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Meta-analysis: ribavirin plus interferon versus interferon monotherapy for chronic hepatitis C – an updated Cochrane review

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Abstract

Background

Multiple randomised trials have been published on antiviral treatment for chronic hepatitis C.

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Aim

To meta-analyse the effect of adding ribavirin to interferon for chronic hepatitis C.

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Methods

The results of randomised trials were combined in cumulative meta-analyses. Trial sequential analyses were used to adjust for spurious results due to random errors and multiplicity. The outcome measures were undetectable hepatitis C virus RNA in serum (sustained virological response) and liver-related morbidity plus all-cause mortality.

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Results

We included 82 randomised trials with 12,615 patients. Trial sequential analysis established clear beneficial effect of interferon plus ribavirin versus interferon on the sustained virological response in 1998 after nine trials (RR: 0.74; 95% CI: 0.64-0.85, $P < 0.0001$, 1734 patients). Subsequently, additional 73 trials were published just narrowing the confidence interval and decreasing the p value. In contrast, trial sequential analysis

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2 found that additional evidence is needed to convincingly detect a beneficial effect of
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4 interferon plus ribavirin versus interferon monotherapy on clinical outcomes.
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8 9 **Conclusion**

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12 The rationale behind several recent trials on adding ribavirin to interferon for chronic
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14 hepatitis C is debatable as the effect on virological response is established. More
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16 evidence is needed to assess if adding ribavirin to interferon improves clinical outcomes.
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INTRODUCTION

Chronic hepatitis C affects about 170 million people worldwide. Three million people are infected each year.¹ Acute hepatitis C infection is usually without symptoms but becomes chronic in the majority of patients.² The natural course of chronic hepatitis C varies, but most chronically infected patients remain asymptomatic.²⁻⁴ The risk of developing cirrhosis depends on several factors, eg, age, race, alcohol abuse, obesity, steatosis, transaminase activity, viral load, and coinfections.⁵ In the United States and Europe, chronic hepatitis C infection accounts for 40% of end-stage cirrhosis and 60% of hepatocellular carcinoma.⁶

Treatment recommendations for chronic hepatitis C are based on surrogate outcomes - that is, clearance of hepatitis C virus from the blood.⁷⁻⁹ Whether virological clearance is able to predict reduced morbidity or mortality is debated.⁷⁻⁹ Epidemiological studies have showed a correlation between virological clearance and liver-related morbidity but this correlation may be biased and has not been validated in randomised trials or meta-analyses.^{4,9} The current treatment recommendation is ribavirin and pegylated interferon.⁵ The dose and duration is modified according to the viral genotype.

There are almost 1,000 publications on randomised trials on antiviral treatment for chronic hepatitis C.¹⁰ The number of trials alone suggests that the rationale for conducting some of the latest trials may be debatable. We conducted a cumulative meta-analysis with trial sequential analysis to address this issue. We assessed the key outcomes for chronic hepatitis C: undetectable serum hepatitis C virus RNA six months after end of

1 treatment (sustained virological response) and the composite outcome of liver-related
2 morbidity and all-cause mortality.
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5 6 7 **METHODS**

8 **Trial eligibility**

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10 This review is an update of our Cochrane Hepato-Biliary Group systematic review.^{11, 12}

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12 We included randomised trials comparing ribavirin plus interferon versus interferon alone
13 for patients with chronic hepatitis C, irrespective of language and publication status. The
14 diagnosis was based on the presence of serum hepatitis C virus RNA plus elevated serum
15 transaminase activity for more than six months or chronic hepatitis documented on liver
16 biopsy. Based on previous antiviral treatment, the patients were classified as naive (not
17 previously treated), relapsers (patients with a transient response to previous antiviral
18 treatment), or non-responders (patients without a response to previous antiviral
19 treatment). We excluded patients who had human immune deficiency virus or had
20 undergone liver transplantation.
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34 **Search methods for identification of trials**

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36 We searched The Cochrane Hepato-Biliary Group Controlled Trials Register,¹³ The
37 Cochrane Library (www.cochrane.org), MEDLINE, EMBASE, and Science Citation
38 Index Expanded and hand searched reviews, abstracts, and proceedings of conferences.
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42 We also searched for ongoing and unpublished trials on <http://controlledtrials.gov>,
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44 <http://clinicaltrials.gov>, and <http://centerwatch.com>. The last search update was March
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Data collection and analysis

Two authors (JB and LLG) independently evaluated whether the trials fulfilled the inclusion criteria and extracted data. Disagreements were resolved by discussion with CG. The investigators of included trials were contacted for any data not presented in the published reports.

The outcome measures were failure of sustained virological response (number of patients with detectable serum (or plasma) hepatitis C virus RNA at least six months after treatment) and liver-related morbidity plus all-cause mortality (number of patients who developed cirrhosis, ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, or died).

Risk of bias was assessed through evaluation of randomisation (allocation sequence generation and allocation concealment) and double blinding using placebo.¹⁴ Trials with adequate randomisation methods and double blinding were classified as having a low risk of bias. Subgroup analysis (comparing trials with high and low risk of bias) and funnel plot analysis were performed.¹²

Statistical methods

Performing cumulative meta-analyses entails a risk of generating spurious results due to multiple testing (similar to repetitive testing in clinical trials) or due to random error.¹⁵⁻²²

This risk is reduced through conducting trial sequential analyses.¹⁷⁻²² Performing trial sequential analysis requires an assessment of the minimal worthwhile intervention effect and a required information size (similar to the minimal clinically relevant difference and

1 the sample size calculations in a single trial).¹⁷⁻²⁰ The information size can be calculated
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3 with or without heterogeneity correction.¹⁷⁻²² Based on this, the trial monitoring
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5 boundaries can be calculated.¹⁷⁻²² The result of a trial sequential analysis allows for an
6
7 assessment of the cumulative evidence.
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11 Trial sequential analysis is able to adjust for the risk of random error, which is
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13 particularly relevant for meta-analyses with small trials, few events, or multiple
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15 updates.¹⁷⁻²² Accordingly, in meta-analyses with such issues, a more restrictive *P* value is
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17 needed to obtain firm evidence. Furthermore, when additional evidence is needed, the
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19 analysis is able to estimate the required number of patients and events (information size)
20
21 needed to obtain firm evidence.¹⁷⁻²²
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26 The meta-analyses were performed using Review Manager 5.0 and Trial Sequential
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28 Analysis version 0.8.^{23, 24} Outcomes were expressed as relative risks (RR) with 95%
29
30 confidence intervals (CI). We conducted random-effects model trial sequential analyses
31
32 with a type 1 error of 5%, type 2 error of 20%, and adjusted for inter-trial heterogeneity
33
34 (I^2)^{17-20, 25} Based on previous evidence, we assumed that the proportion of patients
35
36 without a sustained virological response would be 85% for patients on interferon alone.²⁶
37
38 The relative risk reduction used in the calculation is the minimal worthwhile intervention
39
40 effect of adding ribavirin was set to 10%. The proportion of patients with clinical events
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42 (liver-related morbidity or all-cause mortality) was set to 1% for patients on interferon
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44 alone and the relative risk reduction to 50%.^{11, 12}
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2 Trial sequential analyses were conducted for subgroups of patients who were treatment
3 naïve, relapsers or non-responders, and for trials stratified by the viral genotype of
4 included patients (more or less than 90% with genotype 1). Additional trial sequential
5 analyses were conducted for proportion of patients with cirrhosis (trials including more or
6 less than 25% cirrhotic patients); dose of ribavirin (trials using more or less than 1000 mg
7 daily); and trials using pegylated or non-pegylated interferon.
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14 15 16 **RESULTS**

