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CHBG NEWSLETTER

The Cochrane Hepato-Biliary Group (THE CHBG)

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The numbering is a continuation from Vol. 17, Issue 1, 2013.

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157. Percutaneous ethanol injection for liver metastases. Riemsma RP, Bala MM, Wolff R, Kleijnen J.
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162. Percutaneous cholecystostomy for high-risk surgical patients with acute calculous cholecystitis. Gurusamy KS, Rossi M, Davidson BR.

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57. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Gurusamy KS,

Davidson C, Gluud C, Davidson BR.
58. Early versus delayed laparoscopic cholecystectomy for uncomplicated biliary colic. Gurusamy KS, Koti R, Fusai G, Davidson BR.
59. T-tube drainage versus primary closure after laparoscopic common bile duct exploration. Gurusamy KS, Koti R, Davidson BR.
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61. Day-surgery versus overnight stay surgery for laparoscopic cholecystectomy. Vaughan J, Gurusamy KS, Davidson BR.
62. Abdominal lift for laparoscopic cholecystectomy. Gurusamy KS, Koti R, Davidson BR.
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64. Virtual reality training for surgical trainees in laparoscopic surgery. Nagendran M, Gurusamy KS, Aggarwal R, Loizidou M, Davidson BR.
65. Routine abdominal drainage versus no abdominal drainage for uncomplicated laparoscopic cholecystectomy. Gurusamy KS, Koti R, Davidson BR.
66. Surgical versus endoscopic treatment of bile duct stones. Dasari BVM, Tan CJ, Gurusamy KS, Martin DJ, Kirk G, McKie L, Diamond T, Taylor MA.

NEW AND UPDATED PROTOCOLS

259. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. Goossens N, Isgro G, Negro F.
260. Granulocyte-colony stimulating factor for acute liver failure or acute-on-chronic liver failure. Peng JC, Chang XM, Yang QM, Zhang LJ.
261. Isoprinosine versus other antiviral drugs for chronic hepatitis B. Njei B, Garg SK, Kenta-Bibi E, Kongnyuy EJ.
262. Laparoscopic surgical box model training for surgical trainees with limited prior laparoscopic experience. Gurusamy KS, Nagendran M, Davidson BR.
263. Laparoscopic surgical box model training for surgical trainees with no prior laparoscopic experience. Nagendran M, Toon CD, Davidson BR, Gurusamy KS.
264. Laparoscopic-endoscopic rendezvous versus preoperative endoscopic sphincterotomy for common bile duct stones in patients undergoing laparoscopic cholecystectomy. Vettoretto N, Arezzo A, Famiglietti F, Cirocchi R, Moja L, Morino M.
265. Anterior approach versus conventional liver resection for hepatocellular carcinoma. Wang Q, Zheng B, Ma B, Yang K.
266. Banding ligation versus beta-blockers for primary prophylaxis of oesophageal variceal bleeding in children. Gana JC, Cifuentes LI, Cerda J, Villarroel del Pino LA, Peña A, Rivera Cornejo M.
267. Transient elastography for diagnosis of hepatic fibrosis in people with alcoholic liver disease. Pavlov CS, Casazza G, Nikolova D, Ivashkin VT, Tsochatzis E, Burroughs AK, Gluud C.
268. Protease inhibitors in combination with pegylated interferon and ribavirin for adult patients with chronic hepatitis C virus. Yaseen AlSabbagh ME, Davitkov P, Falck-Ytter Y.
269. Transarterial (chemo)embolisation versus other nonsurgical ablation methods for liver metastases. Bala MM, Riemsma RP, Wolff R, Kleijnen J.
270. Methods to decrease blood loss during liver resection: a network meta-analysis. Simillis C, Li T, Vaughan J, Becker LA, Davidson BR, Gurusamy KS.

