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CHBG NEWSLETTER

The Cochrane Hepato-Biliary Group (THE CHBG)

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The numbering is a continuation from Vol. 16, Issue 2, 2012.

PUBLICATIONS IN THE COCHRANE LIBRARY (THE CLIB). ISSUE 10 OF 2012 TO ISSUE 3 OF 2013

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153. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. Koretz RL, Pleguezuelo M, Arvaniti V, Barrera Baena P, Ciria R, Gurusamy KS, Davidson BR, Burroughs AK.

UPDATED REVIEWS

55. Ursodeoxycholic acid for primary biliary cirrhosis. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C.

NEW AND UPDATED PROTOCOLS

253. Antibiotic prophylaxis for surgical site infection in patients undergoing liver transplantation. Almeida RAMB, Hasimoto CN, Hasimoto EN, El Dib RP.
254. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in patients with portal hypertension. Castellanos ER, Seron P, Gisbert JP, Bonfill Cosp X.
255. Hepatitis B immune globulin for preventing hepatitis B recurrence after liver transplantation. Berdichevski T, Kumar S, Katz LH.
256. Laparoscopic versus open liver resection for benign and malignant hepatic lesions in adults. Rao AM, Ahmed I.
257. Microwave coagulation for liver metastases. Bala MM, Riemsma RP, Wolff R, Kleijnen J.
258. Tests for diagnosis of common bile duct stones. Giljaca V, Gurusamy KS, Vaughan J, Stimac D, Davidson BR.

NEW REGISTERED TITLES

442. Glucerol phenylbutyrate for hepatic encephalopathy. Gluud LL, Thiele M.

443. Stem cell transplantation for chronic liver disease. Zhang K, Li H.
444. Banding ligation and medical interventions alone or combined for secondary prevention in adult patients with oesophageal varices. Thiele M, Gluud LL.
445. Continued lamivudine for lamivudine-resistant chronic hepatitis B adult patients. Mok S, Mohan S.
446. Multi-drug interventions excluding lamivudine for lamivudine-resistant chronic hepatitis B adult patients. Mok S, Mohan S.
447. Multi-drug interventions including lamivudine for lamivudine-resistant chronic hepatitis B adult patients. Mok S, Mohan S.
448. Antifibrinolytics for prophylaxis of variceal haemorrhage in aduts with chronic liver disease. Tibbatts C, Doree C, Jairath V.

DIAGNOSTIC TEST ACCURACY REVIEWS (DTAR) AND CURRENT TITLES

As a result of several telephone conferences, a decision was made that the CHBG shall no longer accept title proposals for DTARs if the titles are too broad and cover different kind of tests as well as diseases with different aetiologies. Instead, people interested in working on a DTAR should follow the formats for title, suggested in The Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Please see **Chapter 4.2.1 of the Handbook:**

"1) [index test 1] versus [index test 2] for [target condition(s)] in [description of participants]
2) [index test 1] versus [index test 2] for [target condition(s)]
3) [index test(s)] for [target condition(s)] in [description of participants]
4) [index test(s)] for [target condition(s)].

The essence of the objective should be captured in the review's title. Typically this involves stating the diagnostic technology together with the key characteristics of the people to whom it is applied and the purpose for which it is used. The key components of the title are therefore:

- the patients (how they present, where they present to, what tests have been done before);

- the target condition (disease, disease stage, or sub-type of a disease eligible for a specific treatment);

- the test or tests being evaluated.

The test that is being evaluated is known as the index test. A review may evaluate and compare the diagnostic accuracy of several index tests, and may elect one as a comparator test with which the diagnostic accuracy of the other index tests is compared, particularly if this test is currently the standard diagnostic practice. The target condition is the condition of interest that the index and comparator test(s) are attempting to detect. The clinical reference standard is usually the test or tests representing the best available method of detecting the target condition. Reference standards, which give results with very little error, are known as 'gold standards'.

Please note the difference between the reference standard and the comparator test: the reference standard is the best test available to detect the target condition (and may not routinely be used in clinical practice) while the comparator test is a routinely used test, the diagnostic accuracy of which we wish to compare with other index tests to decide which is the best for detecting the target condition."

PAST EVENTS

CHBG EXHIBITION STAND DURING THE 63TH ANNUAL AASLD MEETING, BOSTON, USA. NOVEMBER 9 TO NOVEMBER 13, 2012.
Three presentations were shown at the exhibition stand from November 10 to 13, 2012. People, who have passed by it, had a possibility to ask questions and talk to the presenters about the results of the systematic reviews. The presentations were shown on a screen.

FUTURE EVENTS

CHBG EXHIBITION STAND DURING THE 48TH ANNUAL EASL MEETING, AMSTERDAM, THE NETHERLANDS. APRIL 24 TO APRIL 28, 2013
The CHBG booth number is 70. Also this time we will

run presentations of CHBG reviews on a screen. More information on their titles will be found at the stand.

EVIDENCE-BASED CLINICAL PRACTICE WORKSHOP "THE ARCHITECTURE OF DIAGNOSTIC RESAERCH AND CLINICAL REASONING"
The workshop will be run September 29 to October 2, 2013 at "Palazzo Feltrinelli", Gargnano, Lago di Garda, Italy. Information about how to apply and register is published within this Newsletter. The programme is sent out with this Newsletter.

For additional inquiries, please send an email to Ms Sara Comparetti, Centro Interuniversitario "Thomas C. Chalmers"Università degli Studi di Milano, e-mail chalmers@unimi.it.