17 18 **Search of databases**

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20 We identified 2016 references through the electronic searches (Figure 1). Of these
21 references, we excluded clearly irrelevant references, non-randomised studies, and
22 duplicates. Five additional references were identified through manual searches. Twenty-
23 five references referred to 16 studies, which were excluded because they were not clearly
24 randomised or because we were unable to extract the necessary data. Accordingly, 82
25 randomised trials described in 150 references were included (Figure 1) (Appendix).
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34 35 **Characteristics of the included randomised trials**

36 The included trials randomised 12,615 patients and were published from 1995 to 2009.
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38 Twenty-five trials were published only as abstracts. In 18 trials patients were only
39 followed to the end of treatment. In the remaining trials patients were followed for a
40 median of 34 weeks (range 4 weeks to 11 years) after end of treatment. The trials
41 included treatment-naïve patients ($n = 34$ trials), relapsers ($n = 9$), non-responders ($n =$
42 22), mixed ($n = 15$), or unclear ($n = 2$). Most trials excluded patients with other liver
43 diseases, alcohol or intravenous drug abuse, severe co-infections, and cardiovascular
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1 diseases. The mean age of the included patients was 45 years (range 28-54 years). The
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3 median percentage of patients with cirrhosis was 14% (range 0%-74%); of males, 66%
4
5 (range 20%-100%); and of those with hepatitis C virus genotype 1, 61% (range 0%-
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7 100%).
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11 The dose and duration of treatments varied substantially. In 55 trials, ribavirin 1000 to
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13 1200 mg was administered daily for 24 weeks. In 30 trials, the dose of interferon was 3
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15 million units thrice weekly for 24 weeks. In the remaining trials the dose of ribavirin
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17 ranged from 600 to 1200 mg daily for 8 to 48 weeks and the dose of interferon from 3 to
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19 6 million units for the same treatment duration. Pegylated interferon 180 microgram or
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21 1.5 microgram/kg weekly was used in nine trials.
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26 Only 7% ($n = 5$) of included trials were classified as having a low risk of bias, ie, [had](#)
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28 [adequate allocation sequence generation \(eg, use of computer or table of random](#)
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30 [numbers\), had adequate allocation concealment \(eg, use of central](#)
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32 [independent unit or sealed envelopes\), and](#) used adequate methods for blinding ([use of](#)
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34 [placebo](#)).
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37 38 Serological sustained virological response

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40 Of the 82 randomised trials, only 59 reported on serological sustained virological
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42 response. [The remaining trials reported end of treatment virological response or](#)
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44 [biochemical response \(liver enzymes\)](#). Ribavirin plus interferon was significantly better
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46 that interferon alone for patients who were treatment naive (RR: 0.71; 95% CI: 0.67-
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2 0.75), relapsers (RR: 0.62; 95% CI: 0.54-0.71), non-responders (RR: 0.89; 95% CI: 0.84-
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4 0.93), or if all patients were combined (RR: 0.75; 95% CI: 0.71-0.79) (Figure. 2).
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8 Trial sequential analysis found that already in 1998, after nine trials with 1,734 patients
9
10 were published, the evidence clearly showed a benefit of ribavirin plus interferon on
11
12 sustained virological response (RR: 0.74; 95% CI: 0.64-0.85, $P < 0.0001$, $Z = -4.2$)
13
14 (Figure 3). Subsequently, an additional 50 randomised trials involving 7,349 patients
15
16 reported on sustained virological response. The benefits of ribavirin plus interferon for
17
18 naïve patients was established in 1998 (Fig. 4A) and in 1999 for relapsers and non-
19
20 responders (Fig. 4B)
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24 Similar benefits were found in subgroups of trials stratified according to genotype (Fig.
25
26 4C and 4D), proportion of patients with cirrhosis (Fig. 4E and 4F), trials using standard
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28 or low dose of ribavirin (Fig. 5A and B), and trials using pegylated or non-pegylated
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30 interferon (Fig. 5C and D).
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34 Subgroup analyses found no statistically significant difference between trials with high
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36 bias and low bias risk. The funnel plot analysis showed no evidence of bias ($P = 0.43$).
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40 **Liver-related morbidity and all-cause mortality**

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42 Thirteen of the 82 trials reported a total of 41 clinical events (21 patients had liver-related
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44 morbidity and 20 patients died). None of the trials reported whether the patients with
45
46 clinical outcomes had sustained virological response. The cumulative meta-analysis
47
48 found an apparent beneficial effect of ribavirin plus interferon on liver-related morbidity
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1 and mortality (RR: 0.47; 95% CI: 0.26-0.84, $P = 0.03$). However, trial sequential analysis
2 found that additional evidence is needed to convincingly detect a beneficial effect of
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14 **DISCUSSION**

15 The present review suggests that the rationale for performing a number of the recent
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Strengths and weaknesses

We did a comprehensive search of several databases and tried to minimise publication bias and language bias by including trials regardless of publication status and language. Furthermore, two authors independently assessed trials and data to avoid errors. We may not have identified all randomised trials and we were unable to obtain data from some trials. Accordingly, the strength of the combined evidence may be underestimated.

The included patients and intervention regimens varied considerably, which likely causes some of the substantial inter-trial heterogeneity. This heterogeneity can be considered both as a weakness and strength. Limiting our analysis to include trials on one specific

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2 intervention regimen or subgroup of patients would have provided a more focused
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4 answer. However, the variety of intervention regimens and patients increase the external
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6 validity of the results and we adjusted our analysis for heterogeneity.¹⁷
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10 We based our trial sequential analysis information size estimation on event proportions in
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12 the control group from previous trials on interferon monotherapy²⁴ and on estimated
13
14 relative risk reduction (10% for sustained virological response and 50% for morbidity and
15
16 mortality) plus type 1 error of 5% and type 2 error of 20%. Thus, our findings are
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18 appropriate only under these assumptions. It could be judged that other pre-specified
19
20 intervention effects or type 1 and 2 errors are more appropriate for this clinical situation.
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22 However, in the analysis for sustained virological response, realistic alteration in the
23
24 parameters of effect size and error rates would not have changed the overall conclusion.
25
26 Regarding morbidity and mortality, the use of relative risk reduction of 50% may seem
27
28 too optimistic. A choice of smaller effect size would have made the analysis even more
29
30 restrictive and lead to the same conclusion: more evidence is needed regarding clinical
31
32 outcomes.
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34 35 36 **Trial sequential analysis on sustained virological response**