NEW REGISTERED TITLES

449. Transjugular intrahepatic portosystemic shunts for hepatorenal syndrome. Hinojosa Azaola A, Salas Nolasco OI, Gonzalez Garay AG, Chavez-Tapia NC, Solis Galicia C.
450. External beam radiotherapy for unresectable hepatocellular carcinoma. Abdel-Rahman OM, Elsayed Z.
451. Gemcitabine for advanced hepatobiliary carcinomas. Abdel-Rahman OM, Elsayed Z
452. Radioembolisation for unresectable hepatocellular carcinoma. Abdel-Rahman OM, Elsayed Z.
453. Rifaximin for hepatic encephalopathy. Kimer N, Krag A, Bendtsen F, Gluud LL, Møller S.
454. Medical interventions for hepatic encephalopathy: a network meta-analysis. Thiele M, Gluud LL.
455. Medical interventions for alcoholic hepatitis: a

network meta-analysis. Gluud LL, Thiele M.
456. Interventions for primary and secondary variceal bleeding prophylaxis: a network meta-analysis. Gluud LL, Thiele M.

PAST EVENTS

CHBG EXHIBITION STAND DURING THE 48TH ANNUAL EASL MEETING, AMSTERDAM, THE NETHERLANDS. APRIL 24 TO APRIL 28, 2013

We thank all people who stopped by The CHBG booth and inquired about the Group's work. We also thank authors of systematic reviews whose reviews were shown as slide presentations at the booth.

EVIDENCE-BASED CLINICAL PRACTICE WORKSHOP "THE ARCHITECTURE OF DIAGNOSTIC RESAERCH AND CLINICAL REASONING"

The workshop that was planned for September 29 to October 2, 2013 at "Palazzo Feltrinelli", Gargnano, Lago di Garda, Italy, had to be cancelled. However, a new one is planned in October 2014. If you are interested in attending it, please send us an e-mail and we will get you in touch with the organizers.

21ST COCHRANE COLLOQUIUM. QUÈBEC CITY, CANADA. SEPTEMBER 19 TO 23, 2013

This year's theme of the colloquium was "Better Knowledge for Better Health". The schedule included five days of meetings and workshops, along with a full program of scientific sessions. Videos from principal Colloquium sessions and events are available on The Cochrane Collaboration's YouTube channel and in the Multimedia section at cochrane.org. This year's colloquium offered us the opportunity to celebrate the 20th anniversary of The Cochrane Collaboration together with colleagues across the Collaboration.

FUTURE EVENTS

CHBG EXHIBITION STAND DURING THE 64TH ANNUAL AASLD MEETING, WASHINGTON, DC, USA. NOVEMBER 1 TO NOVEMBER 5, 2012

The CHBG booth number is 122. We will be happy to greet and have a chat with anyone stopping by. We will be happy to answer your questions, hear about your professional interest in The CHBG, know about your impression of the work we have been doing and the protocols and materials we publish. We will gladly tell you about our achievements, challenges, and why we need more people like you.

33RD CHBG MEETING DURING THE 64TH ANNUAL AASLD MEETING, WASHINGTON, DC, USA. NOVEMBER 3, 2013

The 33rd biannual CHBG meeting will be held at the Renaissance Washington DC Downtown Hotel 999, 9th Street NW. It is across the street from the Walter E. Washington Convention Center. The room number you have to go to is 10&11. The meeting time is 7:00pm to 8:30pm. Should you forget this information, look for information on the electronic reader boards located in the main lobby, the Meeting Room Level (where the event will take place) and the Ballroom Level. There is no attendance fee. The program for the CHBG meeting is distributed with this CHBG Newsletter, and you will also find it on The CHBG website <hbg.cochrane.org>.
We will be happy to see as many as possible.

VISITORS

Chavdar Pavlov from Russia visited the CHBG Editorial Team Office from 20 to 28 of May. Chavdar continued his work on the 'Transient elastography for diagnosis of hepatic fibrosis in people with alcoholic liver disease' review.

Goran Bjelakovic from Serbia visited the CHBG Editorial Team Office from 28 of April to 3 of June. Goran worked on the update of published systematic reviews as well as on a new review on vitamin D and mortality.

Arturo Martí-Carvajal from Venezuela visited the CHBG Editorial Team Office from 14 June to 13 July. Arturo worked on Cochrane systematic reviews.