21ST COCHRANE COLLOQUIUM. QUÈBEC CITY, CANADA. SEPTEMBER 19 TO 23, 2013.
This year's theme of the collqoquium is "Better Knowledge for Better Health". This year it is also the 20th anniversary of The Cochrane Collaboration.

Consumer and Developing Country stipend applications open 4 April and close 16 May 2013.

Registration opens Monday, 25 March 2013. See registration dates and fees below:

- Early registration: ends 15 July 2013 - $1015.
- Regular registration: 16 July to 6 September - $1265.
- Low- & middle-income country registration: ends 6 September - $615.
- Student registration: ends 6 September - $615.
- Consumer registration: ends 6 September - $615.

Information about the colloquium is to be found at colloquium.cochrane.org.

VISITORS

Chavdar Pavlov, Moscow, Russia, visited the CHBG Editorial Team Office from 15 February until 4 March.

Chavdar worked on the Diagnostic test accuracy systematic review "Transient elastography for diagnosis of hepatic fibrosis in patients with alcoholic liver disease".

NEW STAFF

CHBG Editor
Janus Christian Jacobsen, M.D. from the Copenhagen University, with a specialty in general medicine, is a newly appointed CHBG editor. Janus's main research interests are evidence-based medicine and methodology, biostatistics, psychiatry, acute medicine, general medicine, hepatobiliary medicine, vitamin D, and education in evidence-based medicine.

Janus has been a primary investigator in a number of systematic reviews using Cochrane methodology. Janus is involved in a number of randomized trials, run at Copenhagen Trial Unit (The CTU) [www.ctu.dk]. CTU hosts the CHBG Editorial Team Office.

NEWS

The CHBG has a new website [hbg.cochrane.org]. We hope that all users will find it informative and useful for their work.

We will be happy to receive your comments and suggestions for improvement, or to let us know if something is not working properly or has become outdated.

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 a 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 alpha-spending 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 beta-spending 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.

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

September 29 - October 2, 2013
at "Palazzo Feltrinelli", Gargnano, Lago di Garda, Italy

Please see the course program and application form, send out with this Newsletter.

In the everyday clinical practice, new diagnostic tests, claimed to be accurate and useful, are launched, and clinicians are requested to make the best choice using the most appropriate test, avoiding test overuse not only for decreasing costs but also for reducing adverse effects of false results, be it positive or negative. The main question is: "Will the test results change the treatment decision for the patient?". Clinicians should evaluate what the effect of the incremental information of a new test is and how it will impact their patients: is it really relevant? Diagnostic research can give such information, but a critical approach is needed.

Diagnostic studies have different designs, different inclusion/exclusion criteria depending on the specific research questions they are aimed to answer. The main aim of the common diagnostic study is the appraisal of the accuracy of the index test, its capacity to differentiate between patients with or patients without the target disease. However, a very high accuracy alone should not be the cause for introducing a new diagnostic test in clinical practice without a demonstration of increased benefits and decreased harms for the patients. In addition, the performance of a test should also be reassessed in large observational studies, organised in clinical databases analogously, as well as post-marketing studies in the effectiveness evaluation field.

The aim of this basic, residential course is to learn the appraisal of the architecture of diagnostic research and to be able to link the theory with clinical reasoning and medical decision making. Participants should be able to recognize the different phases of diagnostic study architecture, the appropriate methodology, and the corresponding research questions they are aimed to answer.

While phase 0 studies are pre-clinical and are devoted to the technical development and appraisal of the test, phase 1 studies aim to determine the normal range of values in healthy people. Phase II studies should be considered in four different subgroups or phases. The first two phases, IIa and IIb, compare test results in affected patients with the results obtained in "reference" individuals. Phase IIc studies are the most important ones from the practical point of view. They assess the diagnostic accuracy of the test under evaluation, and, in particular, if their results are able

to distinguish patients with and patients without the target disease by analyzing a clinically relevant population. We will focus on these three study phases in separate, using practical examples. On the last day, we will work with phase II d studies, and due to time constrains, we will make a short presentation on phase III and phase IV studies. (Phase IId, phase III, and phase IV studies will be presented in depth at an advanced course in 2013.) Phase II d studies, also referred to as 'diagnostic exploratory' trials, are conducted on patients suspected to be diseased in order to assess any immediate downstream consequence of testing and offering treatment based on the test result. These studies compare the new diagnostic therapeutic strategy, incorporating the index test with the current best diagnostic strategy, randomising patients and considering relevant outcomes as outcomes. Different study designs to answer these questions will be will be analyzed. The randomised clinical trial is the most appropriate design to answer these questions. We will analyse and discuss methodological problems such as definitions regarding outcomes, efficacy measures, and sample size.

Phase III and phase IV studies aim to assess the efficacy of a new diagnostic test. During the morning sessions, theoretical and interactive lectures will be held including examples from published studies (in the field of liver fibrosis, primary spontaneous peritonitis, hepatocellular carcinoma, ageing dementia) and focusing the participants' attention on major issues inherent to methodology, including assessment of study quality with particular emphasis on biases and the use of checklists.

During the afternoon sessions, there will be break-out sessions, with a supervisor working with each small group on study examples, followed by feedback and lessons learned. All major critical topics will be re-appraised directly by the participants working in small groups, using literature materials, and each group reporting its conclusions in a plenary discussion.

Concluding remarks and take home messages, relevant from the clinical practice point of view, will be finally proposed and discussed with the Faculty.

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