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38 Adding ribavirin to interferon was recommended by consensus in Europe in 1999, and in
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40 United States in 2002.^{6, 27} We found that after 1998, several redundant randomised trials
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42 have been conducted on adding ribavirin to interferon reporting the outcome sustained
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44 virological response (Fig. 3). The results of the 50 subsequent trials, which enrolled
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46 additional 7349 patients since 1998, did not affect the effect size, but simply narrowed
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48 the confidence interval and reduced the p-value. We acknowledge that trial sequential
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1 analysis was performed according to publication date and some trials were initiated
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3 before the accumulated evidence (or consensus recommendations) was available. Thus,
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6 some of the trials that seem redundant by our analysis would have been appropriate at the
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8 time of their launch. Furthermore, we acknowledge that it could be argued that it was fair
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10 to assess the effect of ribavirin in some subgroups. Having said this, we still find that
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12 adding ribavirin to interferon does increase the sustained virological response in all
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14 relevant subgroups and, in retrospect, many trials have been conducted since the time at
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16 which this association was statistically convincing (Figure 4 and 5).
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20 Trial sequential analysis on clinical outcomes

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22 According to our 'traditional' cumulative meta-analysis, there is some evidence ($P =$
23
24 0.03) of benefits on clinical outcomes when adding ribavirin to interferon. However, this
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26 result is not adjusted for the risks of random error and multiple testing. According to trial
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28 sequential analysis it may be a spurious result and we need more evidence to detect (or
29
30 reject) a beneficial effect on clinical outcomes (Figure 6). This could be obtained either
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32 by conducting new trials with a sample size equalling the difference between the accrued
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34 number of patients and the calculated desired information size ($n = 3812$ patients (Figure
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36 6)) or by performing long-term evaluation of patients enrolled in previous trials. Potential
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38 new trials should have long-term follow-up to obtain protracted clinical events, but are
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40 logistically very difficult and dropouts are likely to occur. Such trials may also be
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42 considered unethical as controls are randomised to a treatment (monotherapy) assumed
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44 inferior to that currently recommended.^{6, 28} Long-term evaluation of patients enrolled in
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46 previous trials may, however, be invalid because these patients may have been retreated
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1 with different antiviral regimens due to participation in new trials or as part of clinical
 2 practice.
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 8 We contacted all trial authors and asked whether any long-term clinical outcomes had
 9 been assessed subsequent to the trial publication. Most authors did not reply, many
 10 informed that it was impossible to obtain valid data, but a few authors provided long-term
 11 data or were planning to do so. Hopefully, these additional clinical data will provide
 12 valuable information, within a reasonable time. Even though a beneficial effect of
 13 ribavirin added to interferon will become established we need to remember that ribavirin
 14 is associated with several severe adverse reactions, it is expensive, and the number
 15 needed to treat to prevent one patient from developing liver-related morbidity is likely to
 16 be large.^{11, 12} Such considerations may sometimes be ignored when adding ribavirin as
 17 standard care and conflict current recommendations.⁵
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28 **Sustained virological response as a surrogate outcome**

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 30 Sustained serological virological response is considered the target for chronic hepatitis
 31 treatment, but it is still only a putative surrogate outcome.^{8, 9, 29} Some criteria influence
 32 the validity of a surrogate outcome. First, that the surrogate is biological plausible.
 33 Second, if a correlation is established between the surrogate and the clinical outcome,
 34 e.g., in observational studies. Third, if one or, even better, many randomised trials on
 35 similar drug classes have established that the intervention's effect on the surrogate
 36 captures the effect on the pertinent clinical outcome.³⁰
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1 Interestingly the mechanism of ribavirin is unclear but the rationale for using ribavirin is
 2 biological plausible and epidemiological studies have showed a correlation between
 3 sustained virological response and liver-related morbidity.⁴ Unfortunately, the third
 4 criterion has never been confirmed, ie, randomised trials or meta-analyses have never
 5 established, for any antiviral intervention, that sustained virological response captures a
 6 beneficial effect on liver-related morbidity or mortality. We may therefore risk that the
 7 intervention causes a positive response on a virological response but has no beneficial
 8 effect or even harmful effect on clinical outcomes.

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18 Most of the included trials were partly or fully sponsored by for-profit organisations,
 19 which significantly influence research on hepatitis. These organisations endorse surrogate
 20 outcomes as they provide more events, the events appear faster, and are easier to assess.
 21 The trial process by using, eg, sustained virological response is thereby shortened,
 22 speeding up the implementation of antiviral interventions. However, currently the area of
 23 hepatitis C clinical research seems weakened with too many redundant small trials with
 24 short-term follow-up on potentially useless surrogate outcomes.

36 Conclusion

37 On one hand, too many trials in chronic hepatitis C have assessed the short-term putative
 38 surrogate outcome, sustained virological response. On the other hand, we lack sufficient
 39 data on long-term clinical outcomes from the trials. Despite sustained virological
 40 response is not a validated surrogate outcome, it seems difficult to conduct new trials on
 41 combination therapy versus interferon monotherapy assessing clinical outcomes.

42 Obtaining long-term clinical outcomes in patients from previous trial would be relevant

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2 but this is a logistically difficult, high dropout rates may exist, and retreatment may
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4 interfere. [This should be combined with the fact that the mechanism of ribavirin is still](#)
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6 [unclear](#). Accordingly, research on hepatitis C is in a dilemma. Trial sequential analysis of
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8 cumulative meta-analysis can help planning further clinical trials. In this example of
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10 antiviral treatment for hepatitis C, trial sequential analysis conducted before new trials
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12 were launched could have prevented many redundant trials. It may also have redirected
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14 trial design, leading to sufficient assessment of clinical outcomes.
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Figure 1. The PRISMA flowchart for the selection of publications for the systematic review and meta-analysis.

