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Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle- income countries

PICO 5: Treatment

A systematic review of the effectiveness of antiviral treatment compared with no treatment for chronic HCV infection

Conducted by the Burnet Institute, Melbourne and Health Protection Scotland, Glasgow
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BACKGROUND

Hepatitis C virus (HCV) infection affects more than 3% of the global population and poses a high economic burden (El Khoury et al., 2012, Georgel et al., 2010). Between 130 and 150 million people are chronically infected with hepatitis C, and it is a major cause of hepatocellular carcinoma and liver cirrhosis (Georgel et al., 2010, Coffin et al., 2012). Approved treatments include interferon-alpha (IFN), ribavirin (RBV), and HCV NS3 protease inhibitors. Other classes of agent including additional interferons and direct-acting antiviral agents (DAAs) have been studied for effectiveness and tolerability. The purpose of this rapid review is to assess the effectiveness of HCV anti-viral treatment (IFN, PEG-IFN, RBV) in terms of treatment response, adverse events, quality of life, morbidity, mortality.

METHODS

Narrative review question:

What is the effectiveness of hepatitis C (HCV) anti-viral treatment compared with no antiviral treatment?

PICO Question:

Population: Adults and children with chronic HCV infection

***Intervention*:** Any type of HCV anti-viral therapy

Comparison: No HCV anti-viral therapy

Outcomes: Rates of sustained virological response (SVR), decompensated liver disease, hepatocellular carcinoma, all-cause mortality, treatment-related adverse events leading to discontinuation, quality of life. Cost effectiveness outcomes will require economic modelling which will be conducted separately from this protocol

Study type/limits: Systematic reviews and meta-analyses published from 1994 to the present

Search strategy:

A search was carried out for relevant systematic reviews or meta-analyses, using the following databases and information sources:

- OVID MEDLINE, EMBASE, the Cochrane Library (CENTRAL and DARE) (without language restrictions).
- Reference lists of all relevant reviews
- Relevant articles identified during the conduct of the other systematic reviews

Search terms included combinations of free text and medical subject heading terms (MeSH, Emtree), briefly summarized as: HCV AND Antiviral agents/ HCV treatment AND systematic reviews/meta-analyses (see Appendix 1).

Conduct of the review:

The review process followed the Cochrane methodology for conducting systematic reviews (Smith et al., 2011) and the PRISMA guidelines on review reporting (Liberati et al., 2009). The review was registered with the systematic reviews registry PROPSPERO (University of York). The review was carried out by two reviewers. A third reviewer was consulted on points of difference between the primary and secondary reviewer. The two reviewers assessed all search results, and included those studies that met population, intervention, comparison, and at least one outcome criteria. The bibliographic records and abstracts were used to filter studies that clearly did not meet the inclusion criteria. Full articles were then obtained and assessed to confirm eligibility of potentially relevant studies.

Quality appraisal:

Each review selected for inclusion was assessed for quality by two independent reviewers, using the AMSTAR assessment tool for systematic reviews (Shea et al., 2009).

Data extraction:

Data was extracted from each study by the primary reviewer and secondary reviewer acting independently. The third reviewer was consulted on points of disagreement between the primary and secondary reviewer.

Data were extracted to a standardised spread sheet noting:

- Review characteristics (study designs, study objectives, funding sources);
- Review populations (adults versus children, people who inject drugs [PWID] versus non-PWID);
- Review settings (general practitioner [GP], hospital clinic; low-middle income country [LMIC] versus high-income country [HIC] setting);
- Participant details (age, sex, ethnicity);
- Inclusion/exclusion criteria for reviews;
- Number of studies included;
- Intervention (type of HCV therapy; therapy delivered by specialist versus primary care physician);

- Control (selection and characteristics of control group);
- Analysis (number offered therapy, number accepted therapy, reason for refusal, time to follow-up, study data collection method, statistical analyses, primary and secondary outcomes of study);
- Results (Rates of SVR, decompensated liver disease, hepatocellular carcinoma, all-cause mortality, treatment-related adverse events leading to discontinuation of therapy, quality of life).

GRADE process:

The quality of the body of evidence as a whole was assessed using Grading of Recommendations Assessment, Development and Evaluation methodology (GRADE)(Atkins et al.). GRADE rates the quality of evidence across each outcome of interest (i.e. Rates of SVR, decompensated liver disease, hepatocellular carcinoma, all-cause mortality, and treatment-related adverse events leading to discontinuation of therapy, quality of life, resource use) as high, moderate, low or very low, depending on a number of criteria. These include study design, study quality, study consistency (the similarity of estimates of effect across studies) and study directness (the extent to which the evidence is relevant to the population, intervention, and outcome of interest).

Given this was a 'Review of reviews' our analysis was based on data collected from systematic reviews which had multiple studies assessing similar outcomes. To produce a single estimate of effect for the evidence profile, we selected the systematic review that included the most studies with the highest methodological (AMSTAR) score.

Data synthesis

Where sufficient data relating to any of the outcomes of interest was available, subgroup analyses were considered for the following:

- Outcomes (as above) of administering treatment in adults vs. children;
- Outcomes (as above) of administering treatment by genotype (GT 1, 2/3 vs 4);
- Outcomes (as above) of administering treatment by HIV infection status;
- Outcomes (as above) of administering treatment by PWID/IDU status;
- Outcomes (as above) of administering treatment by fibrosis stage;
- Outcomes (as above) of administering treatment in LMIC vs. HIC settings.

RESULTS

Seven hundred and seventy unique citations were found from database searches. Seven hundred and twelve citations were excluded based on title review and study design criteria (Figure 1). Abstracts for the remaining citations were reviewed, and a further 41 articles were excluded for not meeting the population/ intervention/ comparison/ outcome (PICO) criteria, primarily for failing to compare antiviral therapy to no treatment. Separate systematic reviews of the effectiveness of pegylated interferon versus standard interferon, and direct acting antiviral therapy versus pegylated interferon/ribavirin have been undertaken for the WHO guideline development process.

Seventeen citations were obtained for full-text appraisal. Following full text review, two articles did not meet intervention or comparison criteria: Shepherd et al. (2000) compared IFN-alpha + RBV versus IFN monotherapy alone/with placebo; Pellicelli et al. (2008) compared treatment options within injecting drug users and non-injectors. One further article published in 2011 was republished in 2012 with more complete data (Kimer et al., 2011) and the 2011 version was thus excluded from this analysis (in favour of the 2012 publication).

Fourteen systematic reviews were included in the final synthesis. Six reported data comparing interferon to placebo (Malaguarnera et al. (1995), Carithers and Emerson (1997), Myers et al. (2009), Hu et al. (2010), Koretz et al. (2013), Tine et al. (2005)). Six combined and compared different types of interferon (standard or pegylated interferon [PEG]) alone or with ribavirin to placebo (Fabrizi et al. (2008), Xirouchakis et al. (2008), Kimer et al. (2012), Iorio et al. (2010), Hartwell and Shepherd (2009), Vezali et al. (2010)). One review (Brok et al., 2009b)) evaluated ribavirin monotherapy compared to placebo. Characteristics of these reviews are expanded on in Table 1.

The systematic reviews of effectiveness of interferon monotherapy compared with placebo universally showed IFN was superior to placebo in achieving SVR. Individual reviews reported combined relative risk of IFN reducing treatment failure (“failure to achieve SVR”) between 0.11 and 0.96 (6 studies) (Table 2). There were inconsistent or statistically non-significant effects of IFN on hepatocellular carcinoma (OR ranged from 0.50 to 0.81; 2 studies), liver-related morbidity (RR 1.07, 95% confidence interval [CI] 0.70-1.63) and all-cause mortality (RR 1.3, 95% CI 0.95-1.79). No reviews studies were found that reported quality of life changes with IFN versus placebo.

The systematic reviews of effectiveness of different interferon types (IFN or PEG), in combination with ribavirin or alone compared with placebo showed clear benefit of HCV treatment in achieving SVR (Table 3). The presentation of pooled effect estimates of effect in these systematic reviews prevented assessment of individual antiviral agents effectiveness versus no treatment, and it was not possible to disaggregate the data. There were inconsistent or statistically non-significant effects of Pegylated IFN with ribavirin on hepatocellular carcinoma, liver-related morbidity and all-cause mortality during treatment and the follow up period in the short-medium term afterwards. No IFN versus placebo reviews reported comparative data on quality of life to make any statistical comparisons. Two reviews presented data among individuals with cirrhosis on treatment showing a marked improvement in SVR for those receiving treatment (OR 8.84, 95%CI 3.29 to 23.77).

