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Review article

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EVIDENCE-BASED CLINICAL PRACTICE AND THE COCHRANE HEPATO-BILIARY GROUP

SUMMARY

The article gives an overview of the structure, aims, products, and achievements of The Cochrane Hepato-Biliary Group (CHBG) in its 12th-year of existence. The article informs about the process of systematic review preparation, the central role of randomised clinical trials for making evidence-based decisions on benefits and harms of interventions, and discusses factors that may lead to biased evaluation of the studied interventions. Systematic reviews are mostly based on meta-analyses of randomised clinical trials. The importance of methodological evaluation of trial reports using a number of components that may detect systematic errors ('bias') is discussed. 'Trials sequential analysis' as a way to control risk of random errors ('play of chance') due to repetitive testing on accumulating data in cumulative meta-analyses is introduced. The CHBG reviews are published in The Cochrane Library as well as in paper journals. The practice to look for or conduct a systematic review before planning a clinical trial or write a clinical guideline should become routine.

Key words: **Cochrane Hepato-Biliary Group, systematic review, randomised clinical trial**

INTRODUCTION

The Cochrane Hepato-Biliary Group (CHBG) is a non-profit, international, collaborative research group, which gathers people with interest in evidence-based clinical practice, dealing with hepato-biliary diseases. The CHBG is part of The Cochrane Collaboration (www.cochrane.org). The Cochrane Collaboration is named after a British epidemiologist, Archie Cochrane, who was a champion of randomised trials. The first comprehensive meta-analyses were conducted within the pregnancy and childbirth field in Oxford under the leadership of Sir Iain Chalmers. In 1989, a two-volume book, *Effective Care in Pregnancy and Childbirth*, with data on 600 interventions, was published based on these meta-analyses (1). These activities lead to the formation of The Cochrane Collaboration in October 1993 (www.cochrane.org).

In April 1996, The CHBG was formed. From a handful of enthusiastic people, aspiring to base their medical decisions on evidence, The CHBG presently numbers more than 1400 people with medical and non-medical background. The CHBG has grown into a well-established group. Out of the fifty-one Collaborative Review Groups within The Cochrane Collaboration, The CHBG ranked fifth in terms of a number of protocols for reviews and finalised reviews in The Cochrane Library Issue 2, 2008.

The structure and products of The CHBG

The structure of The CHBG resembles the structure of any other Cochrane group, and in respect to the editorial work performed, a parallel, to a great extent, can be made with a journal publishing editorial office. The Editorial Team Office of The

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CHBG is located in the Copenhagen Trial Unit at Rigshospitalet, Denmark and is run by a small staff consisting of a Co-ordinating Editor, Managing Editor/Co-ordinator, and Trials Search Co-ordinator assisted by IT managers (http//ctu.rh.dk/chbg).

CHBG reviews are systematically conducted reviews of the intervention literature, in which the best evidence of interventions regarding prevention, diagnosis, treatment, and care is collected based on a peer-reviewed, published protocol. The systematic reviews of the identified health-care interventions on patients with hepato-biliary diseases are conducted according to the guidelines of The Cochrane Collaboration (2).

All CHBG protocols and reviews undergo strict peer reviewing process; a contact editor and at least two peer reviewers comment on a protocol and later on a review. All CHBG reviews are additionally commented on and approved by The CHBG Editors before publication. Consumer representatives, whose constant input is highly respected, also comment on all CHBG reviews before publication. CHBG peer reviewers are from all over the world and are chosen according to their speciality and field of expertise.

A Cochrane review is synonymous with evidence-based medicine. According to Sackett et al, "evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (3).

But why shall we think that Cochrane systematic reviews are the best guidance that exists for practitioners, policy makers, and consumers? There are a number of valid reasons for this claim. Cochrane reviews are prepared following rigorous Cochrane methodology; they unite strategies to minimise bias and maximise precision. Hereby, the risks of systematic errors and random errors are controlled in order to maximise internal validity (2,4,5). Only by having the best internal validity, it becomes of interest to discuss external validity and to consider general use of interventions.

A published, peer-reviewed protocol is preceding the published Cochrane review (2). In this way, we want to prevent biased, post-hoc decisions. Cochrane reviews are retrospective observational studies. As all such retrospective studies, the risks of biased decision making must be kept at a minimum. Cochrane titles for systematic reviews, similarly to the registration of randomised clinical trials before the first participant is recruited (http://www.clinicaltrials.gov), are registered within The CHBG and as a minimum contain the intervention studied and the disease in a defined population group, eg, 'Ribavirin monotherapy for chronic hepatitis C' (6).