NEWS

The CHBG new website [hbg.cochrane.org] was visited by 658 visitors since mid April until October 9, 2013.

The unique visitors were 431 people, coming from 59 countries around the world. We do hope that all users find the information on the website useful. We welcome comments and ideas for improvement.

FOR NEW OR CURRENT AUTHORS OF PROTOCOLS UNDER DEVELOPMENT

METHODS USED IN REVIEWS

The following text contains the CHBG recommendations to authors of protocols for systematic reviews (See: hbg.cochrane.org)

Outcomes
The CHBG works on standardisation of hepato-biliary outcomes in CHBG review protocols based on the disease condition reviewed. We do already have a standardised set of outcomes for hepatitis B and C. Suggestions for standardised outcomes in other diseases are most welcome.

In general, selection of outcomes in review protocols and their listing shall follow the Guidelines of The Cochrane Handbook for Systematic Reviews of Interventions.1 In the Handbook, on p.88 to p.90 you will read:

''5.4.2 Prioritizing outcomes: main, primary and secondary outcomes

Main outcomes
Once a full list of relevant outcomes has been compiled for the review, authors should prioritize the outcomes and select the main outcomes of relevance to the review question. The main outcomes are the essential outcomes for decision-making, and are those that would form the basis of a 'Summary of findings' table. 'Summary of findings' tables provide key information about the amount of evidence for important comparisons and outcomes, the quality of the evidence and the magnitude of effect (see Chapter 11, Section 11.5). There should be no more than seven main outcomes, which should generally not include surrogate or interim outcomes. They should not be chosen on the basis of any anticipated or observed magnitude of effect, or because they are likely to have been addressed in the studies to be reviewed.

Primary outcomes
Primary outcomes for the review should be identified from among the main outcomes. Primary outcomes are the outcomes that would be expected to be analysed should the review identify relevant studies, and conclusions about the effects of the interventions under review will be based largely on these outcomes. There should in general be no more than three primary outcomes, and they should include at least one desirable and at least one undesirable outcome (to assess beneficial and adverse effects respectively).

Secondary outcomes
Main outcomes not selected as primary outcomes would be expected to be listed as secondary outcomes. In addition, secondary outcomes may include a limited number of additional outcomes the review intends to address. These may be specific to only some comparisons in the review.

For example, laboratory tests and other surrogate measures may not be considered as main outcomes as they are less important than clinical endpoints in informing decisions, but they may be helpful in explaining effect or determining intervention integrity (see Chapter 7, Section 7.3.4).

Box 5.4.a summarizes the principal factors to consider when developing criteria for the 'Types of outcomes'.'' (end of citation)

2. Review protocol outcomes should include clinical outcomes no matter the clinical outcomes reported in the trials one is going to include in the review. Trial culture shall never be the culture of systematic reviews, as most trialists, for example, select ten to fifteen outcomes but report only on a selected few.

3. Mortality should stand alone, and it should be the first primary outcome.

4. Morbidity from the disease could be the second primary outcome.

5. Adverse events should be included as a primary outcome unless the review topic or title formulation precludes the occurrence of an adverse event.

6. Quality of life, even that it is seldom reported, should be included as a primary outcome or as one of the secondary outcomes.

7. Surrogate outcomes (especially non-validated ones) should be included only as secondary outcomes.

8. Health economics. This outcome should preferably be the subject of a separate review, see Chapter 15 in the Handbook.

9. Composite outcomes. If trial authors have failed in reporting the separate components of composite outcomes in separate, it is up to the judgement of the review authors if they would meta-analyse them together or not."

The CHBG continues working on defining fixed outcomes depending on the review topic, eg, as we have already done with interventions for chronic hepatitis B or chronic hepatitis C. In addition to better understanding of the reviews' outcomes by patients, physicians, and other users, authors will also be helped in the preparation of overview of reviews and when designing 'Summary of findings' tables in the intervention reviews, as data for the same meaningful outcomes are expected to be found across reviews.