The systematic review comparing ribavirin with placebo showed no significant beneficial effect of ribavirin in achieving SVR (Risk difference 0.0%, 95% CI -0.03 to 0.02), reducing all-cause mortality (RD 0.0%, 95% CI -0.02 to 0.03) or quality of life (RD -0.11 QALY, 95% CI -0.27 to 0.06). Treatment discontinuation was observed as an adverse event in 5% of the intervention group and there was no improvement in quality of life with ribavirin intervention (Table 4).

One study reported on the virological outcomes and adverse effects of treatment among children (SVR IFN 45% v. no treatment 9%, p=0.06; RR 0.45 (0.28 to 0.72) (Hu, Doucette et al., 2010). None of the interventions reported differential SVR findings among PWID or HIV-infected individuals as these were most often exclusion criteria for the studies themselves. However, one review among HIV co-infected patients did make other comparisons of different treatment regimens (eg PEG versus IFN) which is addressed in a separate systematic review as part of the WHO HCV evidence review process (Refer to PICO 6 Treatment: PEG vs IFN).

All reviews of IFN, PEG or RBV versus placebo synthesised randomised controlled trials using appropriate meta-analytical methods and received moderate to high quality scores using the AMSTAR rating. Overall outcome ranking according to GRADE criteria saw outcomes rated down for imprecision where small events occurred (mortality and morbidity during the study period, SVR among children, and serious adverse events), or short duration of follow up (mortality and HCC detection during the study period). Inconsistency within previous meta-analyses reduced outcome ratings for liver-related and all-cause mortality. Finally, at least moderate risk of bias identified in primary RCTs downgraded effect estimated for SVR among treatment experienced individuals and treatment discontinuation due to adverse events.

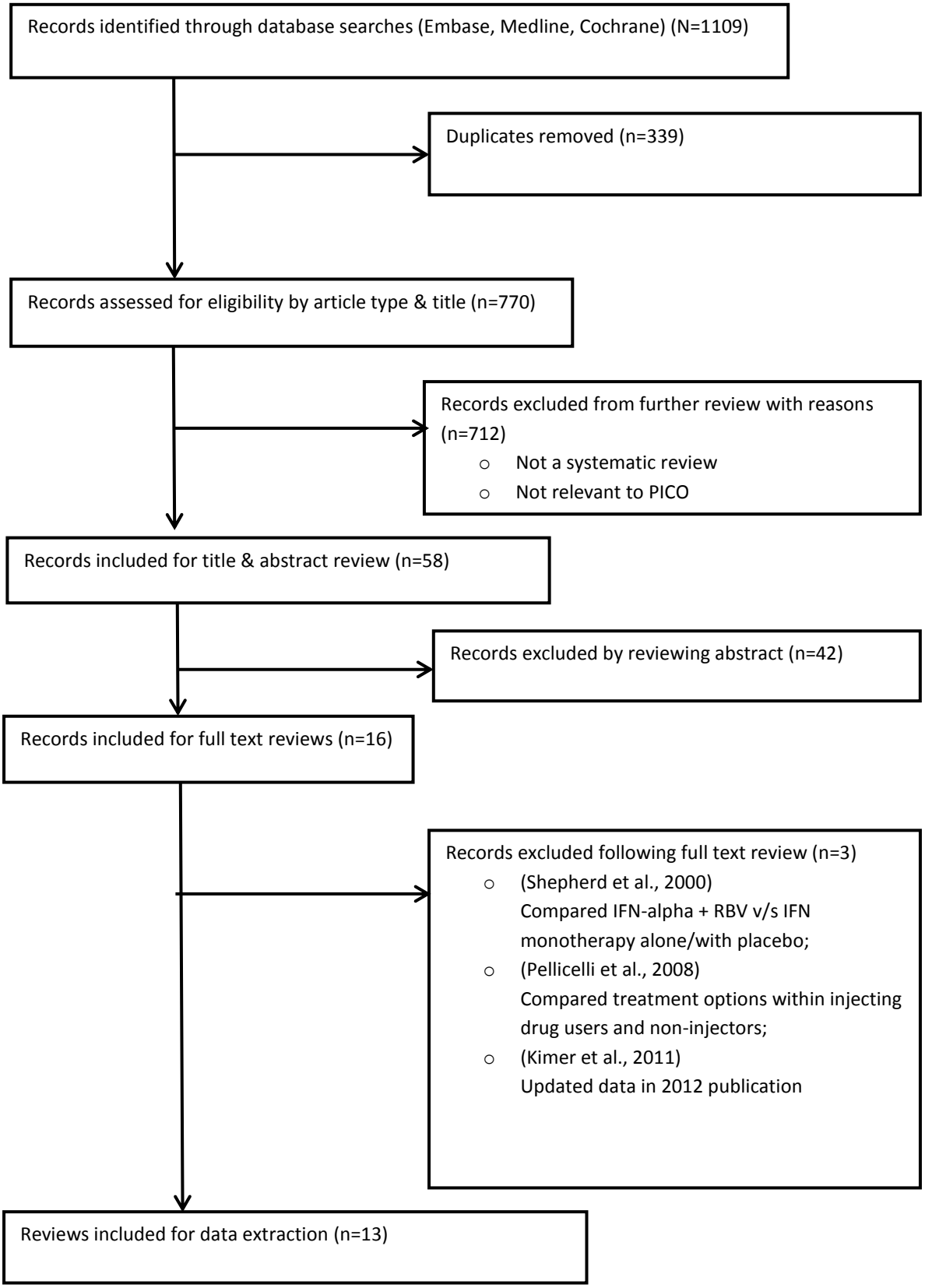

Figure 1: Flow chart describing selection of included studies

CONCLUSIONS

Overall, IFN or PEG used alone or with RBV, is effective in achieving sustained virological response. With evolving research, numerous regimens have become available for the treatment of chronic HCV. The only anti-viral regimens that have been reported in systematic reviews in comparison to either no therapy or placebo are IFN, PEG and RBV.

Treatment with interferon (alfa-2a, alpha-2b) significantly improves the likelihood of achieving SVR and reducing liver related mortality but is associated with adverse events.

Treatment with ribavirin mono-therapy has no significant effect on SVR, end of treatment virological response, liver-related morbidity and mortality during treatment but significantly increases the risk of adverse reactions, including anaemia.

Implications for clinical practice

There is evidence demonstrating the efficacy of antiviral therapy in achieving SVR but less conclusive evidence supporting improvements in mortality, morbidity and quality of life.

Implications for research

Translational and implementation research into developing cost-effective treatment regimens, improving side-effects profiles and delivering medications in low and middle income countries especially are now needed to see successful therapies implemented.

TABLES

Table 1: Characteristics of systematic reviews included for data synthesis

Review 1: Malaguarnera, Restucciaet al.1995

Study Objectives	The aim of this study was to assess the long term efficacy of Interferon-alpha treatment in chronic HCV
Methods	27 Randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Abstracts that had at least 5 studies for statistical analysis o Abstracts presented at international congresses Exclusion Criteria: o Studies by the same author containing a different number of patients and if it was not clear whether the same patients had been included in both studies.
Study characteristics	Country: Not stated Study Setting: Unclear Study size: 1579 Funding source: Not stated Study Population: Adults with chronic HCV Age (Mean): Not stated Sex (% male): Not stated Ethnicity: Not stated Follow up: 33.9 weeks (Median 25 weeks, Range =2 to 74 weeks)
Intervention (N)	IFN- alfa2a or IFN-alfa2b or Lyphoblastoidalfa or IFN-alpha (918)
Control (n)	No treatment (661)
Outcomes	SVR o Overall (Complete long term remission): Intervention= 30.0% v. Control= 10.1% ; OR 4.44 (3.42-5.75) o Recombinant IFN-alpha2a: Intervention= 31.5% v. Control= 1.6%; OR 8.44 (4.48-15.8) o Recombinant IFN-alpha2b : Intervention= 18.5% v. Control= 4.0%; OR 4.58 (2.8-7.46) o Lymphoblastoid IFN- alpha: Intervention= 40.4% v. Control= 1.9%; OR 8.66(4.66-15.79) o 3 million units [MU] IFN- alpha: Intervention= 44.5% v. Control=22.3%; OR 3.25(2.27-4.66) o 3 or 1 MU IFN-alpha: Intervention= 17.4% v. Control=3.4%; OR 3.83 (2.11-6.88)
Results	IFN capable of modifying the natural history of HCV. Marked improvement in the histological picture and long term remission seems to occur with doses of 3MU/week. Elevated long term efficacy seen in studies adopting lymphoblastoid IFN alpha (OR8.66). Inferior results obtained in studies utilising IFN-alpha2b and it is less efficacious than lymphoblastoid IFN-alpha and IFN-alpha2a.
Comments	Amstar rating: 7

Review 2: Carithers and Emerson (1997)

