-utility of re-treating patients who have failed to respond to interferon apha monotherapy with pegylated interferon and ribavirin. We will search recent conference abstracts for other new trials but will deal with studies only available in abstract by narrative review only, and with caution. If evidence is not available we will examine the effectiveness of re-treatment with interferon alpha and ribavirin. This will be based upon data from the 13 RCTs identified in the previous appraisal report, supplemented by a search for any further evidence published since then.

C.4 Mild chronic hepatitis C and the need for biopsy

Standard practice at present is to perform liver biopsy before starting treatment, because the consensus is that patients with only mild liver disease should not be treated. Although the diagnosis of chronic hepatitis C does not need liver biopsy, there is evidence that biopsies are still indicated to improve diagnosis[19].

There are, however, a number of scenarios in which liver biopsy would not be required. The first would be if blood tests such as hyaluronic acid (HA) were a sufficiently good correlate of histology. There is some evidence to suggest that this might be the case. Serum HA was compared with conventional liver function tests including alanine aminotransferase (ALT), a-glutathione-S transferase (GST) and serum HCV RNA in a study of 130 patients with chronic hepatitis C in order to determine which identified the stage of liver fibrosis most accurately as assessed by liver biopsy[20]. Serum HA had a higher sensitivity and specificity than ALT and GST, suggesting it as a useful marker of liver fibrosis. However, use of such tests assumes that treatment is dependent on severity of liver changes, and there would be less justification for biopsy in patients in whom treatment was being considered because of systemic symptoms - the biopsy need not be done if it was decided to treat the symptoms. The clinical-effectiveness and cost-effectiveness of non-invasive tests compared with liver biopsy will be examined, where evidence is available, but since this is a subsidiary question, we will allocate only 7 person-days, including searches.

The second scenario would be if it were demonstrated that treating patients with mild disease was cost-effective. An HTA funded RCT of dual therapy (interferon alpha and ribavirin) in patients with mild chronic hepatitis C is currently in progress and is due for completion around mid 2003. If this trial showed that it was of benefit in those patients (either in terms of preventing long-term complications or in improving immediate quality of life), the need for biopsy would again be reduced. There are occasional deaths after biopsy, but the audit in England and Wales found a death rate of between 0.13% and 0.33%[21]. The complication rate, as indicated by bleeding after biopsy, was lower (by about two-thirds) in those whose biopsies were done by more experienced operators, and this was more common in gastroenterology patients (compared with general medicine ones). Patients with hepatitis C are more likely to be cared for in specialist centres and to have a complication rate lower than the average in the audit. There is, however, an uncertainty about treating patients with mild disease because we do not fully know the natural history in this patient group, and hence precisely what we are preventing with treatment. Expert opinion suggests that some clinicians may be reluctant to treat those with minimal symptoms due to uncertainty regarding whether they derive substantial benefit. However, it might be cost-effective to treat this group, even if only a proportion go on to develop more aggressive disease, because others may have symptoms due to hepatic or extra-hepatic disease which would improve after treatment. Contact will be made with the principal investigator of the UK HTA funded trial of dual therapy for mild hepatitis C to explore the possibility of incorporating data on clinical-effectiveness and quality of life into the appraisal report. This trial is due to complete in mid 2003, thus it may not prove possible to obtain full data from the trial within the timescale of the TAR.

The third scenario is the treatment of patients with genotypes 2 and 3 regardless of histology. Sustained virological response rates for these patients in some of the phase III RCTs of pegylated interferon dual therapy identified to date were between 75-80%[9;22]. Consequently support for treating

these patients without biopsy is gaining ground amongst clinicians. Furthermore, French guidelines also suggest these patients need not undergo a biopsy.