Study selection

The CHBG recommends inclusion of randomised clinical trials for assessment of benefits and harms of interventions. As adverse events may not be caught in small or even large randomised clinical trials, The CHBG encourages also the inclusion of quasi-randomised studies, cohort studies, and case-control studies when dealing with reports of harmful effects of interventions. Evidence on harm from non-randomised studies shall not be combined with evidence on harms from randomised trials in meta-analyses. The CHBG does not recommend extensive searches for non-randomised studies, as our knowledge on how to do this best is limited. However, we appeal to review authors to consider adverse events from both randomised clinical trials and non-randomised studies, the latter usually identified through the searchers for randomised trials.

Authors must follow the guidelines in Chapter 14 of the The Cochrane Handbook for Systematic Reviews of Interventions about adverse events. Two authors should generally perform the selection of studies and data extraction independently. Therefore, the Editorial Team encourages at least two authors to work on a systematic review.

Assessment of risk of bias in randomised trials

The bias risks of the randomised trials included in the reviews is assessed separately and independently by authors of the review using the assessment criteria defined in the protocol. This should follow the The Cochrane Handbook for Systematic Reviews of Interventions. Eventual differences in the bias risk of trials are resolved by discussion in order to reach consensus.

Methodological studies indicate that trials with unclear or inadequate methodological quality may be associated with risk of bias (systematic error) when compared to trials using adequate methodology.[1-14] Such bias may lead to overestimation of intervention benefits and underestimation of harms.

There is evidence that trials with adequate randomisation (both sequence generation and allocation concealment), blinding, and follow-up generate the most valid results. Unfortunately, such trials are often not available for meta-analyses. Of 370 drug trials, 28% reported adequate generation of the allocation sequence, 22% reported adequate allocation concealment, and 63% were double blind.[7] Accordingly, only 4% were adequate regarding all components.[7] Subgroup analyses and meta-regression analyses are, therefore, important to evaluate the influence of risk of bias on the results.

Based on the recommendations in the The Cochrane Handbook for Systematic Reviews of Interventions and methodological studies[2-4;6], we suggest that authors of systematic reviews use the below definitions in the assessment of bias risk of a trial.

Please note that specific circumstances may sometimes necessitate changes in the definitions or the use of additional risk of bias domains.

We suggest that authors perform overall assessment of the bias risk of trials irrespective of outcome as well as according to outcome. The latter can be displayed in Summary of Findings tables.

Domains for bias risk assessment

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

*Blinding of participants, personnel, and outcome assessors**

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
- Uncertain risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding.

*The CHBG does not request authors to assess blinding at an outcome level. However, trials can be assessed for bias risk according to who was blinded in the trial.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, has been employed to handle missing data.
- Uncertain risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all outcomes were pre-defined and reported, or all clinically relevant and reasonably expected outcomes were reported.
- Uncertain risk of bias: it is unclear whether all pre-defined and clinically relevant and reasonably expected outcomes were reported.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported, and data on these outcomes were likely to have been recorded.

For a trial to be assessed with low risk of bias in the selective outcome reporting domain, the trial should have been registered either on the www.clinicaltrials.gov website or a similar register, or there should be a protocol, eg, published in a paper

journal. In the case when the trial was run and published in the years when trial registration was not required, the review authors are expected to carefully scrutinize all publications reporting on the trial to identify the trial objectives and outcomes. If usable data on all outcomes specified in the trial objectives are provided in the publications results section, then the trial can be considered low risk of bias trial in the *Selective outcome reporting* domain.

For-profit bias
- Low risk of bias: the trial appears to be free of industry sponsorship or other kind of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Uncertain risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship is provided.
- High risk of bias: the trial is sponsored by the industry or has received other kind of for-profit support.

*Other bias**
- Low risk of bias: the trial appears to be free of other components (for example, academic bias) that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias (for example, authors have conducted trials on the same topic, etc).

*Authors should think what other bias in addition to the above defined biases may be relevant for their review, and if other bias specific to their review question is identified, then authors should report on it, adapting the text in the above pattern.