Study Objectives	To systematically examine the bio-chemical, virological and histological outcomes of patients with chronic HCV enrolled in well-designed RCT's of IFN alfa-2b therapy
Methods	20 Randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Adult patients (>18 years) with chronic hepatitis and no previous history of treatment with IFN. Exclusion Criteria: o Studies with inadequate information, lack of randomization, inclusion of previously treated patients, inadequate treatment duration, studies of acute HCV
Study characteristics	Country: Not stated Study Setting: Unclear Study size: 552 Funding source: Not stated Study Population: Adults with chronic HCV ; 25% of patients were cirrhotic Age (Mean): 54 years Sex (% male): 68 Ethnicity: Not stated
Intervention (N)	IFN-alfa2b 2MU three times daily for a minimum of 24wks (Not stated)
Control (n)	Placebo or No treatment (Not stated)
Outcomes	SVR: Absence of circulating RNA(maintained for 6months after discontinuation of therapy) o Intervention=8% v. control=1%; OR 8.6 (1.0-74.8) Normalisation of ALT levels 6months post treatment (not based on HCV RNA) assessed in 18 studies: o Intervention=23% v. Control=2%; OR 17.8 (8.5-37.3) End-of treatment virological response: o Intervention=29% v. Control=5%: OR 9.4 (3.4-25.7)
Results	IFN alfa-2b is effective as therapy for chronic Hep C
Comments	Amstar rating: 8

Review 3: Myers et al. (2009) (initially published 2002, updated 2009)

Study Objectives	To evaluate the response to IFN (at a standard dose) in IFN naïve patients with chronic HCV. The effect of treatment dose and duration and the response in patients with cirrhosis and those with normal aminotransferases was also investigated
Methods	24 Randomized clinical trials; Meta-analysis performed Inclusion Criteria: o RCTs comparing IFN with placebo, no treatment or different regimens of IFN in treatment naive patients were selected, studies with at least one of the following: biochemical ETR, biochemical SR, virological ETR, virological SR Exclusion Criteria: o Abstracts, patients post liver transplantation or infected with HBV and or HIV, trials involving previously treated patients, interim reports and studies employing an initial run-in period of IFN treatment were excluded
Study characteristics	Country: Not stated Study Setting: Not stated Study size: 1213 meeting PICO (total review n=6545) Funding source: o Dr. V. Feinman Hepatology Fellowship from the Canadian Association for the Study of the Liver o Detweiler Travelling Fellowship from the Royal College of Physicians o Surgeons of Canada, Recherche et Partage o Association Francaise pour l'Etude du Foie o Club Francophone de l'HypertensionPortale Study Population: Adults with chronic HCV; Treatment naive patients Age (Mean): Not stated Sex (% male): Not stated Ethnicity: Not stated
Intervention (N)	IFN 3MU thrice/weekfor 6 months (619)
Control (n)	No intervention or control (594)
Outcomes	SVR o IFN v. Control Intervention = 32% v. Control=2%; OR 8.30 (4.65 – 14.80) o IFN 3MU thrice weekly for 6 months: Intervention= 23% v. control= 1%; OR 8.05 (3.82-16.96) o IFN 3MU thrice weekly for 12 months: Intervention= 17% v. Control= 3%; OR 4.60 (1.53-13.85) o Two RCT's in patients with normal aminotransferases: Intervention= 8% v. Control= 0%; OR 7.48 (0.43-130.05) o Two RCT's in cirrhotic patients: Intervention=17% v. Control=0%; OR 8.84 (3.29-23.77) HCC o IFN v. Control (Results from two studies): Intervention= 13% v. Control= 24%; OR 0.50 (0.21-1.21) o Cirrhotic patients (Results from three RCT's): Intervention= 43% v. Control= 46%; OR 0.74 (0.38-1.47)
Results	IFN is effective in achieving viral clearance and improving liver bio-chemistry and histology in IFN naïve patients with chronic HCV. It is also associated with benefits in cirrhotic patients. The most effective regimen of IFN monotherapy for this outcome appears to be at least 6MU thrice/weekly for 12 months treatment duration but at a cost of more adverse events.
Comments	Amstar rating: 11 Only one of the included RCTs had adequate allocation concealment and was double blinded.

Review 4: Tine et al. (2005)

Study Objectives	To review HCV trials before the introduction of interferon and Ribavirin as standard treatment of chronic HCV and give insight into the complexity of the data and to explain the heterogeneity of interferon effects
Methods	36 randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Published RCTs assessing IFN-alpha for their activity in patients with chronic HCV and amino-transferase elevation which had never been treated before. Exclusion Criteria: o Letters, Non English papers ,Clinical series, Trials in patients with acute Hep-C, Trials in patients with normal ALT , Trials in non-responders or relapsers after interferon, pPatients with co-infections (HBV,HIV) or in OLT carriers, patients with commonly associated HCV diseases (haemophilia, thalassemia orcyoglobulinemia), trials in haemodialysis patients.
Study characteristics	Country: Not stated Study Setting: Not stated Study size: 2454 Funding source: o MIUR ex 60%, 1998, Massimo AttanasioMIUR ex60%,2002, Massimo Attanasio Study Population: 64% genotype 1 ; 31%cirrhotic/fibrosis Age (Mean): 49years Sex (% male): 61% Ethnicity: not stated
Intervention (N)	9MU or 18MU of IFN/week for 6-12months o IFN alpha-2b (58.3%) o IFN alpha-2a(22.2%) o Other types of IFN(19.5%)
Control (n)	Placebo (albumin or sterile water) or untreated (80)
Outcomes	Sustained ALT normalization: o IFN v. placebo/no treatment (Pooled result): OR 9.5 (6.3-14.2) AE: o Patients who stopped IFN: 83.3% o Patients who had reason to stop: 77.8%
Results	This meta-analysis included RCT's conducted in naïve, relapsers and non-responders and analysed HCV-RNA as end point.Sustained response was most likely in experimental arms of IFN+ribavirin or other drugs, arms using yearly schedule, trial principle from Asia, trial sample size >200, and arms enrolling less than 50% cirrhotics.
Comments	Amstar rating: 9

Review 5:Fabrizi et al. (2008)

Study Objectives	To evaluate efficacy and safety of antiretroviral therapy for HCV in patients with **chronic kidney disease**
Methods	13 Prospective CCT's and Randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Full articles published in peer-reviewed journals, CCT's on chronic kidney disease patients receiving antiviral therapy versus controls not receiving therapy, studies on patients with long term dialysis or renal transplant patients were eligible Exclusion Criteria: o Studies enrolling HBsAg and HIV positive patients, abstracts, interim reports, letters and review articles, and clinical studies with combined transplant (kidney/pancreas or other organs)
Study characteristics	Country: 8 studies in Europe (61.5%) and 3 Saudi Arabia, 3 France, Argentina, 2 Spain, 2Turkey, Egypt, Italy. Study Setting: Not stated Study size: 539 Funding source: Project glomerulonephritis Study Population: 10 studies enrolled patients on maintenance dialysis, 3 studies on replacement therapy, 2 studies with acute hep c patients, 76.9% of the studies enrolled patients on maintenance dialysis or were replacement therapy recipients Age (Mean): 35.9(+- 10.6) to 49.4 (+-8.0) Sex (% male): 41.6-76% Ethnicity: Not stated
Intervention (N)	IFN alpha or alpha2b or Ribavirin or PEG IFN or Lymphoblastoid-IFN or alpha2a+ ribavirin or Ribavirin+Amantadine (244)
Control (n)	Placebo or No intervention (295)
Outcomes	"Failure to achieve SVR": Treatment v. Control o Pooled relative results (Pooled proportion in each treatment arm not available): OR 0.081 (0.029 - 0.230) o Subset using dialysis (n=6): OR 0.054 (0.019-0.150) AE: Treatment v. Control o Overall dropout rate: OR 0.385 (0.155- 0.957) ; o In dialysis patients dropout rate: OR 0.920 (0.367-2.311)
Results	Viral response greater in patients with chronic kidney disease who received ARV therapy than controls, Immune compromise conferred from chronic uraemia does not affect viral response to ARV Rx for HCV
Comments	Amstar rating: 9 Information on drop-outs unclear, significant heterogeneity between studies in the primary analysis

Review 6: Xirouchakis et al. (2008)