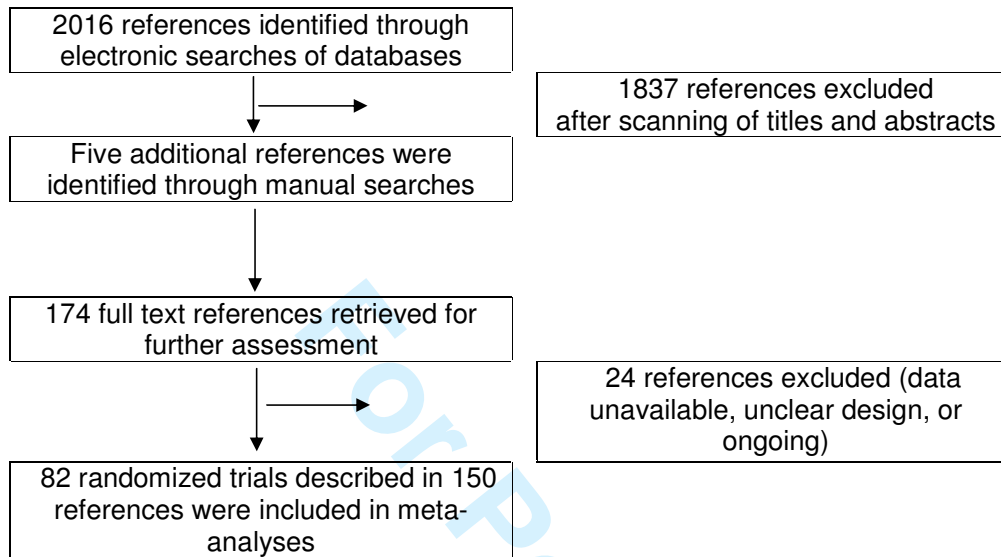
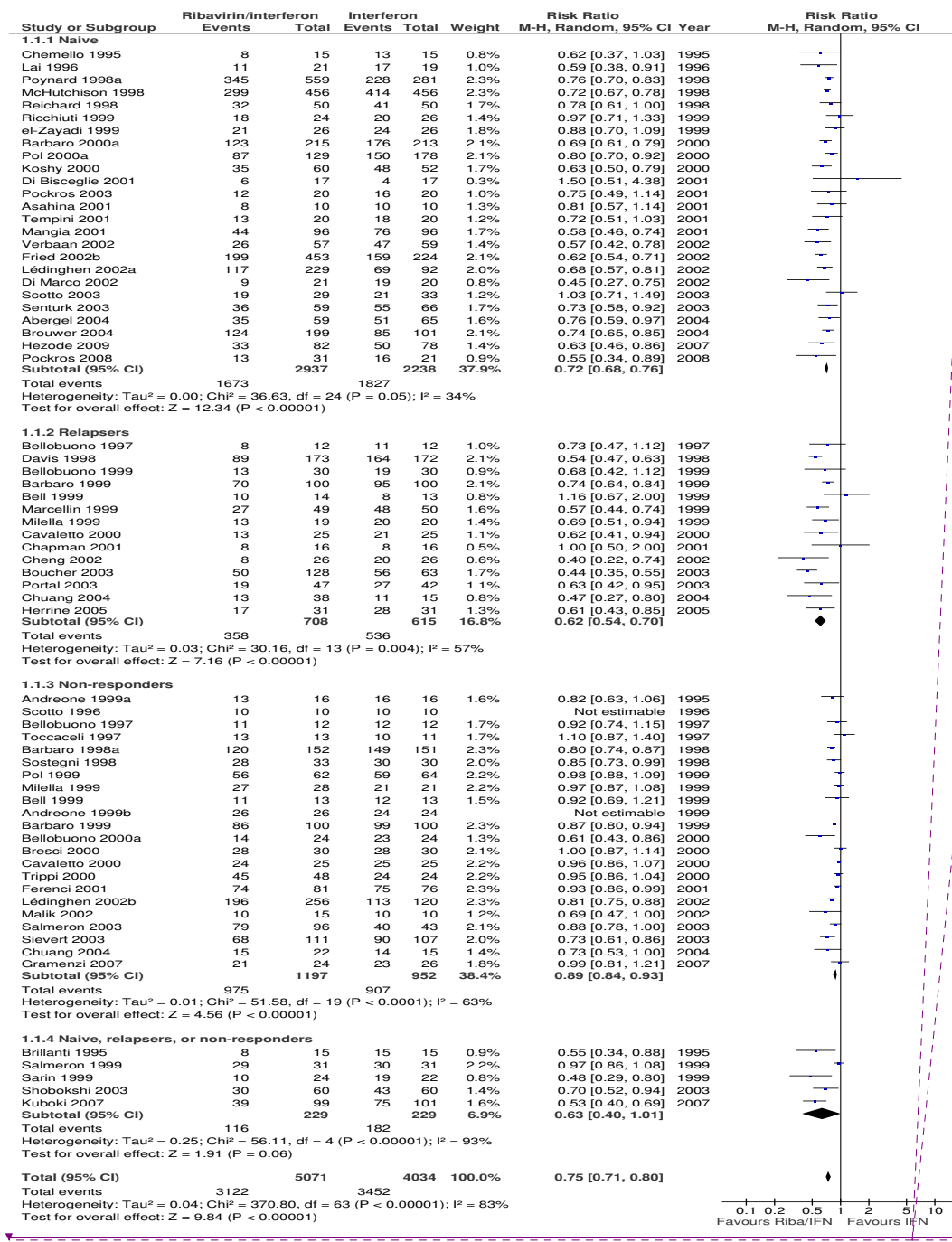


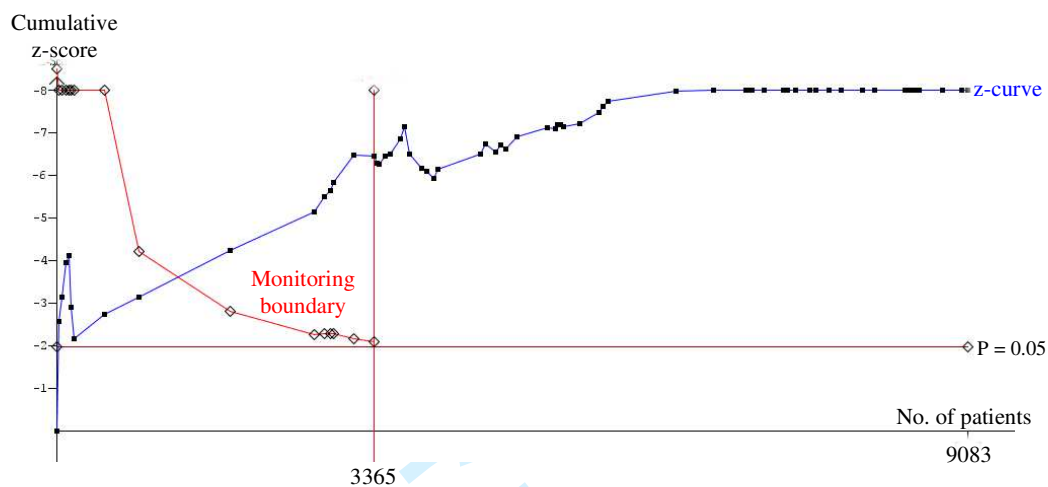
Figure 2. Meta-analysis of 59 randomised trials on ribavirin plus interferon versus interferon for chronic hepatitis C on sustained virological response. Subgroups according to response to previous antiviral therapy