Authors should also consider design issues, eg, the administration of inappropriate treatment being given to the controls such as suboptimal dosage of medication or a supraoptimal dosage of medication that may bias a comparison.

The domains 'baseline imbalance' and 'early stopping of trials' shall not be routinely judged when assessing the risk of bias in an included trial of a systematic review. The argumentation for not considering baseline imbalance is that this imbalance may occur due to random error ('play of chance'), and that such a random error is likely to be levelled out by conducting a meta-analysis of several trials. The argumentation for not considering early stopping is that such trials - although they are likely to overestimate intervention effects - are counterbalanced by trials finding no significant difference.

Trials assessed as having 'low risk of bias' in all of the specified in the review individual domains shall usually be considered 'trials with low risk of bias'[1-14]. Trials assessed as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified in the review individual domains shall be considered trials with 'high risk of bias'[1-14].

In a large number of reviews, such optimal division of trials may not be possible, simply due to the fact that there are no or there are very few trials with low risk of bias. If review authors have a suspicion that this may be so, they should try to formulate alternative ways of defining trials with 'lower risk of bias' based on fewer domains. Such definitions should preferably be considered at the protocol stage, that is, well before embarking on data extraction and analyses.

However, when drawing conclusions, it has to be remembered that no or only few trials with low risk of bias existed. Hence, the chance to know the 'true' intervention effect is low or absent.

Data collection
Generally, two or more authors should extract data independently regarding inclusion criteria (design, participants, interventions, and outcomes), criteria for risk of bias, and results. When data are missing in a published report, authors should contact the corresponding author of the trial report. Collection of data from unpublished studies must be performed by writing to authors of previously published studies as well as the industry or manufacturers of the

intervention. Any substantial piece of information regarding unpublished data should be entered as a reference. For the correct type of the reference, please see The Cochrane Style Guide.

Analysis

Statistical methods of RevMan Analyses are used for analysing the data. All analyses should include an analysis according to the intention-to-treat method. We urge authors of systematic reviewers to follow the instructions in The Cochrane Handbook for Systematic Reviews of Interventions regarding statistical analyses. Sensitivity analyses may be performed. Furthermore, the short instructions below can assist in writing the statistical methods section in your review.

How to write the 'Statistical methods' section in Cochrane reviews on interventions

Before you start writing the 'statistical methods' section in a protocol for a Cochrane review, you need to consider thoroughly which methods would be most appropriate with regard to your specific question. You should consult The Cochrane Handbook[1] where you will find a thorough presentation of most of the statistical methods used in meta-analysis. Overall, the writing of 'statistical methods' in a review is not fixed and should be changed according to the need and characteristics of every unique systematic review. Below, you will find a very brief introduction on how to prepare the 'statistical methods' section including some examples. You need to specify the main software used in the review. This is of usually The Review Manager (RevMan): 'We will use the software package RevMan 5 provided by The Cochrane Collaboration (Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.).' Any additional software could also be mentioned here. You should specify the summary statistics for the kind of data you plan to analyse in your review (eg, relative risk for dichotomous data and mean difference for continuous data). The CHBG recommends applying both a fixed- and random-effects model meta-analyses. In case of discrepancies, both results are reported, otherwise only one of the results is reported. An example of wording could be: 'For dichotomous variables, we will calculate the relative risks with 95% confidence interval. We will use a random-effects model[15] and a fixed-effect model[16] meta-analyses. In case of discrepancy between the two models (eg, one giving a significant intervention effect, the other no significant intervention effect) we will report both results; otherwise, we will report only the results from one of the meta-analyses models.'

Heterogeneity between trials should always be explored by considering the bias risk of trials including domains (see above) and design, clinical setting, patients involved, the interventions, etc. Subgroup analyses, sensitivity analyses, or meta-regression may be appropriate. It is important to define the subgroup analyses at the protocol stage and follow them in the review stage. (If you need to do post hoc subgroup analyses, you should specify the reason sufficiently in the review and interpret the results with great caution.)