Study Objectives	To assess efficacy, tolerability and safety of Peg/ribavirin in **liver transplant candidates and recipients**
Methods	3 CCT (NRT) + one randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Published abstract of full paper; CCT or RCT, Cirrhotic candidates for liver transplantation or transplanted patients with Hep-C; SVR was stated, therapy with PEG-IFN alpha-2a or alpha-2b and ribavirin; Combination therapy used for at least 24 weeks Exclusion Criteria: o Mixed sequential regimens containing Peg IFN only in part; Patients co-infected with HIV or HBV; Patients with cirrhosis not considered for transplantation
Study characteristics	Country: Not stated Study Setting: Not stated Study size: 244 Funding source: The Hellenic Foundation for Gastroenterology and Nutrition (ELIGAST) Study Population: Liver transplant candidates and recipients with HCV cirrhosis; Studies included 69% - 100% of patients with genotype 1 Age (Mean): Not stated Sex (% male): Not stated Ethnicity: Not stated
Intervention (N)	Intervention 1: PEG-IFN 1.0µg + rb 0.8 to 1.0g for 24 weeks (129) Intervention 2: PEG-IFN 1.5mcg + RBV 600 to 800 mg for 24+24 weeks if RNA negative (48) Intervention 3: PEG-IFN 1.5mcg + RBV 800-1000mg for 48 weeks (48) Intervention 4: PEG-IFN 1.5mg + RBV 800mg 48 weeks (54)
Control (n)	No treatment (not stated)
Outcomes	SVR: Overall Treatment v. no treatment or low dose treatment o Intervention=41% v. Control=9.2%; Risk Difference 0.316 (0.18- 0.44) Outcomes for liver transplant candidates with HCV related cirrhosis: o Intervention1= 19.6% v. No treatment=0% Outcomes in patients transplanted for HCV related cirrhosis with recurrent disease: o Intervention 2=33.3% v. No treatment= 0% o Intervention 3= 29.6% v. No treatment= 0% o Intervention 4= 48% v. No treatment= 0% AE: Overall Treatment v. No treatment: RD -0.010 (0.044- -0.064) o Intervention=5% v. Control= 6.4%; Treatment discontinuation in liver transplant candidates with HCV related cirrhosis (Intervention 1): o Intervention = 19.6% v. No treatment= 0% Mortality: Overall Treatment v. no treatment or low dose treatment o Intervention= 7% v. Control=5%; Risk Difference 0.042 (0.027 to -1.55)) Outcomes for liver transplant candidates with HCV related cirrhosis (End of follow up) o Intervention= 7.5% v. No treatment= 6.3% ; Risk difference between study groups= 1.2% (CI ; OR 1.2 (95%CI 0.25-6.4)
Results	PEG-IFN with Ribavirin in optimal standard doses is efficacious, in both liver transplant candidates, and in recipients, to treat recurrent HCV disease. However it is associated with low median SVR of19.6% (19.6-50%) in liver transplant candidates and 41% (29.6-77.7%) in those with recurrent disease after liver transplantation.
Comments	Amstar rating: 10 No of studies and patients included in each study was small and the comparison groups were not Homogenous

Review 7: Brok et al. (2009a)

Study Objectives	To assess the beneficial and harmful effects of ribavirin mono-therapy for patients with chronic HCV
Methods	11 Randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Patients with chronic HCV for more than 6 months o Patients with chronic HCV documented on liver biopsy o Patients diagnosed with non-A, non-B chronic hepatitis. Exclusion Criteria: o Excluded patients with HIV co-infection or who had undergone liver transplantation o Quasi-randomized trials and observational studies
Study characteristics	Country: Not stated Study Setting: Not stated Study size: 523 (657) Funding source: The Hellenic Foundation for Gastroenterology and Nutrition (ELIGAST) Study Population: Adults with Chronic HCV (treatment naive patients, non-responders, relapsers): Genotype-1: 73% (Median) (Range- 40-97%) Cirrhotic/Fibrosis: 15% (Median) (Range- 0-35%) Age (Median): 45 years (Range 38-50 years) Sex (% male): 74% (median): range 63-100% Ethnicity: Not stated
Intervention (N)	Ribavirin administered in clinical trial setting between 8-52 weeks (283) Five trials -1200mg/day, Four trials - 1000-1200mg/day, One trial- 800-1000mg/day, One trial- 15mg/kg/day, One trial- dose not reported
Control (n)	Placebo or no intervention (240)
Outcomes (RD= Risk Difference)	SVR: In 5 studies with 353 participants o Intervention=0% v. Control= 0%; RD 0.00 (-0.02 - 0.03) Adverse events: o Depression- RD 0.17 (0.01-0.33) o Anaemia- 16%; RD 0.16(0.11-0.22) o Fatigue- RD 0.05(-0.01- 0.11) o Irritability- RD 0.03(-0.03-0.08) o Anxiety- RD 0.03(-0.06- 0.12) o Pruritus-RD 0.06(-0.00- 0.12) o Infections- RD 0.17(0.03-0.32) o Cough- RD 0.21(0.04-0.38) o Chest Pain- RD 0.07(0.00-0.14) o Skin disorders- RD 0.14 (0.06-0.23) o Nervous systemic disorders- RD 0.14(0.06-0.23) o Gastro-intestinal- RD 0.03 (-0.04-0.09) o Headache- RD 0.03(-0.04-0.09) o Vasculitis- RD 0.02 (-0.04-0.09) ; o Dose reductions- 11%; RD 0.11 (0.06-0.16) o Treatment discontinuations- 5%; RD0.05 (0.01-0.10) Mortality and morbidity o 3%; RD 0.00(-0.02 - 0.03) in 11 studies with 521 patients QOL: o Intervention=0.828 v. Control=0.933; RD -0.11(-0.27- 0.06)
Results	Ribavirin had no significant effect on SVR, end of treatment virological response, liver-related morbidity and mortality but significantly increased the risk of adverse reactions, including anaemia.
Comments	Amstar rating: 11 Majority of trials had inadequate or unclear control of bias.

Review 8: Hartwell and Shepherd (2009)

Study Objectives	To assess the clinical effectiveness of pegylated and non -pegylated IFN-alfa and ribavirin for treatment of adults with histologically mild HCV.
Methods	Three randomized clinical trial of treatment versus no treatment; Meta-analysis performed to compare IFN monotherapy with three trials of IFN +Placebo and one trial of IFN + RBV Inclusion Criteria: o RCT's or systematic reviews of RCT's o Studies evaluating PEG-2a or Peg-2b as dual therapy with RBV or mono-therapy for those unable to tolerate RBV o Studies of IFN-2a or IFN-2b with RBV o Studies reporting ≥ 70% of adult patients at baseline with histologically mild HCV Exclusion Criteria: o Studies where it was not possible to determine the severity of HCV
Study characteristics	Country: Not stated Study Setting: Not stated Study size: 687 Funding source: Not stated Study Population: Studies reporting >70% of adult patients at baseline with histologically mild HCV Age (Mean): 36-49 Sex (% male): Not stated Ethnicity: Not stated
Intervention (N)	Different durations of treatment. no treatment: o PEG-alpha2a 180µg + RBV 800mg for 24 weeks (212) o PEG-alpha2a 180µg + RBV 800mg for 48 weeks (210) o IFN-alpha2b3MU + RBV 1000-1200mg for 48 weeks (98)
Control (n)	No treatment (167)
Outcomes	SVR: Relative Risk = 1.7 o PEG-alpha2a 180µg + RBV 800mg for 24 weeks: Intervention=30% v. Control= 0% o PEG-alpha2a 180µg + RBV 800mg for 48 weeks: Intervention=52% v. Control=0% o IFN-alpha2b 3MU + RBV 1000-1200mg for 48 weeks (98): Intervention=33%v. Control=0% Adverse events: o Influenza symptoms (Headache, fatigue, fever, myalgia); o Depression; o Dose modifications in HIV co-infected patients treated with PEG QOL: o PEG trial- At 24 weeks after end of treatment-HRQoL scores were significantly better in patients with an SVR compared with untreated patients (PEG trial) o IFN trial- Body pain
Results	SVR was higher in IFN+ RBV compared with no treatment; SVR was higher for patients with genotype non-1 compared with genotype 1 for Peg+RBV and IFN+RBV Treatment
Comments	Amstar rating: 10 RCTs had poor reporting of randomization methods and blinding of assessors

Review 9: Iorio et al. (2010)

Study Objectives	To evaluate the benefits and harms of antiviral treatment for chronic HCV in patients with **Human immunodeficiency virus (HIV) co-infection**
Methods	One randomized clinical trial; Meta-analysis performed Inclusion Criteria: o Patients with chronic HCV and stable HIV co-infection; Included irrespective of previous antiviral therapy, level of plasma HIV RNA and CD4 positive cell counts Exclusion Criteria: o Excluded quasi-randomised trials and observational studies
Study characteristics	Country: USA or Europe Study Setting: Not stated Study size: 30 Funding source: Not stated Study Population (mean): Studies included 44-78% of genotype-1 participants Age (Mean): 36-45 Years (all trials) Sex (% male): 60%-90% (all trials) Ethnicity: Not stated
Intervention (N)	IFN 3MU 3 times weekly + RBV (18)
Control (n)	No treatment (12)
Outcomes (RR= Risk Ratio)	SVR: o Not reported End of treatment virological response: o Intervention= 0.39% v. Control= 0%; (Fishers exact P=0.02) AE o Drop-out rate Intervention= 0.11% v. Control=0% o Flu-like symptoms: Intervention= 0.83% v. Control= 0%; (Fishers exact P <0.01)
Results	No SVR data was available for the treatment v no treatment comparison. Treatment increased the risk of adverse events including anaemia and flu-like symptoms and serious adverse events including fatal lactic acidosis, liver failure and suicide due to depression.
Comments	Amstar rating: 11