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Study or Subgroup	Events	Total
1.1.1 Naive		
Chemello 1995	8	15
Lai 1996	11	21
Reichard 1998	29	456
Poynard 1998a	345	559
McHutchison 1998	299	456
el-Zayadi 1999	21	26
Ricchiuti 1999	18	24
Barbaro 2000a	123	215
Pol 2000a	87	129
Koshy 2000	35	60
Di Bisceglie 2001	6	17
Pockros 2003	12	20
Asahina 2001	8	10
Mangia 2001	44	96
Tempini 2001	13	20
Verbaan 2002	26	57
Fried 2002b	199	453
Lédinghen 2002a	117	229
Di Marco 2002	9	21
Scotto 2003	19	29
Senturk 2003	36	59
Abergel 2004	35	59
Brouwer 2004	124	199
Hezode 2009	33	82
Pockros 2008	13	31
Subtotal (95% CI)		
Total events	1695	2937
Heterogeneity: Tau ² = 0.01; Chi ² = 41.23, c		
Test for overall effect: Z = 11.94 (P < 0.0000)		
1.1.2 Relapsers		
Bellobuono 1997	8	12
Davis 1998	89	173
Barbaro 1999	70	100
Marcellin 1999	27	49
Bellobuono 1999	13	19
Milella 1999	13	25
Cavaletto 2000	13	25
Chapman 2001	8	16
Cheng 2002	8	26
Boucher 2003	50	128
Portal 2003	19	47
Chuang 2004	13	38
Boucher 2003	50	128
Chuang 2004	13	38
Subtotal (95% CI)		
Total events	341	708
Heterogeneity: Tau ² = 0.03; Chi ² = 30.19, c		
Test for overall effect: Z = 6.60 (P < 0.0000)		
1.1.3 Non-responders		
Andreone 1999a	13	16
Scotto 1996	10	10
Bellobuono 1997	11	12
Toccaelli 1997	13	13
Barbaro 1998a	120	152
Sostegni 1998	28	33
Pol 1999	56	62
Milella 1999	27	28
Bell 1999	11	13
Andreone 1999b	26	26
Barbaro 1999	86	100
Bellobuono 2000a	14	24
Bresci 2000	28	30
Cavaletto 2000	24	25
Trippi 2000	45	48
Ferenci 2001	74	81
Lédinghen 2002b	196	256
Malik 2002	10	15
Salmeron 2003	79	96
Sievert 2003	68	111
Chuang 2004	15	22
Gramenzi 2007	21	24
Subtotal (95% CI)		
Total events	975	1197
Heterogeneity: Tau ² = 0.01; Chi ² = 51.58, df = 19 (P < 0.0001); I ² = 63%		
Test for overall effect: Z = 4.56 (P < 0.00001)		
1.1.4 Naive, relapsers, and non-responders		
Brillanti 1995	8	15
Salmeron 1999	29	31
Sarin 1999	10	24
Shobokshi 2003	30	60
Kuboki 2007	39	99
Subtotal (95% CI)		
Total events	116	229
Heterogeneity: Tau ² = 0.25; Chi ² = 56.11, df = 4 (P < 0.00001); I ² = 93%		
Test for overall effect: Z = 1.91 (P = 0.06)		
Total (95% CI)		
Total events	3122	5071

Figure 3. Trial sequential analysis of 59 trials on ribavirin plus interferon versus interferon for chronic hepatitis C on sustained virological response



Trial sequential analysis of 59 trials (marked with black dots) illustrating that the cumulative z-curve crossed the monitoring boundary after nine trials, which is needed to obtain firm evidence adjusted for risk of multiplicity and random error. Subsequently 50 more trials have been published.

The information size is calculated to 3365 patients (vertical line) based on sustained virological response in the interferon monotherapy group of 15%, a relative risk reduction of 10% in the ribavirin plus interferon group, type 1 error of 5%, and type 2 error of 20%. The red line is the trial sequential monitoring boundary calculated accordingly. The horizontal line is the z-score of -1.96, equal to two-sided $P=0.05$. X-axis: the number of patients randomised, Y-axis: the z-score. The z-score is truncated at -8.0. The z-score obtained after 59 trials was $z=-10.9$, giving $P<0.00001$.

Figure 4. Trial sequential analysis of trials on ribavirin plus interferon versus interferon on serum sustained virological response in naive patients (4A), relapsers and non-responder patents (4B), genotype 1 (4C). on-genotype 1 (4D), cirrhotic patients (4E), and non-cirrhotic patients (4F). See fig. 3 for further explanation.