An example of wording:

'The chi-squared test for heterogeneity was used to provide an indication of between-trial heterogeneity. In addition, the degree of heterogeneity observed in the results was quantified using the I-squared statistic[17], which can be interpreted as the percentage of variation observed between the trials attributable to between-trial differences rather than sampling error (chance). We will perform a subgroup analysis in order to compare the intervention effect in trials with low risk of bias (see above) to that of trials with unclear or high risk of bias (ie, trials that lack one or more adequate domain).[2-4,10]'

It is difficult to handle trials with missing data (drop-outs/withdrawals).[18] We recommend that you always seek to perform intention-to-treat analysis. You can include missing data by considering them as treatment failures or treatment successes. Furthermore, you could do extreme case analyses where you consider the drop-outs as failures or successes in the experimental group and as successes

or failures in the control group. You need to consider what would be the most appropriate assumption for your specific review.

An example of wording of each of the situations mentioned above is:

Intention-to-treat analyses
Regarding the primary outcomes, we will include patients with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios.[18]

- Poor outcome analysis: assuming that drop-outs/participants lost from both the experimental and the control arms experienced the outcome, including all randomised participants in the denominator.
- Good outcome analysis: assuming that none of the drop-outs/participants lost from the experimental and the control arms experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the experimental intervention ('best-worse' case scenario: none of the drop-outs/participants lost from the experimental arm, but all of the drop-outs/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the control ('worst-best' case scenario): all drop-outs/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.

Per protocol analyses
Interpretation of per protocol analyses should be cautious as they may be biased.

Cross-over trials
We recommend to those who want to include cross-over trials in their systematic reviews to consider using the analytical methods described by Elbourne et al 2002[19] as well as The Cochrane Handbook.[1]

Visual inspection and analysis of bias
Publication bias and other biases can be explored by visual estimation of funnel plots and different statistical methods. The results of these methods vary with the magnitude of the treatment effect, the distribution of trial size, and whether a one- or two-tailed test is used.[20] Therefore, several methods should be explored. We can briefly describe the plans as follows:

"Funnel plot of the primary outcome will be used to provide a visual assessment of whether treatment estimates are associated with study size. We will use two tests to assess funnel plot asymmetry, adjusted rank correlation test,[21] and regression asymmetry test.[22]"

Risks of random errors
When few and small trials are combined in meta-analyses, the risk of introducing random errors increase due to sparse data and due to multiplicity when conducting cumulative meta-analyses with repeating analyses of the same data.[26,27]
The CHBG, therefore, advises review authors to employ trial sequential analyses of their important meta-analyses. [26-30]

An example of a text in a protocol can be:

'Trial sequential analysis
Trial sequential analysis will be applied as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data.[26] To minimise random errors, we will calculate the required information size (ie, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect).[26]
The required information size calculation should also account for the heterogeneity or diversity present in the meta-analysis.[26,30] In our meta-analysis, the required information size will be based on the event proportion in the control group; assumption of a plausible RR reduction of 20% on the RR reduction observed in the included trials with low risk of bias; a risk of type I error of 5%; a risk of type II error of 20%; and the assumed diversity of the meta-analysis.[30]
The underlying assumption of trial sequential analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We will

add the trials according to the year of publication, and if more than one trial has been published in a year, trials will be added alphabetically according to the last name of the first author. On the basis of the required information size, trial sequential monitoring boundaries will be constructed.[26,31] These boundaries will determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size; if the trial sequential monitoring boundary is crossed before the required information size is reached, firm evidence may perhaps be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential boundaries.'

One may access the Trial sequential analysis software application at www.ctu.dk/tsa.

Reporting of reviews

For policies on the reporting of reviews (for example on the discussion of results, the use of tables and figures, and the naming of studies), authors must follow the recommendations of The Cochrane Handbook for Systematic Reviews of Interventions.

The Cochrane Collaboration's training page for authors is a good source of information and developing skills.