The next step is formulation of the protocol. When it has been through peer review, it is published on The Cochrane Library, and the work with the CHBG review can start. Cochrane reviews aim at identifying and proving interventions that reduce harms and produce maximum benefit. This is accomplished through mainly resorting to comparisons from randomised clinical trials that study experimental interventions against placebo or no intervention, or against other standard interventions. The results of the systematic reviews can be used for formulating guidelines that can inform local clinical practice.

Methodological quality and bias risks

Methodological assessment of trial reports is of fundamental significance for minimising the risk of obtaining unlikely results. Randomised trials are the gold standard for evaluating health-care interventions when there is uncertainty about how good an intervention is (2,4,5,7,8). The randomisation process is the best way to ensure that known and unknown factors, which may independently affect intervention outcomes, are likely to be equally distributed between the trial groups. If correct randomisation is achieved, the differences observed between or among groups may be ascribed to the effects of the intervention. Generation of allocation sequence and allocation concealment, if adequately conducted in a trial, decrease the risk of systematic errors (selection 'bias') of the trial (2,4,5,7,8). Other criteria for assessing the risk of systematic errors of a trial are blinding, number of withdrawals or drop outs, intention-to-treat analyses, full reporting of all relevant outcomes (and not only those with significant results), sample-size calculations, independence of sponsorship, etc. (2,4,5,7,8,9,10).

Blinding relates to performance and reporting bias, and assessment bias (2,4,5,7,8). The perceived efficacy of an intervention may be influenced by factors like appearance and colour, size, smell, taste, and way of delivery of a drug. Knowing the intervention administered may distort the trial result. Trials may be single-blinded (eg, the participant or the investigator/care giver is blinded), double-blinded (eg, participant and investigator/care giver), or evaluator-blinded. Preferably, all parties ought to be blinded, including those managing the data, conducting the statistical analyses, and drawing the conclusions. When blinding is reported, the best approach when assessing the trial for this criterion is to document exactly the parties who were blinded. Blinded assessment of outcomes may also be achieved even if the trial is open (ie, non-blinded) in order to avoid detection bias.

All randomised participants should be accounted for in the analysis to avoid attrition bias. Intention-to-treat, when used in a trial, will include the number of randomised participants in each group, regardless of whether they have received or stuck to the allocated intervention. This will help to establish with greater likelihood the effect of the intervention in the real world settings. Withdrawals or drop-outs should be carefully documented, and together with the number lost to follow-up, they may be included as successes or failures in best-case and worst-case scenario sensitivity analyses. When documenting data for the final review analyses, one should make a distinction between intention-to-treat analysis and per-protocol analyses where participants with protocol deviations are removed.

Insufficient sample size of the trials as well as lack of sample-size calculations to ensure that the number needed to treat is reached (ie, the number of patients who need to be treated in order to determine if one has to accept or reject a certain intervention effect) is associated with type I and type II errors (9). The vast majority of randomised trials are severely undersized and less than half report a sample size estimation (5,6). Such small trials run risk of random errors ('play of chance') (see below). Therefore, small trials with few outcomes are very prone to report wrong results. Research has also shown that a number of trials are selectively reporting outcomes, preferring to report significant beneficial effects and abstaining from reporting harmful effects (10). Lack of reporting of outcomes should raise suspicion of outcome measure reporting bias (10). This may distort evaluation of interventions. This form of bias may introduce about the same amount of bias as trials being conducted with inadequate methodological quality (11).

A number of studies have shown that sponsorship may also dictate the outcome results of a trial, so information on funding should be heeded (12,13).

Methodological evaluation of the trial quality to identify the risk of bias is a central element after the stage of deciding on the trials fulfilling the inclusion criteria of a review and before extracting and double checking of data for analyses. Grouping the studies into low risk of bias trials and high risk of bias studies may eliminate false-positive conclusions on the intervention effect.

Risks of random errors

As stated above, small trials are very prone to observe random errors. Coupled with our human wish-bias selectivity, preferential publication of positive results lead to publication bias and hence overestimation of intervention effects. When such overestimated positive results are meta-analysed, this leads to overestimated meta-analysis results, and hence introduction of wrong interventions into clinical practice. Trial sequential analysis using trial sequential monitoring boundaries is a way to detect spurious findings in cumulative meta-analyses, reducing the risks of random errors (14,15).