Review 10: Hu et al. (2010)

Study Objectives	To assess the efficacy and safety of HCV therapy in **children**
Methods	Two of four Randomized clinical trials; 31 non-randomized studies; Meta-analysis not performed Inclusion Criteria: o Studies including children (≤ 18 years of age) o Provided details of treatment regimen o Provided data for SVR (as negative HCV RNA at least 24 weeks after therapy cessation) Exclusion Criteria: o No criteria
Study characteristics	Country: Italy Study Setting: Not stated Study size: 48 Funding source: Not stated Study Population: **Children (<18) with HCV** Age (Mean): Not stated Sex (% male): Study 1: Group A= 63% males; Group B = 40% males Study 2: Group A= 50% males; Group B = 38% males Genotype: Study1 Group A= 58% ; Group B= 70% Study 2 Group A= 50%; Group B = 46% Ethnicity: Not stated
Intervention (N)	Study 1 intervention - IFN-alpha 3MU/$m^2$3 times weekly for 12 months (11) Study 2 intervention - IFN-alpha-2b 5MU/m^2 3 times weekly for 12 months (14)
Control (n)	No intervention (23)
Outcomes	SVR o Study 1: At 30 months: Intervention= 45% v. No treatment=9%; OR 8.3 (0.6-432.5) o Study 2: At 24 months: Intervention= 69% v. No treatment= 0%, OR indeterminate but 95%CI OR>7.4 AE: No comparative data presented for treatment v. no treatment. All treatment patients showed transient influenza flu-like symptoms (other effects: anorexia, asthenia, irritability, headache, abdominal pain, leukopenia, pruritus, weight loss).
Results	SVR rates are significantly higher in children with genotype 2 or 3 compared to genotype 1
Comments	Amstar rating: 7

Review 11: Vezali, Aghemo et al. (2010)

Study Objectives	This review highlights the efficacy and safety of HCV infection in **cirrhotic** patients with respect to the clinical stage of the disease
Methods	5 of 45 Randomized, prospective, observational , retrospective clinical trials; Meta-analysis not performed Inclusion Criteria: o Adults> 18 years with chronic Hep-C infection treated with IFN or RBV; studies with baseline characteristics and involving cirrhotic and non-cirrhotic patients.. Exclusion Criteria: o Review articles were not used, except to identify papers
Study characteristics	Country: Not stated Study Setting: Not stated Study size: 1676 Funding source: Helenic Association for the study of Liver Diseases ; Schering-Plough, Roche, Bristol-Myers Squibb, Gilead sciences Inc, Bayer healthcare AG Study Population: Combine data not available Age (Mean): 55-63 years of age Sex (% male): combined data not available Ethnicity: Not stated
Intervention (N)	Intervention in study 1: IFN (193) – retrospective cohort Intervention in study 2: : IFN-alpha2b for 48 weeks (47) - RCT Intervention in study 3: PEG IFN-alpha2b 1.0µg/kg/wk and RBV 800-1000mg/d for 24 weeks in decompensated cirrhotics (66) – non-randomised prospective trial
Control (n)	Study 1: Untreated (136) Study 2: Untreated (52) Study 3: Patients who refused treatment (63)
Outcomes	Study 1: HCC (annual incidence) : Untreated 2.3%v. Treated1% (p=0.09) Hepatic decompenstation: Untreated 1.5% v. Treated 5.7% (p=0.07) Study 2: HCC(annual incidence) : Untreated-17%v.Treated-11% Hepatic decompenstation: Untretaed-10% v. Treated – 15% 3- year mortality: Treated 21% v untreated 10%; OR 2.5 (0.7-10.2) Study 3: SVR: 19.5% (13/66) treated, 0% (0/63) untreated; OR N/A (cannot calculate) AE : Risk of infections with PEGIFN=0.95/1000 v. Controls= 0.38/1000 patients months [IRR 2.43 (1.02-5.77)] Hepatic decompensation at 30 months: 88.1% untreated, 59.0% treated, OR 0.19 (0.06-0.53) Mortality (all cause) at 30 months: 32.2% untreated, 16.4% treated, OR 0.41 (0.15-1.06)
Results	Anti HCV treatment in cirrhotic patients is less effective than in non-cirrhotic patients. Viral eradication reduces the risk of liver complications and improved survival in non-cirrhotic. Therapy has a significant effect on patients with compensated cirrhosis while decompensated patients need to weigh the risks versus benefits of treatment
Comments	Amstar rating: 11

Review 12: Kimer et al. (2012)

Study Objectives	To determine whether antiviral therapy reduces the risk of developing hepatocellular carcinoma in patients with chronic HCV
Methods	Eight Randomized clinical trials and five prospective studies; Meta-analysis was performed with primary analysis using RCTs Inclusion Criteria: o All trials on IFN or PEG-IFN alone or with RBV were included; o Trials on patients with HCV related cirrhosis or fibrosis treated with antiviral therapy were included. Exclusion Criteria: o Trials on HIV and hepatitis-B patients were excluded
Study characteristics	Country: France, Italy, Spain, Japan and USA Study Setting: Not stated Study size: 2230 Funding source: Not stated Study Population: Patients with cirrhosis (8 RCTs); Cirrhotic patients (41%); All patients in intervention group underwent ultrasound, serological testing and liver biopsy at baseline Age (Mean): Not stated Sex (% male): Not stated Ethnicity: Not stated
Intervention (N)	Intervention :IFN monotherapy (Five RCTs); Peg-IFN (Two RCTs); IFN +RBV (One RCT) (1156) Therapy ranges from 1 to 5 years, and follow up from 2 to 8.7 years
Control (n)	No intervention (1074)
Outcomes (RR= Risk Ratio)	Hepatocellular carcinoma: o Intervention =7.01% v. control=12.01%: RR 0.53 (0.34 - 0.81) Morbidity: Liver related: o Intervention= 8.5% v. control=10.8% ; RR 0.73 (0.48 - 1.11) Mortality:(Recorded from 4 trials) All cause: Intervention= 10.1%v. Control=9.7% ; RR 0.81 (0.33-2.03) Liver related: RR 0.71(0.2 -2.51), no proportion available
Results	Antiretroviral therapy may reduce the risk of hepatocellular carcinoma in HCV related cirrhosis and fibrosis. Effects of ARV therapy are seen irrespective of virological response, but are more pronounced in responders compared to non-responders. Hepatocellular carcinoma incidence is diminished in both virological responders and non-responders.
Comments	Amstar rating: 11

Review 13: Kortez *et al* (2013)

Study Objectives	To assess the benefits and harms of interferon mono-therapy retreatment in chronic HCV patients who are **non-responders to and relapsers o**f previous interferon therapy.
Methods	7 Randomized clinical trials; Meta-analysis performed Inclusion Criteria: o Trials comparing interferon mono-therapy with no treatment in non-responding and relapsing patients with chronic HCV. Exclusion Criteria: o Patients who had undergone liver transplantation, were co-infected with HBV and/or HIV, and/or had evidence of hepatic decompensation.
Study characteristics	Country: Not stated Study Setting: Unclear Study size: 1676 Funding source: National institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Study Population: Patients with chronic HCV who are non-responders to and relapsers ofprevious IFN therapy Age (Mean): Not stated Sex (% male): Not stated Ethnicity: Not stated
Intervention (N)	IFN monotherapy ranging from 24 weeks (3 studies), 48 weeks (1), 96 weeks (1) and 3-5 years treatment (2 studies)
Control (n)	Placebo or no treatment (Not stated)
Outcomes (RR= Risk Ratio)	SVR: o Intervention=3.6% v. Control=0.2%: OR 0.046 (0.0 – 0.29) Hepatocellular carcinoma: o RR 0.81(0.55-1.19), baseline proportion unavailable Mortality (o All cause: Intervention= 9.3% v. Control= 7.2% ; RR 1.30 (0.95-1.79) o Liver related: Intervention=7.7% v. Control =7.2%; RR 1.07 (0.70-1.63) Morbidity comparing maintenance IFN monotherapy for 3-5 years with no therapy among patients with severe histologic disease (grade 3 or 4 fibrosis) who have failed previous antiviral therapy):: o Hepatic encephalopathy: RR 0.92 (0.38-2.26) o Variceal bleeding: Intervention= 0.5% v. Control= 2.1%; RR 0.26(0.09-0.71) o Ascites: RR 1.12 (0.62-2.00) o Spontaneous bacterial peritonitis: RR 0.38(0.04-3.54) AE: o Any adverse event- RR 1.02 (0.99-1.05) o Serious adverse event- RR 1.18(0.99-1.41) o Hematologic- RR 2.41(1.71-3.39) o Psychiatric events – RR 1.44(0.94-2.19) o Infections- RR 1.51(1.05-2.16) o Gastrointestinal- RR 0.99(0.87-1.14) o Systemic symptoms – RR 1.82(1.61-2.05) o Cardiopulmonary – RR 0.96(0.74-1.25) o Musculoskeletal – RR 1.13(0.82-1.56) o Dermatologic- RR - 2.78(1.95-3.97) o Metabolic – RR 0.84(0.35-2.03) o Neoplasms – RR 0.74(0.33-1.65) o Other systems- RR 0.82(0.47-1.41) o Hospital Admission – RR 0.0 (0.0-0.0)
Results	Interferon mono- therapy is not effective when used to retreat patients, especially those with severe fibrosis.
Comments	Amstar rating: 11 Number of trials used for systematic review is small(n=7) and only some provided clinical data