References

1. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.
2. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.
3. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609-13.
4. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of Internal Medicine 2001;135:982-9.
5. Jüni P, Altman D, Egger M. Assessing the quality of controlled clinical trials. BMJ (Clinical Research Ed.) 2001;323:42-6.
6. Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technology Assessment 2003;7:1-76.
7. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events. JAMA 2003;290:921-8.
8. Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. The Cochrane Database of Methodology Reviews 2002, Issue 4. Art. No.: MR000012. DOI: 10.1002/14651858.MR000012.
9. Kjaergard LL, Liu JP, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. JAMA 2003;289:217-22.
10. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ (Clinical Research Ed.) 2008;336(7644):601-5.
11. Gluud LL, Thorlund K, Gluud C, Woods L, Harris R, Sterne JA. Correction: reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of Internal Medicine 2008;149(3):219.
12. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J et.al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Annals of Internal Medicine 2012;157:429-38.
13. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, Als-Nielsen B, Balk EM, Gluud C, Gluud LL, A Ioannidis JP, Schulz KF, Beynon R, Welton NJ, Wood L, Moher D, Deeks JJ, Sterne JA. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Health Technology Assessment 2012;16(35):1-82.
14. Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: MR000033. DOI: 10.1002/14651858.MR000033.pub2.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7(3):177-88.
16. DeMets DL. Methods of combining randomized clinical trials: strengths and limitations. Statistics in Medicine 1987;6(3):341-50.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research Ed.) 2003;327:557-60.

18. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ (Clinical Research Ed.) 1999;319:670-4.
19. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International Journal of Epidemiology 2002;31:140-9.
20. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Statistics in Medicine 2001:20:641-54.
21. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:(4):1088-101.
22. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. BMJ (Clinical Research Ed.) 1997;315(7109):629-34.
23. Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technology Assessment 2003;7:1-76.
24. Kjaergard LL, Liu JP, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. JAMA 2003;289:217-22.
25. Gluud LL, Thorlund K, Gluud C, Woods L, Harris R, Sterne JA. Correction: reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of Internal Medicine 2008;149(3):219.
26. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of Clinical Epidemiology 2008;61:64-75. 27. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses.Journal of Clinical Epidemiology. 2008. DOI:10.1016/j.jclinepi.2007.10.007.
28. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. International Journal of Epidemiology. 2009;38(1):287-98.
29. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, Gluud LL, Als-Nielsen B, Gluud C. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? International Journal of Epidemiology. 2009;38(1):276-86.
30. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Medical Research Methodology 2009;9:86.
31. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark. 2011;1-115. Available from www.ctu.dk/tsa.

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THE COCHRANE HEPATO-BILIARY GROUP

MEETING PROGRAMME

THE CHBG

The 33rd biannual Cochrane Hepato-Biliary meeting will take place November 3, 2013, from 7:00pm to 8:30pm in room number 10&11 at the Renaissance Washington DC Downtown Hotel 999, 9th Street NW (across the street from the Walter E. Washington Convention Center).

Attendance is free.

Chair: Christian Gluud, DK

7:00pm to 7:05pm	Welcome and program introduction	C Gluud (DK)
7:05pm to 7:25pm	Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. A Cochrane Hepato-Biliary Group systematic review.	RL Koretz (USA), M Pleguezuelo (ES), V Arvaniti (GR), P Barrera Baena (ES), R Ciria (ES), KS Gurusamy (UK), BR Davidson (UK), AK Burroughs (UK).
7:25pm to 7:45pm	Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C. A Cochrane Hepato-Biliary Group systematic review.	G Hauser (HR), T Awad (DK), J Brok (DK), K Thorlund (USA), D Štimac (HR), M Mabrouk (EG), C Gluud (DK), LL Gluud (DK).
7:45pm to 8:05pm	Is sustained virological response in patients with chronic hepatitis C a validated surrogate outcome?	C Gluud (DK), KS Gurusamy (UK).
8:05pm to 8:25pm	Multiple-treatments for alcoholic hepatitis: a network meta-analysis. A Cochrane Hepato-Biliary Group systematic review.	M Thiele (DK), C Del Giovane (I), G Askgaard (DK), A Krag (DK), LL Gluud (DK).
8:25pm to 8:30pm	Discussion and any other business.	