In a single trial, interim analyses increase the risk of type I error. To avoid an increase of overall type I error, monitoring boundaries can be applied to decide whether a single randomised trial could be terminated based on a sufficiently small P-value. Likewise, analogous monitoring boundaries can be applied to meta-analysis, ie, trial sequential monitoring boundaries in trial sequential analysis. There is no evidence to suggest that the standards for a meta-analysis should be less rigorous than those for a single randomised trial (14,15). The underlying assumption for this analysis is that significance testing is conducted each time a new trial is published. Trial sequential analysis depends on the quantification of the required information size. Cumulative meta-analysis of trials are at risk of producing random errors because repetitive testing of accumulating data is conducted in cumulative meta-analysis (14,15).

Pre-defined statistical monitoring boundaries are indicators for correct judgement in trials. The values that have to be pre-determined for the monitoring boundaries are type I error, eg, set at two-sided P = 0.05 and type II error, eg, set at 0.1 as well as the control event proportion and the expected minimal relevant intervention effect (14). Not reaching the pre-defined monitoring boundaries would imply the lack of sufficient evidence to support the intervention. Thus, trial sequential analysis may reduce the number of false positive results and the number of critically inaccurate estimates of treatment effects (14,15).

Bias risks and random error risks of gastroenterology and hepato-biliary randomised clinical trials

We have studied the methodological quality and size of randomised clinical trials published in the journals 'Hepatology' between 1981 and 1998, 'Liver' between 1981 and 1998, 'Journal of Hepatology' between 1985 and 1997, and 'Gastroenterology' for the years 1964 to 2000 (16-19). All these studies concluded to the insufficient reporting on the randomisation procedure and double-blinding of hepato-biliary randomised clinical trials, though a significant trial report improvement had been proven in the mid-1990s in the 'Gastroenterology' trials (19). Preventive measures against inadequately performed and insufficiently reported trials have

been worked out by respective quorums, and the recommendations and the requirements must be followed to the greatest detail. Investigators of clinical trials are advised to follow the Consolidated Standards of Reporting Trials (CONSORT) (http://www.consort-statement.org/). The CONSORT Group improves continuously the initiatives to minimise the problems ensuing from inadequate reporting of randomised controlled trials.

Most of the randomised trials were very small and the majority did not report on sample size estimation (4,5,16-19). Such trials run the risk of overestimating intervention effects (20).

CHBG reviews

CHBG reviews are published in The Cochrane Library (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). By May 2008, The CHBG had published more than 167 protocols for systematic reviews and more than 100 systematic reviews. A number of these reviews have been updated since their first publication.

Being able to deliver reliable, high-quality, and relevant Cochrane systematic reviews is of fundamental importance to The CHBG. Justifying the harms that most interventions carry while being led by the expected benefit questions whether number-needed-to treat has been defined correctly in a trial and a meta-analysis. Patients, physicians, and decision-makers take different perspectives on the effects of an intervention. The practice to look for a Cochrane systematic review before planning of a trial has become more regularly established. In this way, Cochrane reviews become the meeting point in the discussion arena of all evidence-based adherents.

In all the 12-year period of The CHBG existence, educating people with interest in how to prepare and critically read Cochrane systematic reviews is a daily task. The CHBG reviews are not industry-sponsored and conflict of authors and peer reviewers is always declared. This highlights the transparency of the recommendations for practice and research in CHBG reviews. The CHBG is open to all and will accept also you as a collaborator.

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KLINIČKA PRAKSA BAZIRANA NA DOKAZIMA I KOHRAN HEPATO-BILIJARNA GRUPA

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SAŽETAK

Članak pruža pregled strukture, ciljeva, produkata i dostignuća Kohran Hepato-Bilijarne Grupe (KHBG) nakon dvanaest godina njenog postojanja. Takođe, članak nas informiše o načinu pripreme sistematskih revija, centralnoj ulozi randomizirajućih kliničkih studija za donošenje odluka baziranih na dokazima o povoljnim i lošim aspektima intervencija i analizira faktore koji mogu da dovedu do odstupanja u procenama analiziranih intervencija. Sistematske revije se uglavnom baziraju na meta-analizama randomiziranih kliničkih studija. U radu je predstavljen značaj metodološke procene kliničkih studija primenom komponenti koje mogu da detektuju sistematske greške (''odstupanja''). Uvodi se ''sekvencionalna analiza studija'' kao način za kontrolu rizika od slučajnih grešaka (''igra šanse'') zbog ponavljanog testiranja prikupljenih podataka u kumulativnim meta-analizama. KHBG revije se objavljuju u Kohran biblioteci kao i u ostalim časopisima. Praksa traženja sistematskih revija pre planiranja kliničkih studija ili pisanja kliničkih vodiča trebalo bi da postane rutina.

Ključne reči: **Kohran Hepato-Bilijarna Grupa, sistematska revija, randomizirajuća klinička studija**