The fourth scenario would be if it were shown that treatment early after infection was indicated, in which case patients would be treated before the severity of future liver disease could be known. A recent study of 24 weeks treatment with interferon alpha monotherapy in 44 patients known or suspected to have been exposed to HCV in the previous 4 months showed encouraging results[23]. In all patients HCV RNA became undetectable after initiation of treatment (average time 3.2 weeks, range 2 to 12). However, this study has been criticised due to the inclusion of a historical control group, and the fact that the study population were atypical of those with early infection, comprising only patients with clinical features of infection[24;25]. It was also questioned whether the observed effect could be attributed to the treatment, or to the natural history of symptomatic acute infection[24]. We will not formally search for and appraise evaluations of treatment for patients with acute hepatitis C, but will discuss narratively any identified through the course of searching for chronic hepatitis C studies. Particular attention will be paid to any implications for the diagnosis and treatment of chronic hepatitis C.

D. Report Methods

D.1 Search strategy

- A sensitive search strategy will be developed in order to capture the range of study types relevant to this systematic review.
- The strategy will be cover the period 2000 to the present (the time period for non-invasive tests may be longer).
- Electronic databases to be searched:
  - Cochrane Systematic Reviews Database (CDSR); Cochrane Controlled Trials Register (CCTR); Database of Abstracts of Reviews (DARE); NHS CRD HTA database (University of York); NHS Economic Evaluation Database (NEED), Medline (Silverplatter), PubMed (Pre-Medline); Embase (Silverplatter), and the National Research Register (NRR). Searches will be limited to English language studies.
- Recent abstracts of RCTs will be identified from the databases: BIOSIS, Web of Science Proceedings, and Science Citation Index (SCI), though abstracts will only be used for awareness of current research.
- Contact will be made with experts in the field to identify relevant trials.
- Internet sites dealing with hepatitis and liver disease will be searched.

D.2 Inclusion and exclusion criteria

- Relevant interventions include:
  - Dual therapy (pegylated interferon alpha and ribavirin) versus dual therapy (interferon alpha and ribavirin)
  - Monotherapy (pegylated interferon alpha) versus monotherapy (interferon alpha)
  - Screening for hepatitis C will not be examined. However, we will include evaluations of non-invasive tests of liver fibrosis/cirrhosis in comparison to biopsy.

- Patient group: those with moderate to severe chronic hepatitis C infection (either those who have not been previously treated, or those who have relapsed/not responded to previous treatment), regardless of source of infection. If sufficient data from the HTA mild chronic hepatitis C trial become available the patient group will be extended to include those with mild disease.

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

- Tests for fibrosis/cirrhosis:
  - it is acknowledged that there may be few, if any, RCTs in which case other study designs will be included, such as case series.
- General background:
  - natural history studies; incidence/prevalence studies

- Outcome measures: sustained clearance of infection, as shown by absence of viral RNA 6 months or longer after the end of treatment; adverse effects of treatment, quality of life measures. For economic appraisal, predicted reductions in long-term complications avoided, such as cirrhosis and cancer, and liver transplantation.

D.3 Data extraction strategy

- Data extraction will be undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion. A standard template will be used to enter and display data.

D.4 Quality assessment strategy

- Included clinical-effectiveness and cost-effectiveness studies will be appraised using a checklist adapted from that devised by the NHS Centre for Reviews and Dissemination (NHS CRD) (see Appendices A & B).
- Included quality of life studies will be appraised using an instrument currently being piloted by SHTAC/Inter-TASC.
- Included systematic reviews will be appraised using the NHS CRD criteria for assessing the quality of reviews included in the Database of Abstracts of Reviews of Effectiveness (DARE) (Appendix C).
- All quality criteria will be applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

D.5 Methods of analysis/synthesis

- A narrative synthesis will be undertaken with the main results of the included clinical-effectiveness and cost-effectiveness studies described qualitatively, and in tabular form. A meta-analysis of the clinical-effectiveness studies will be performed, using Cochrane Reference Manager Software. This will be based on the meta-analysis performed for the previous TAR on dual therapy with interferon alpha.