Fig 4A

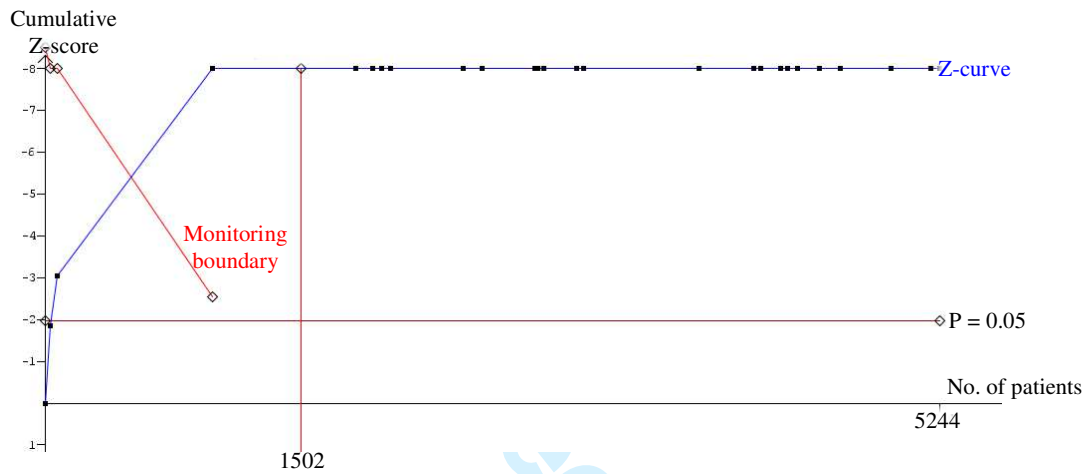


Fig. 4B

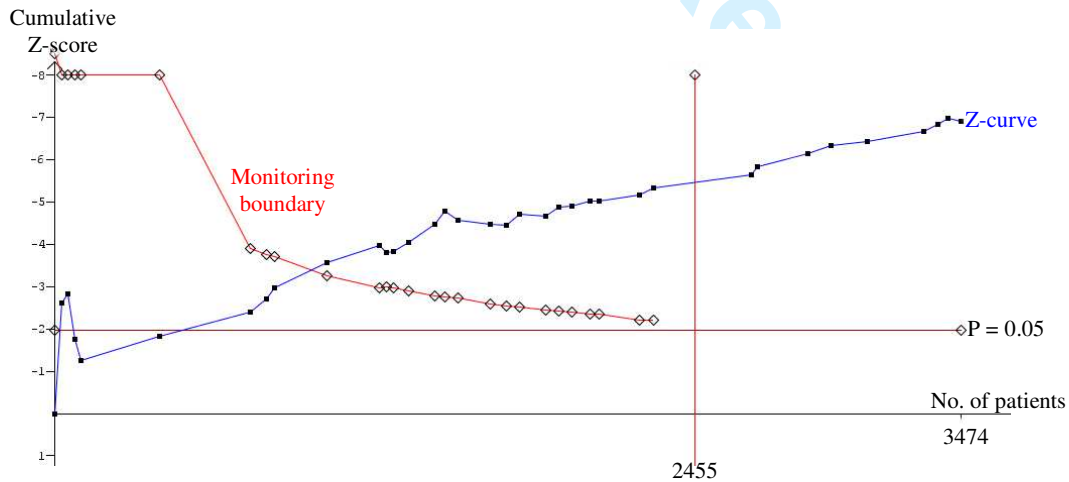


Fig. 4C

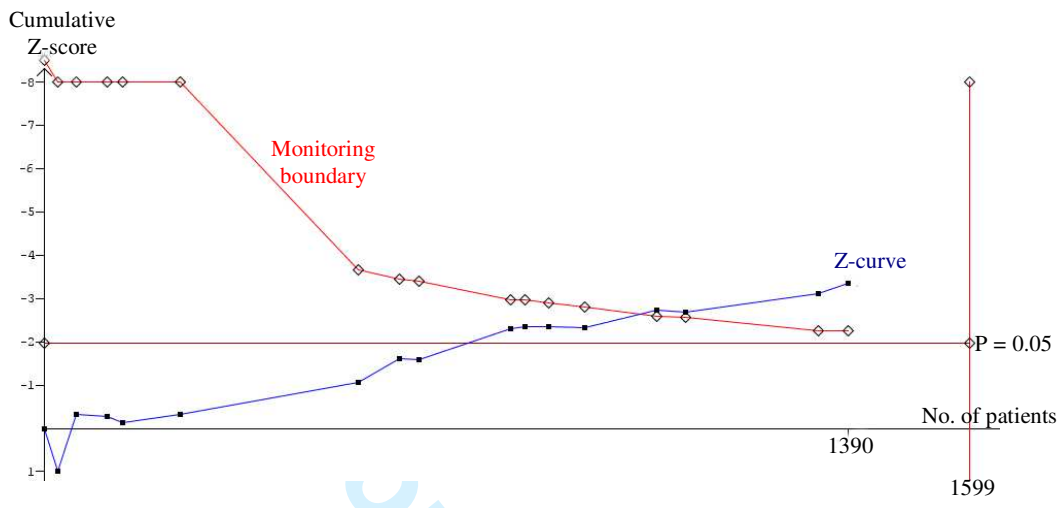


Fig. 4D

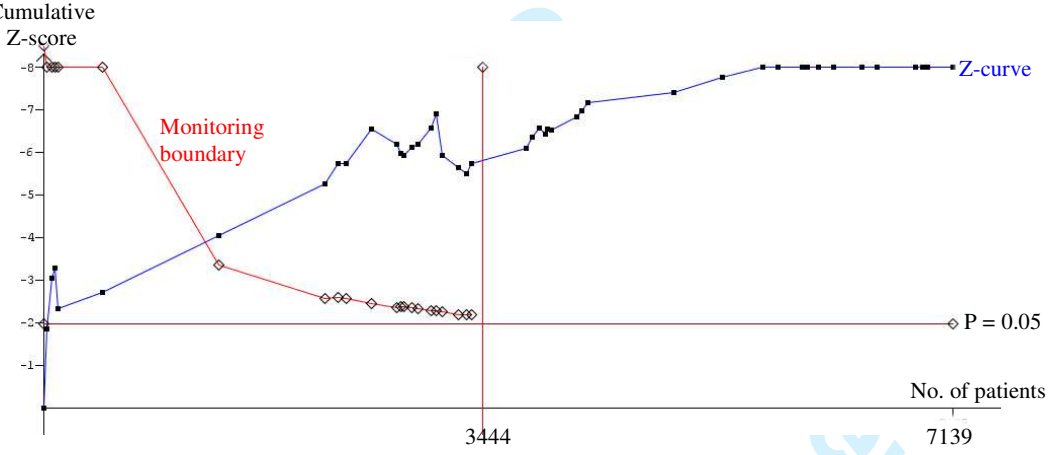


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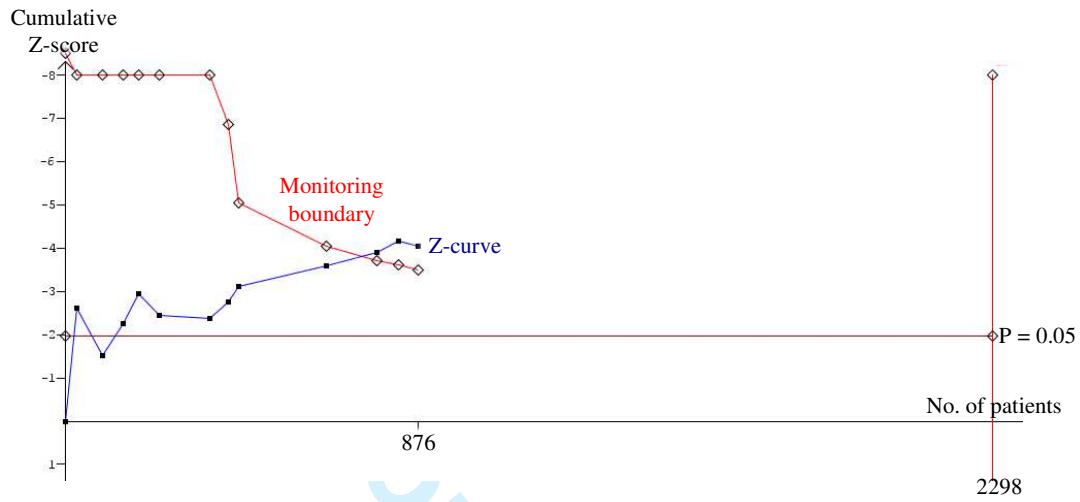
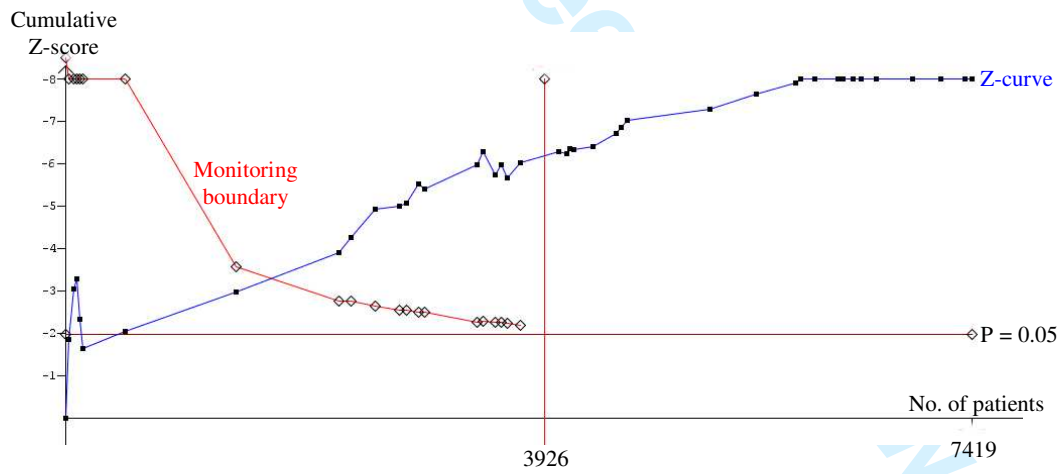


Fig. 4F



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Figure 5. Trial sequential analysis of trials on ribavirin plus interferon versus interferon on serum sustained virological response in trials using low dose ribavirin (5A). ‘standard’ dose ribavirin (5B). pegylated interferon (5C). non-pegylated interferon (5D).

