The Cochrane Hepato-Biliary Group as a Resource Example of Evidence-Based Medicine for All

O Cochrane Hepato-Biliary Group como um Exemplo de Recurso de Medicina Baseada na Evidência

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INTRODUCTION

The Cochrane Hepato-Biliary Group (the CHBG) is a non-profit and not-for-profit independent, international, specialty research group within The Cochrane Collaboration (http://www.cochrane.org). Since its formation in 1996, The CHBG has established itself as a reliable source of evidence-based systematic reviews of interventions within the area of hepato-biliary diseases to which more than 1 600 people contribute primarily as authors, peer reviewers, and editors. The CHBG has also developed a Hepato-Biliary Controlled Trials Register containing references to about 13 500 randomised clinical trials. CHBG reviews and the Register are published in the Cochrane Library (http://www.thecochranelibrary.com).

In the seventeen year period of its existence, The CHBG has registered 448 titles for systematic reviews, has published 258 review protocols, and 153 systematic reviews. By the end of the year, another 15 protocols and 30 reviews, all of them in editorial, would be finalized.

What Cochrane systematic reviews and non-Cochrane reviews and meta-analyses have in common is that they are all retrospective, observational studies. The main difference, however, is that Cochrane systematic reviews are preceded with a title registration followed by the publication of a peer reviewed protocol on The Cochrane Library. The published protocol defines the methods and the statistics for the conductance of the systematic review, thus protecting the review from bias and data-driven results while being conducted or updated.

The Cochrane reviews may be on prevention, diagnosis, treatment, or care. The people involved in the production of these reviews follow the guidelines of The Cochrane Collaboration provided in The Cochrane Handbook for Systematic Reviews of Interventions[1] as well as the more-specific guidelines of The CHBG (http://hbg.cochrane.org).

The format of Cochrane systematic reviews of interventions is the same for every review, which provides the advantage of finding information easy. But will consumers, practitioners, researchers, or decision-makers find the information they need? Even that information is collected every day by hundreds of people working on systematic reviews we may become frustrated when we search The Cochrane Library for the benefits or harms of an intervention for the disease of our interest. We may not find such a review. In this case, one may submit a review proposal form to the respective Cochrane group.

If we find a Cochrane review, then we may still be bound for surprises. Many systematic reviews contain no or only a few randomised clinical trials. Accordingly, their results may still be unreliable.

Can we put the blame on the systematic review authors when we know that the evidence used for the review preparation comes from conducted randomised trials and also that the insufficiency of data causes lack of statistical power of the assessed interventions?[2] Review authors make attempts to identify unpublished trials and are required to contact trial investigators for missing data in the trial reports. On average, the response is 30%. Review authors' frustration is additionally challenged in the cases when they identify trials fulfilling the protocol inclusion criteria but find that the outcomes assessed in the trial are clinically irrelevant, i.e., putative surrogate outcomes[3]. Hence, limitations reflect on review's conclusions and recommendations for practice and research. The ongoing AllTrials campaign 'All trials registered - All trials reported' is a promising initiative for systematic reviews (http://www.alltrials.net).

Some of The CHBG reviews may include on average five or six randomised trials per outcome, but these reviews may still lack firm conclusions, as the traditional meta-analyses used to analyse the data for the review outcomes suffer from type I and type II errors.[4] Such errors may occur due to random errors because of sparse data or because of repetitive testing of the trial data, as the cumulative meta-analysis implies addition of new trials. To control for type I and type II errors and being inspired by the methodology used for interim analyses of a single trial, The CHBG in close collaboration with The Copenhagen Trial Unit (http://www.ctu.dk) (also hosting The CHBG Editorial Team Office)

has developed methodology of trial sequential analysis (TSA)[5,6] (http://www.ctu.dk/tsa/index.html). Conventional meta-analysis methods as those used in Review Manager disregard the information size of the individual randomised trials when meta-analysed. If the meta-analysis result comes with a statistically significant intervention effect, then we take it for granted, and if it shows the opposite, then we may conclude that the intervention does not work. About 25% of conventional meta-analyses with a small number of events and patients may come with false statistically significant effects.[7] With the knowledge that the aim of a meta-analysis is to identify the benefits and harms of an intervention earliest possible, by adding repeatedly new trials we test the significance of an intervention all the time. However, repeated significant testing on accumulating data inflates the overall risk of type I error. To avoid the failures of the conventional meta-analysis, the TSA methodology uses a combination of techniques which provides a required information size, a threshold for a statistically significant effect (thus avoiding type I errors), and a threshold for futility (i.e., the uncertainty of obtaining a chance-negative finding in relation to the accumulated number of participants) (type II errors).[5,6]

TSA has been applied in a number of Cochrane reviews, and results obtained through the conventional meta-analyses were ascertained, disproved, or questioned. As TSA seems to be convincingly showing its advantages over the conventional meta-analyses, we encourage researchers to use it.

The third group of reviews that we may find in The Cochrane Library is the reviews that include sufficient number of low risk of bias trials and patients, and firm conclusions could be made for most of the clinically relevant outcomes. However, such reviews may come with surprising findings.[8]

We, as users of synthesized evidence-based medicine, are in constant need of reliable, up-to-date evidence from high-quality systematic reviews combining empirical knowledge and meta-analysed results of randomised trials performed with rigorous methodology, with inherent minimal risk of bias, and reliable statistic.

Finding published and unpublished randomised trials irrespective of language, place, and year; assessing the evidence from trials not yet included in systematic reviews; conducting trials with interventions introduced in clinical practice with no former assessment of their benefits and harms; proving the best methods of statistics to meta-analyse the data in a systematic review are of paramount importance for the reliability of the conclusions and implications for practice or research.

The CHBG urges people from all over the world with interest in evidence-based medicine and systematic reviewing to contact the relevant Cochrane editorial team (there are presently 53) to work together to fill the gaps of evidence through systematic reviewing. It may be the best preventive medicine for you to avoid becoming 'burned-out' as a clinician.

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