D.6 Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY

- The economic evaluation will be based upon a model devised by the former Scottish Health Purchasing Information Centre (SHPIC) and used in their original review of interferon alpha for Hepatitis C in 1998[26;27]. The model was adapted and used in the appraisal of combination therapy produced by SHTAC which informed the guidance issued by NICE in 2000.
- The model follows a hypothetical cohort of 1000 individuals with hepatitis C for 30 years. It aims to predict the natural history of the disease, the health states or intervention through which the cohort passes (e.g. percentages developing cirrhosis, ascites, variceal bleeds, hepatocellular cancer, liver transplantation), how long they stay in such states, and the NHS costs of treating them. The natural history is based on the published literature and clinical consensus.
- The model will be used to estimate the *additional* cost per QALY incurred when moving from one treatment option to another.
- The treatment options will include:
  - no treatment (except symptomatically)
  - dual therapy (interferon alpha and ribavirin) for 48 weeks
  - dual therapy (pegylated interferon and ribavirin) for 48 weeks
  - monotherapy (interferon alpha) for 48 weeks, or for shorter periods if data are available

    - monotherapy (pegylated interferon) for 48 weeks, or for shorter periods if data are available.
- The model will be revised to incorporate new data on natural history. The assumptions will be reviewed and updated if new research suggests this is necessary. Drug costs for pegylated interferon will be added.
- Information on investigation and monitoring costs will be provided by the Finance Department of Southampton University Hospitals Trust. Costs will also be sought from Aberdeen Royal Hospitals Trust.
- Other sources of cost information will include the British National Formulary (BNF) for drug costs; and the most up to date 'Unit Costs of Health and Social Care' from the Personal Social Services Research Unit for general practitioner/outpatient/in-patient costs.

- Where data are provided we will also pay attention to:
    - the effectiveness of treatment for 24 weeks, particularly for patients with genotypes 2 and 3.
    - response rates at 12 weeks of therapy (where provided) as a potential justification for stopping treatment in those who have responded.
    - differences in effectiveness between fixed dosing and dosing according to body weight.
    - differences in effectiveness between pegylated interferon 2a and 2b, particularly at high viral loads (this will have consequences for the pre-treatment evaluation of a patient and subsequent choice of drug).
    - differences in effectiveness for different sub-groups of patients (e.g. current intravenous drug users, current heavy users of alcohol, haemophiliacs, cirrhotics, patients infected with HIV, ethnic minorities, patients with genotype 4 and end-stage renal patients).

E. Handling the company submission(s)

The industry submission will be used in the following ways:

- As a source of data, looking for studies that meet our inclusion criteria (systematic reviews; RCTs; cost-effectiveness and cost-utility studies)
- To briefly compare the industry model with our model. However, we will also make available our economic model (as used in the previous TAR) to the relevant pharmaceutical companies. If our model is used by industry we will compare differences in the assumptions and costs entered.

F. Project Management

a. **Timetable/milestones** - submission of:

Draft protocol to NCCHTA: 18th November 2002
Final protocol to NCCHTA: 9th December 2002
Progress report: 14th March 2003
Complete and near final draft to external reviewers and the NICE Technical Lead: 4th April 2003
Draft final report to NCCHTA – 29th May 2003

b. **Competing Interests**

None

c. **External reviewers**:

An advisory panel will be assembled which will include:

- Hepatologists
- Infectious diseases specialists
- Health economists

- Representatives from consumer groups (The British Liver Trust, The Haemophilia Society)

The Technology Assessment Report will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the TAR encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. All reviewers are required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will send external reviewers' signed copies to the NCCHTA editors but not to NICE. Comments from external reviewers and the Technical lead, together with our responses to these will be made available to NCCHTA only in strict confidence for editorial review and approval in preparation for the publication of the HTA monograph.