Fig 5A.

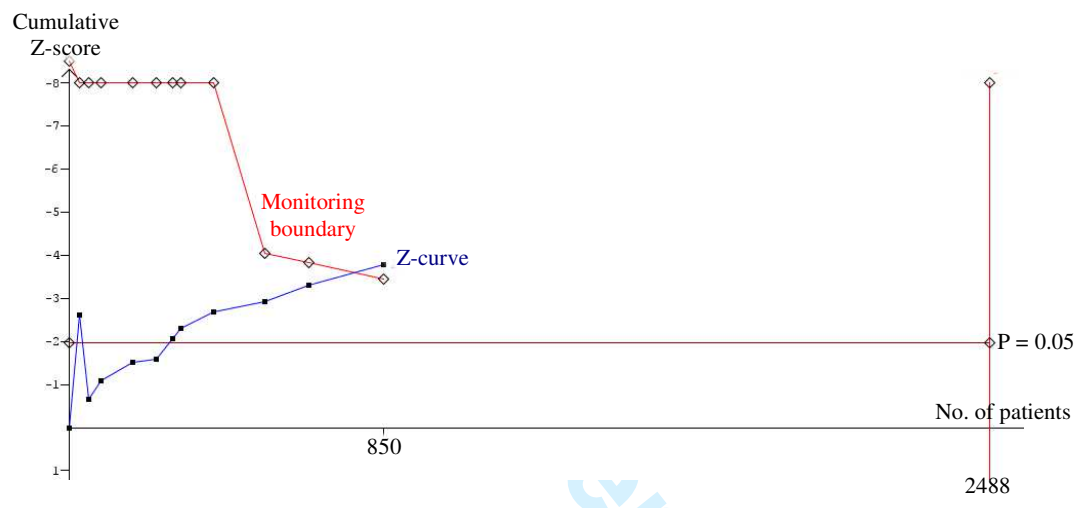


Fig. 5B

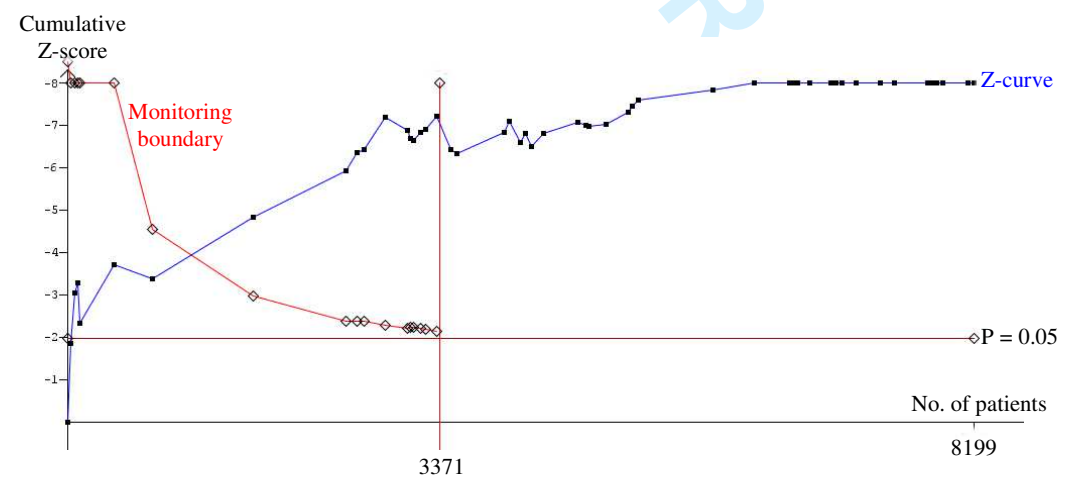


Fig. 5C

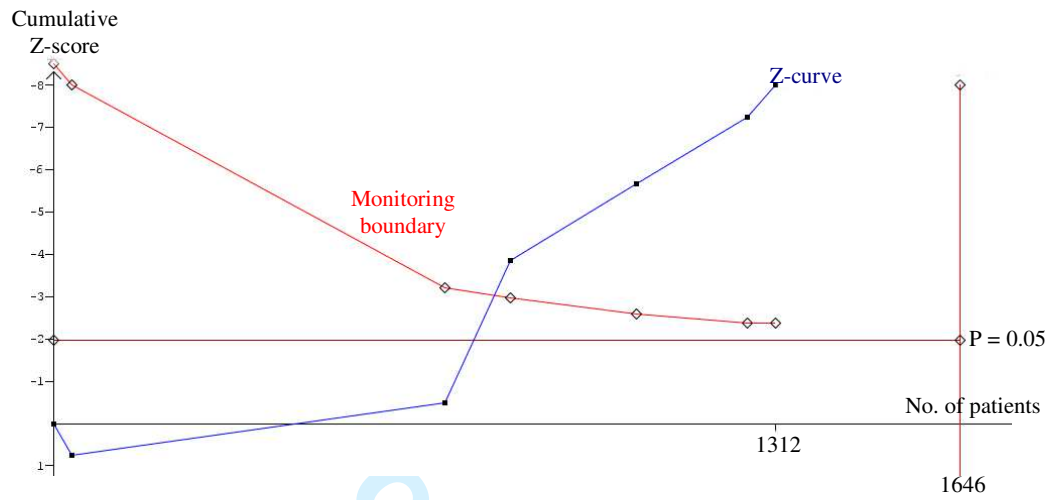


Fig. 5D

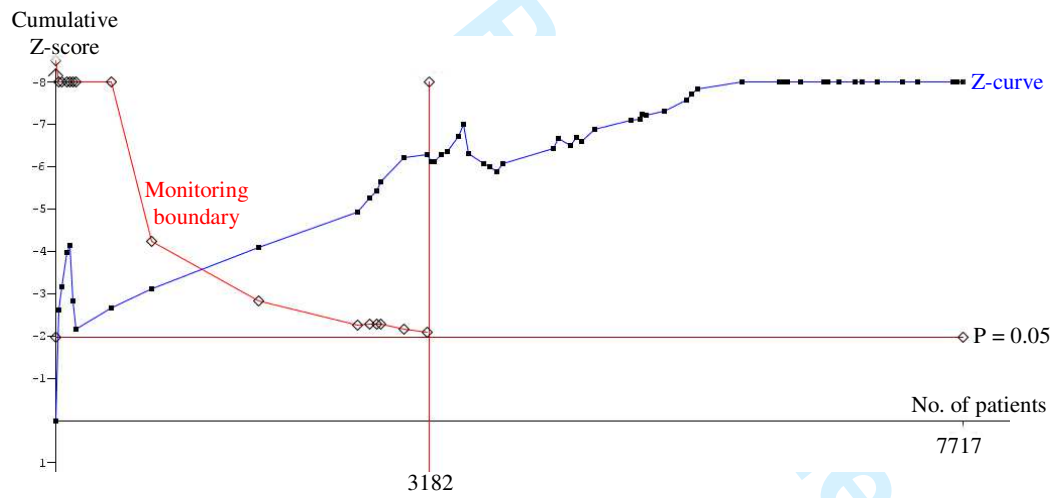
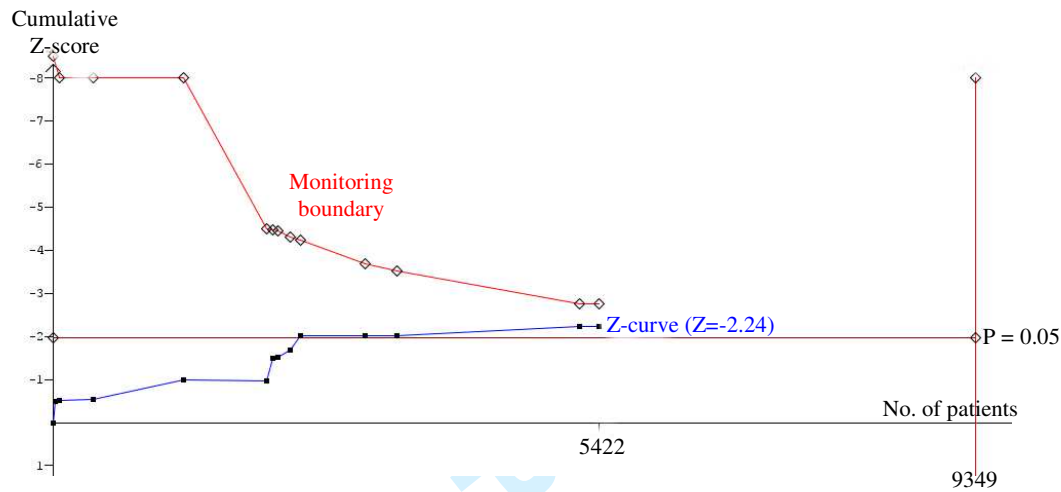


Figure 6. Trial sequential analysis of 13 trials on ribavirin plus interferon vs. interferon for chronic hepatitis C on the composite clinical outcome of liver-related morbidity or all-cause mortality.



Trial sequential analysis of 13 trials (marked with black dots) illustrating that the cumulative z-curve has not crossed the monitoring boundary or surpassed the information size. Thus, we need more evidence to detect (or reject) clinical effects of adding ribavirin to interferon. Additionally 3812 (9349 - 5422) patients are needed to detect this effect size.

The information size is calculated to 9349 (vertical line) based on a proportion of 1% with the composite outcome in the interferon monotherapy group, a relative risk reduction of 50% in the ribavirin plus interferon group, a type 1 error of 5%, and type 2 error of 20%. The red line is the trial sequential monitoring boundaries calculated accordingly. The horizontal line is the z-score of -1.96, equal to two-sided P=0.05. X-axis: the number of patients randomised. Y-axis: the z-score.

Competing interest

All authors declare that the answers to the questions on your competing interest form are all no and therefore have nothing to declare.

Contributors

JB, LLG, and CG conceived and designed the study. JB and LLG wrote to authors of papers for additional information. JB and LLG extracted and analyzed data. All authors drafted and revised the review. JB is guarantor.

Ethical approval and patient signed consent

Not required.

Funding

The Copenhagen Trial Unit, Center for Clinical Intervention Research. All authors worked independent of any funders.

Responsibility

All authors have full access to the data and take responsibility for the data analyses.

PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2-3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5-6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	5
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Additional table

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4	Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6
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9	Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	6
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13	Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	6
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19	Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6
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25	Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	6-8
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28	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	7-8
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34	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	6
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39	Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	7-8
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45	Results			
46	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	8
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52	Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	8-9
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57	Risk of bias	19	Present data on risk of bias of each study and,	10
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4	within studies	if available, any outcome-level assessment (see item 12).	
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7	Results of individual studies	20 For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	23
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13	Synthesis of results	21 Present results of each meta-analysis done, including confidence intervals and measures of consistency	9-10