EVIDENCE PROFILES

Table 2: Evidence profile: Interferon versus no treatment for chronic HCV

Question: Should Interferon vs Placebo be used for chronic HCV treatment?										
Quality assessment							**Summary of Findings**			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Interferon**		**Risk with Placebo**	**Risk difference with Interferon** (95% CI)
Failure to achieve SVR (Treatment naive) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Myers 2009)											
409 (8 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	198/200 (99%)	176/209 (84.2%)	**OR 0.15** (0.076 to 0.30)	**990 virological failures per 1000**	**53 fewer virological failures per 1000** (from 23 fewer to 107 fewer)
Failure to achieve SVR (Treatment experienced) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Kortez 2013)											
1136 (4 studies) 72 weeks	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	578/579 (99.8%)	537/557 (96.4%)	**RR 0.96** (0.95 to 0.98)	**998 virological failures per 1000**	**40 fewer virological failures per 1000** (from 20 fewer to 50 fewer)
Failure to achieve SVR (Children only) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Hu 2010)											
48 (2 studies) 24-30 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to imprecision	23/24 (95.8%)	10/24 (41.7%)	**RR 0.45** (0.28 to 0.72)	**958 virological failures per 1000**	**527 fewer virological failures per 1000** (from 268 fewer to 690 fewer)
Failure to achieve SVR (Cirrhotic patients) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Myers 2009)											
201 (3 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	101/101 (100%)	83/100 (83%)	**OR 0.11** (0.03 to 0.39)	**1000 virological failures per 1000**	**170 fewer virological failures per 1000** (from 30 more to 390 more)[3]
Serious adverse events during treatment (CRITICAL OUTCOME; assessed with: unspecified serious AEs; Kortez 2013)											
1103 (2 studies) 3-5 years	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	157/560 (28%)	180/543 (33.1%)	**RR 1.18** (0.99 to 1.41)	**0 events per 1000**[**]	**50 more events per 1000** (from 3 fewer to 115

											more)
All-cause mortality during or after treatment (CRITICAL OUTCOME; assessed with: Kortez 2013)											
1710 (3 studies) 1-5 years	no serious risk of bias	serious[5]	no serious indirectness	serious[6]	undetected	⊕⊕⊖⊖ **LOW**[5,6] due to inconsistency, imprecision	62/867 (7.2%)	78/843 (9.3%)	**RR 1.30** (0.95 to 1.79)	**72 deaths per 1000**	**21 more deaths per 1000** (from 4 fewer to 56 more)
Liver-related mortality during or after treatment (CRITICAL OUTCOME; assessed with: Kortez 2013)											
1084 (2 studies) 3-5 years	no serious risk of bias	serious[5]	no serious indirectness	serious[6]	undetected	⊕⊕⊖⊖ **LOW**[5,6] due to inconsistency, imprecision	40/552 (7.2%)	41/532 (7.7%)	**RR 1.07** (0.70 to 1.63)	**72 deaths per 1000**	**5 more deaths per 1000** (from 22 fewer to 46 more)
Hepatocellular carcinoma detected during study (IMPORTANT OUTCOME; assessed with: HCC detected by any method; Myer 2009)											
128 (2 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	undetected	⊕⊕⊖⊖ **LOW**[7] due to imprecision	16/67 (23.9%)	8/61 (13.1%)	**OR 0.50** (0.21 to 1.21)	**239 diagnoses per 1000**	**103 fewer diagnoses per 1000** (from 177 fewer to 36 more)

[1] High-risk bias identified by Kortez review for some of primary studies used in the pooled result
[2] Imprecision given small number of events
[3] Estimated absolute difference assumed baseline risk of 100% failure to achieve SVR among untreated cirrhotic individuals
[4] Imprecision due to inconsistent definition of serious adverse events
[5] Inconsistency due to heterogeneity between studies
[6] Imprecision given small event numbers and short duration of follow up for mortality
[7] Imprecision in short duration of follow up, and inadequate ascertainment of HCC disease free at study outset
**Absolute risk of serious adverse events estimated to be 0 per 1000 among patients not on treatment

Table 3: Evidence profile: Any IFN alone or with RBV interventions versus no treatment for chronic HCV

Question: Should Any interferon alone or with ribavirin vs Placebo be used for chronic HCV?											
Quality assessment							**Summary of Findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	**With Any interferon alone or with ribavirin**		**Risk with Placebo**	**Risk difference with Any interferon alone or with ribavirin** (95% CI)
Failure to achieve SVR (Treatment naive) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Myers 2009[1])											
409 (8 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	198/200 (99%)	176/209 (84.2%)	**OR 0.15** (0.076 to 0.30)	**990 virological failures per 1000**	**53 fewer virological failures per 1000** (from 23 fewer to 107 fewer)
Failure to achieve SVR (cirrhotics pre or post transplant) (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Xirouchakis 2008)											
279 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	125/135 (92.6%)	102/144 (70.8%)	**RR 0.71** (0.64 to 0.79)	**926 virological failures per 1000**	**269 fewer virological failures per 1000** (from 194 fewer to 333 fewer)
Treatment discontinuation due to adverse events (CRITICAL OUTCOME; assessed with: treatment stopped; Xirouchakis 2008)											
129 (1 study) 72 weeks	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to risk of bias	0/63 (0%)	13/66 (19.7%)	**RD 0.20** (0.09 to 0.30)	**0 discontinuation per 1000**	**197 more discontinuation per 1000** (from 90 more to 300 more)
Liver-related morbidity during or after treatment (CRITICAL OUTCOME; assessed with: Composite definition; Kimer 2012 [3])											
789 (4 studies) 5-9 years	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊕⊖ **MODERATE**[4] due to imprecision	42/389 (10.8%)	34/400 (8.5%)	**RR 0.73** (0.48 to 1.11)	**108 deaths per 1000**	**29 fewer deaths per 1000** (from 56 fewer to 12 more)
Hepatic decompensation during or after treatment (Cirrhotic patients) (IMPORTANT OUTCOME; assessed with: composite definition; Vezali 2012)											
99 (1 study) 30 months	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊕⊕⊖ **MODERATE**[5] due to imprecision	5/52 (9.6%)	7/47 (14.9%)	**RR 1.55** (0.59 to 3.45)	**96 decompensation per 1000**	**53 more decompensation per 1000** (from 39 fewer to 236 more)
All-cause mortality during or after treatment (Cirrhotic patients) (CRITICAL OUTCOME; assessed with: deaths; Vezali 2012)											
99	no serious	no serious	no serious	serious[5]	undetected	⊕⊕⊕⊖	5/52	10/47	**RR 2.21**	**96 deaths per 1000**	**116 more deaths per**

(1 study) 30 months	risk of bias	inconsistency	indirectness			**MODERATE**[5] due to imprecision	(9.6%)	(21.3%)	(0.69 to 8.25)		**1000** (from 30 fewer to 697 more)
All-cause mortality during or after treatment (CRITICAL OUTCOME; assessed with: deaths; Kimer 2012)											
1850 (4 studies) 5-9 years	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[6] due to inconsistency	90/932 (9.7%)	93/918 (10.1%)	**RR 0.81** (0.33 to 2.03)	**97 deaths per 1000**	**18 fewer deaths per 1000** (from 65 fewer to 99 more)
Hepatocellular carcinoma during or after treatment, patients with compensated advanced fibrosis (IMPORTANT OUTCOME; assessed with: HCC detection not specified; Kimer 2012)											
2230 (8 studies) 2-9 years	no serious risk of bias	serious[7]	no serious indirectness	serious[8]	undetected	⊕⊕⊖⊖ **LOW**[7,8] due to inconsistency, imprecision	129/1074 (12%)	81/1156 (7%)	**RR 0.53** (0.34 to 0.81)	**120 diagnoses per 1000**	**56 fewer diagnoses per 1000** (from 23 fewer to 79 fewer)