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G. Appendices

Appendix A - Quality Assessment Scale - experimental studies

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

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

Some instructions for using a checklist for RCTs

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

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

Appendix B – Quality Assessment Scale – Economic Evaluations

From NHS Centre for Reviews and Dissemination (NHS CRD) Report 4 (adapted from Drummond et al, 1997[28])

Is there a well defined question?
Is there comprehensive description of alternatives?
Are all important and relevant costs and outcomes for each alternative identified?
Has clinical effectiveness been established?
Are cost and outcomes measured accurately?
Are cost and outcomes valued credibly?
Are costs and outcomes adjusted for differential timing?
Is there an incremental analysis of costs and consequences?
Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?
How far do study results include all issues of concern to users?
Are the results generalisable to the setting of interest I the review?

Appendix C – Quality Assessment Scale – Systematic reviews

Adapted from Inclusion criteria for systematic reviews included in the of Database of Abstracts of Reviews (DARE); NHS CRD HTA database (University of York)

- **Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?**

  A good review should focus on a well-defined question, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies.

  The criteria should relate to the four components of study design, participants, health-care intervention or organisation, and outcomes of interest.

  In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

- **Is there evidence of a substantial effort to search for all relevant research?**

  This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided.

  The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

- **Is the validity of included studies adequately assessed?**

  Authors should have taken account of study design and quality, either by restricting inclusion criteria, or systematic assessment of study quality. For example, if inclusion criteria have been restricted to 'double-blind randomised controlled trials, with at least 200 participants' then the need for quality assessment is not so crucial as when authors have less stringent inclusion criteria and/or include less rigorous study designs.

  A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomisation, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

- **Is sufficient detail of the individual studies presented?**

  The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), efficacious results and side-effects (adverse events).

- **Are the primary studies summarised appropriately?**

  The authors should attempt to synthesise the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews which incorporate a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

For some reviews, it may be inappropriate to include a meta-analysis, and therefore a narrative synthesis of studies should be presented. It is not usual to include a formal assessment of heterogeneity or to introduce weighting in such syntheses, so a discussion relating to the main differences between studies, and the better sources of evidence, should be highlighted.

- **Reviewer's other comments**

Appendix D - Background:

Indications/contraindications: drugs for chronic hepatitis C

Pegasys (Pegylated interferon 2a, Roche)

Indications:

- "for the treatment of histologically proven chronic hepatitis C in adult patients with elevated transaminases and who are positive for serum HCV-RNA, including patients with compensated cirrhosis. The optimal way to use Pegasys in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped. Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin" [29]

Contra indications:

- Hypersensitivity to the active substance, to alpha interferons,; autoimmune hepatitis; severe hepatic dysfunction or decompensated cirrhosis of the liver; neonates and young children up to 3 years old (excipient benzyl alcohol); pre-existing cardiac disease in previous 6 months; pre-existing psychiatric condition; pregnancy and lactation[29].

ViraferonPeg (Pegylated interferon 2b, Schering Plough)

Indications:

- "ViraferonPeg is indicated for the treatment of adult patients with histologically proven chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV RNA or anti HCV. The best way to use ViraferonPeg in this indication is in combination with ribavirin. This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed"[31]

Contra indications

- Same as for 'Pegasys' and also: severe debilitating medical conditions including chronic renal failure or creatinine clearance <50ml/minute; pre-existing thyroid disease; epilepsy and/or compromised central nervous system (CNS) function[31].

Ribavirin

Indications:

- Severe respiratory syncytial virus bronchiolitis in infants and children; in combination with peginterferon alfa-2b or interferon alfa for chronic hepatitis C not previously treated in patients without liver decompensation and who have fibrosis or high inflammatory activity or for relapse following previous response to interferon alpha

Contra indications:

- Pregnancy; breast feeding, pre-existing cardiac disease in previous 6 months, haemoglobinopathises (thalassaemia and sickle cell anaemia); chronic renal failure; history of severe psychiatric conditions; severe hepatic dysfunction, decompensated cirrhosis of the liver; autoimmune hepatitis; pre-existing thyroid disease.