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18	Risk of bias across studies	22 Present results of any assessment of risk of bias across studies (see item 15)	10
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21	Additional analysis	23 Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	9-10
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25	Discussion		
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27	Summary of evidence	24 Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	11 15-16
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33	Limitations	25 Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	11-12
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39	Conclusions	26 Provide a general interpretation of the results in the context of other evidence, and implications for future research	15
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43	Funding		
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45	Funding	27 Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	29
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Database	Search strategy	Search
The Cochrane Hepato-Biliary Group Controlled Trials Register	(ribavirin OR riba OR copegus OR rebetol OR ribasphere OR vilona OR virazole) AND (interferon OR IFN OR roferon* OR intron* OR multiferon* OR rebif* OR avonex OR cinnovex OR betaseron OR betaferon OR pegasys OR pegasus OR reiferon OR reliferon OR pegetron OR pegintron OR rebetron OR alferon OR infergen OR actimmune) AND ((chronic AND ('hepatitis C' OR 'hep C' OR HCV)) OR CHC)	Last search performed 06.03.09. 512 references were identified
The Cochrane Central Register of Controlled Trials in The Cochrane Library	#1 MeSH descriptor Ribavirin explode all trees 613 #2 ribavirin OR riba OR copegus OR rebetol OR ribasphere OR vilona OR virazole 1551 #3 (#1 OR #2) 1551 #4 MeSH descriptor Interferons explode all trees 3588 #5 interferon OR IFN OR roferon* OR intron* OR multiferon* OR rebif* OR avonex OR cinnovex OR beta?eron OR pegas?s OR reiferon OR reliferon OR peg*tron OR rebetron OR alferon OR infergen OR actimmune 7792 #6 (#4 OR #5) 7792 #7 MeSH descriptor Hepatitis C, Chronic explode all trees 840 #8 (chronic AND ('hepatitis C' OR 'hep C' OR HCV)) OR CHC 1393 #9 (#7 OR #8) 1701 #10 (#3 AND #6 AND #9) 766	Last search performed 06.03.09. 649 references were identified
MEDLINE (via OVID SP)	1. exp Ribavirin/ 2. (ribavirin or riba or copegus or rebetol or ribasphere or vilona or virazole).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 3. 1 or 2 4. exp Interferons/ 5. (interferon or IFN or roferon* or intron* or multiferon* or rebif* or avonex or cinnovex or beta?eron or pegas?s or	Last search performed 06.03.09. 613 references were identified

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title, abstract, name of substance word,
subject heading word]

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11. (random* or blind* or placebo* or meta-
analysis).mp. [mp=title, original title,
abstract, name of substance word, subject
heading word]

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EMBASE (via OVID SP)

1. exp Ribavirin/

2. (ribavirin or riba or copegus or rebetol or
ribasphere or vilona or virazole).mp.
[mp=title, abstract, subject headings,
heading word, drug trade name, original
title, device manufacturer, drug
manufacturer name]

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4. exp Interferon/

5. (interferon or IFN or roferon* or intron*
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cinnovex or beta?eron or pegas?s or
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HCV)) or CHC).mp. [mp=title, abstract,
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12. 11 and 10

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peg*tron OR rebetron OR alferon OR
infergen OR actimmune)
1 10,152 TS=(ribavirin OR riba OR
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List of included randomised trials

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