[1] Myers et al 2009 examined IFN v placebo. Used as a reference point for benefits of treatment compared with no treatment to compare with other outcomes
[2] Review rated primary studies as having significant risk of bias
[3] Liver morbidity defined as variceal bleeding, hepatorenal syndrome, liver failure, spontaneous bacterial peritonitis
[4] Imprecision given composite outcome and short-medium term follow up post treatment
[5] Imprecision given short duration of follow-up for mortality
[6] Inconsistency due to heterogeneity between studies with high I-square
[7] Significant heterogeneity in results
[8] Imprecision in inadequate ascertainment of HCC disease free at study outset

Table 4: Evidence profile: Ribavirin versus no treatment

Question: Should Ribavirin monotherapy vs Placebo be used for chronic HCV?										
Quality assessment							**Summary of Findings**			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Placebo	**With Ribavirin monotherapy**		**Risk with Placebo** / **Risk difference with Ribavirin monotherapy** (95% CI)
Failure to achieve SVR (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment; Brok 2009)										
353 (5 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	153/154 (99.4%)	198/199 (99.5%)	**RD 0.00** (-0.02 to 0.03)	**994 virological failures per 1000** / **0 fewer virological failures per 1000** (from 20 fewer to 30 more)
All-cause mortality during AND liver-related mortality (CRITICAL OUTCOME; assessed with: Combined end-point; Brok 2009)										
521 (11 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	1/239 (0.42%)	2/282 (0.71%)	**RD 0.00** (-0.02 to 0.03)	**4 deaths per 1000** / **0 fewer deaths per 1000** (from 20 fewer to 30 more)
Treatment discontinuations due to adverse events (IMPORTANT OUTCOME; assessed with: treatment stopped; Brok 2009)										
428 (6 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	8/192 (4.2%)	21/236 (8.9%)	**RD 0.05** (0.01 to 0.10)	**42 discontinuations per 1000** / **50 more discontinuations per 1000** (from 10 fewer to 100 more)
Quality of life (IMPORTANT OUTCOME; assessed with: Fatigue at end of treatment; Brok 2009)										
59 (1 study) 48 weeks	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[2] due to indirectness	28/30 (93.3%)	24/29 (82.8%)	**RD -0.11** (-0.27 to 0.06)	**933 quality of life per 1000** / **110 fewer quality of life per 1000** (from 270 fewer to 60 more)

[1] Significant imprecision given 2 events in RBV arm and 1 event in control arm and short duration of follow-up

[2] Fatigue used as indirect measure of quality of life

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APPENDICIES

Appendix 1: Search syntax for electronic databases

MEDLINE

268 citations

1. exp Hepatitis C/
2. hepacivirus.ti,ab,hw.
3. HCV.ti,ab,hw.
4. Hepatitis C.ti,ab,hw.
5. HepC.ti,ab,hw.
6. hepC.ti,ab,hw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Antiviral Agents/
9. antiviralagents.ti,ab,hw.
10. (antiviral agent* adj6 (hepC or hepatitis C or HCV or hepacivirus)).ti,ab,hw.
11. ((therapy or treat* or drug*) adj2 (hepC or hepatitis C or HCV or hepacivirus)).ti,ab,hw.
12. exp Ribavirin/
13. exp Interferon-alpha/
14. ribavirin.ti,ab,hw.
15. pegylatedinterferon.ti,ab,hw.
16. Interferon-alpha.ti,ab,hw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 7 and 17
19. exp Meta-Analysis/
20. meta-analys?s.ti,ab,hw.
21. systematic adj2 review*).ti,ab,hw.
22. metaanalys?s.ti,ab,hw.
23. 19 or 20 or 21 or 22
24. 18 and 23
25. limit 25 to yr="1994 -Current"

EMBASE

750 citations

1 exp Hepatitis C/
2 hepacivirus.ti,ab,hw.
3 HCV.ti,ab,hw.
4 Hepatitis C.ti,ab,hw.
5 HepC.ti,ab,hw.
6 hepC.ti,ab,hw.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Antiviral Agents/
9 antiviralagents.ti,ab,hw.
10 (antiviral agent* adj6 (hepC or hepatitis C or HCV or hepacivirus)).ti,ab,hw.
11 ((therapy or treat* or drug*) adj2 (hepC or hepatitis C or HCV or hepacivirus)).ti,ab,hw.
12 exp Ribavirin/
13 exp Interferon-alpha/
14 ribavirin.ti,ab,hw.
15 pegylatedinterferon.ti,ab,hw.
16 Interferon-alpha.ti,ab,hw.

17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 exp Meta-Analysis/
19 meta-analys?s.ti,ab,hw.
20 systematic adj2 review*).ti,ab,hw.
21 metaanalys?s.ti,ab,hw.
22 19 or 20 or 21 or 22
23 18 and 23
24 limit 25 to yr="1994 -Current"

COCHRANE

91 Citations

1 MeSH descriptor: [Hepatitis C] explode all trees
2 hepacivirus:ti,ab,kw (Word variations have been searched)
3 HCV:ti,ab,kw (Word variations have been searched)
4 Hepatitis C:ti,ab,kw (Word variations have been searched)
5 HepC:ti,ab,kw (Word variations have been searched)
6 hep C:ti,ab,kw (Word variations have been searched)
7 #1 or #2 or #3 or #4 or #5 or #6
8 MeSH descriptor: [Antiviral Agents] explode all trees
9 antiviral agents:ti,ab,kw (Word variations have been searched)
10 (antiviral agent* near/6 (hepC or hepatitis C or HCV or hepacivirus)):ti,ab,kw (Word variations have been searched)
11 ((therapy or treat* or drug*) near/2 (hepC or hepatitis C or HCV or hepacivirus)):ti,ab,kw (Word variations have been searched)
12 MeSH descriptor: [Ribavirin] explode all trees
13 MeSH descriptor: [Interferon-alpha] explode all trees
14 "ribavirin":ti,ab,kw (Word variations have been searched)
15 "pegylated interferon":ti,ab,kw (Word variations have been searched)
16 "interferon-alpha":ti,ab,kw (Word variations have been searched)
17 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
18 #7 and #17
19 MeSH descriptor: [Meta-Analysis] explode all trees
20 meta-analys?s:ti,ab,kw (Word variations have been searched)
21 (systematic near/2 review*):ti,ab,kw (Word variations have been searched)
22 metaanalys?s:ti,ab,kw (Word variations have been searched)
23 #19 or #20 or #21 or #22
24 #18 and #23

Appendix 2: Summary of all study data

Appendix Table 1: Summary of study data - Interferon versus no treatment for chronic HCV

Outcome	Study (year)	No of participants (Studies)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with treatment
Failure to achieve SVR	Malaguarnera *et al* (1995)	1579 (27)	OR 0.22 (0.29- 0.17)	899 failures per 1000	198 fewer failures per 1000
	Carithers *et al* (1997)	552 (20)	OR 0.11 (0.01- 1.0)	990 failures per 1000	70 fewer failures per 1000
	Kortez *et al* (2013)	1136 (4)	RR 0.96 (0.95 – 0.98)	998 failures per 1000	40 fewer failures per 1000
	Myers *et al* (2009)	409 (8) 201 (3)	OR 0.15 (0.076 - 0.30) **SVR among cirrhotic patients:** OR 0.11 (0.03 - 0.39)	990 failures per 1000 1000 failures per 1000	53 fewer failures per 1000 170 fewer failures per 1000
	Hu *et al* (2010)	48 (2)	**SVR among children:** Study 1: RR 0.45 (0.28 to 0.72) Study 2: OR : NA Intervention= 69% vs. No treatment= 0%	 958 failures per 1000 1000 failures per 1000	 527 fewer failures per 1000 690 fewer failures per 1000
Rates of hepatocellular carcinoma	Myers *et al* (2009)	128 (2)	OR 0.50 (0.21-1.21) **SVR among cirrhotic patients:** OR 0.74 (0.38-1.47)	239 cases per 1000 460 cases per 1000	103 fewer cases per 1000 30 fewer cases per 1000
	Kortez *et al* (2013)	1710 (3)	RR 0.81 (0.55-1.19)	62 cases per 1000	12 fewer cases per 1000
Rates of Decompensated liver disease	Kortez *et al* (2013) Kortez *et al* (2013) Kortez *et al* (2013) Kortez *et al* (2013)	1676 (2) 1710 (3) 1084 (2) 1676 (2)	Hepatic encephalopathy RR 0.92 (0.38-2.26) Variceal bleeding RR 0.26 (0.09-0.71) Spontaneous bacterial peritonitis RR 0.38 (0.04-3.54) Ascites RR 1.12 (0.62-2.00)	12 case per 1000 21 cases per 1000 4 cases per 1000 25 cases per 1000	1 case fewer per 1000 16 fewer cases per 1000 3 cases fewer per 1000 3 more cases (10 fewer to 25 more) per 1000
All-cause Mortality during or after treatment (3-5 years)	Kortez *et al* (2013)	1710 (3)	**Among cirrhotic patients previous failed treatment:** All-cause mortality RR 1.30 (0.95-1.79)	72 deaths per 1000	21 more deaths (4 fewer to 56 more) per 1000
Liver-related morality during or after treatment (3-5 years)	Kortez *et al* (2013)	1084 (2)	Liver related mortality RR 1.07 (0.70-1.63)	72 deaths per 1000	5 more deaths (22 fewer to 46 more) per 1000
Serious adverse events	Kortez *et al* (2013)	1103 (2)	RR 1.18 (0.99-1.41)	0 events per 1000	50 more events per 1000

Appendix Table 2: Summary of study data – Any Interferon alone or with RBV interventions versus no treatment for chronic HCV

Outcome	Study	No of participants (Studies)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with treatment
Failure to achieve SVR	Fabrizi *et al* (2008) (Among patients with renal failure)	539 (13)	Treatment v control OR 0.081 (0.029 - 0.230) Subset using dialysis (n=6): Treatment v control OR 0.054 (0.019-0.150)	Baseline proportion not reported Baseline proportion not reported	NA NA
	Xirouchakis *et al* (2008)	279 (4)	RR 0.71 (0.64-0.79)	926 failures per 1000	269 fewer failures per 1000
	Hartwell *et al* (2009)	687 (3)	PEG-alpha2a 180µg + RBV 800mg for 24 weeks: Intervention=70% v. Control=100% PEG-alpha2a 180µg + RBV 800mg for 48 weeks: Intervention= 48% v. Control=100% IFN-alpha2b 3MU + RBV 1000-1200mg for 48 weeks: Intervention= 67% v. Control=100%	1000 failures per 1000 1000 failures per 1000 1000 failures per 1000	300 fewer failures per 1000 520 fewer failures per 1000 330 fewer failures per 1000
	Vezali *et al* (2010)	188 (1)	**SVR among cirrhotics:** OR= NA Intervention 19.5 % v. Control 0%,	1000 failures per 1000	195 fewer failures per 1000
Rates of hepatocellular carcinoma	Vezali *et al* (2010)	329 (1) 99 (1)	**HCC among cirrhotics:** Study 1: HCC(annual incidence): RR1.55 (0.59 to 3.45) Untreated-2.3%v. Treated-1% Study 2: HCC(annual incidence): Untreated-17%v.Treated-11% RR= 0.612	96 decompensations per 1000 17 cases per 1000	53 more decompensation per 1000 6 fewer cases per 1000
	Kimer *et al* (2012)	2230 (8)	RR 0.53 (0.34 – 0.81)	120 diagnoses per 1000	56 fewer diagnoses per 1000
Morbidity	Xirouchakis *et al* (2008)	244 (4)	RD 0.042 (0.027 –-1.55) Intervention= 7% v. Control=5%;	50 deaths per 1000	20 more deaths per 1000
	Vezali *et al* (2010)	329 (1) 99 (1) 129 (1)	**Morbidity among cirrhotics:** Study 1:Hepatic decompenstation: Untreated-1.5% v. Treated – 5.7% (P=0.07) Study 2:Hepatic decompenstation: Untretaed-10% v. Treated – 15% Study 3:Hepatic decompensation (30th Month) :OR 0.19 (0.06-0.53), Untreated 88.1% v. 59.0% treated	15 cases per 1000 100 cases per 1000 881 cases per 1000	42 more cases per 1000 50 more cases per 1000 291 fewer per 1000
	Kimer*et al* (2012)	789 (4)	Liver related: RR 0.73 (0.48 - 1.11) Intervention= 8.5 % v. control=10.8%	108 cases per 1000	29 fewer cases per 1000
All-cause Mortality	Fabrizi *et al* (2008)	539 (13)	Dropout rate-Overall: OR 0.39(0.16- 0.96) Dropout rate-Dialysis patients: OR 0.92 (0.37-2.31)	Baseline proportion not reported Baseline proportion not reported	NA NA
	Vezali *et al*	99(1)	**Mortality among cirrhotics**	96 deaths per 1000	116 more deaths per

	2010		All-cause mortality at 30 months RR 2.21 (0.68 to 8.25)		1000
	Kimer*et al* (2012)	1850 (4)	All cause: RR 0.81 (0.33-2.03) Intervention= 10.1% v.Control=9.7% Liver related: (4 trials) RR 0.71 (0.2- 2.51)	97 deaths per 1000 Baseline proportion not reported	18 fewer deaths per 1000 NA
Adverse events leading to treatment discontinuation	Xirouchakis *et al* (2008)	129 (1)	RD 0.20 (0.09 to 0.30)	0 events per 1000	197 more discontinuations per 1000
	Hartwell *et al* (2009)	687 (3)	Influenza-like symptoms; Depression; Dose modifications in HIV co-infected patients treated with PEG.	Baseline proportion not reported	NA
	Hartwell *et al* (2009)	687 (3)	24 weeks after end of treatment: HRQoL scores significantly better in patients with an SVR compared with untreated patients (PEG trial)	Baseline proportion not reported	NA
	Iorio *et al* (2010)	30 (1)	**AEs among HIV co-infection:** Drop-out rate Intervention= 11% v. Control=0%, RR na, p=0.50. Flu-like symptoms: Intervention= 83% v. Control= 0%; RR na, p <0.01)	0 cases per 1000 0 cases per 1000	110 more cases per 1000 830 more cases per 1000
	Vezali *et al* (2010)	129 (1)	**AEs among cirrhotics:** Risk of infections RR 2.43 (1.02-5.77)	Baseline proportion not reported	NA
Quality of life assessment	No data				

Appendix Table 3: Summary of study data – Ribavirin versus placebo

Outcome	study	No of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with treatment
Failure to achieve SVR	Brok *et al* (2009)	353 (5)	RD 0.00 (-0.02 to 0.03)	994 treatment failures per 1000	0 fewer virological failures per 1000
Morbidity and mortality (All-cause)	Brok *et al* (2009)	521 (11)	RD 0.00(-0.02 to 0.03)	4 deaths per 1000	0 fewer deaths per 1000
Adverse events leading to dose reduction	Brok *et al* (2009)	387 (6)	RD 0.11 (0.06-0.16) Dose reductions: 11%	0 events per 1000	110 more events per 1000
Adverse events leading to treatment discontinuation	Brok *et al* (2009)	428 (6)	RD 0.05 (0.01-0.10) Treatment discontinuations: 5%	42 discontinuations per 1000	50 more discontinuation per 1000
Quality of life assessment (measured as fatigue at end of treatment)	Brok *et al* (2009)	59 (1)	RD -0.11(-0.27 to 0.06) Intervention=82.8%v. Control=93.3%;	933 quality of life per 1000	110 fewer quality of life per 1000

Appendix 3: AMSTAR – a measurement tool to assess the methodological quality of systematic reviews

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

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2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

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3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

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4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

---

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

---

6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies

□ Yes
□ No
□ Can't answer
□ Not applicable

analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
Note: Acceptable if not in table format as long as they are described as above.

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7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

---

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

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9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

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10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

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11. Was the conflict of interest included?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

□ Yes
□ No
□ Can't answer
□ Not applicable

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

Appendix 4: GRADE approach to assessing the quality of evidence across studies

<table>
<tr><th>Quality of Evidence (summary score)</th><th>Study Design</th><th>Downgrading Factors</th><th>Upgrading Factors</th></tr>
<tr><td>High (4) =Further research is very unlikely to change our confidence in the estimate of effect.</td><td>Randomized trials or valid accuracy studies for diagnostic tests begin with a score of High (4)</td><td rowspan="4">Study Limitations:
-1 Serious
-2 Very serious

Consistency:
-1 Serious
-2 Very serious

Directness:
-1 Serious
-2 Very serious

Precision:
-1 Serious
-2 Very serious

Publication Bias:
-1 Serious
-2 Very serious</td><td rowspan="4">Large effect
+1 Large
+2 Very large

Plausible confounding would change the effect
+1

Dose-response gradient
+1 if Present</td></tr>
<tr><td>Moderate (3) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td><td></td></tr>
<tr><td>Low (2) = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td><td>Observational studies or indirect accuracy studies for diagnostic tests begin with a score of low (2).</td></tr>
<tr><td>Very low (1) = Any estimate of effect is very uncertain.</td><td></td></tr>
</table>