

Seminarios de diabetes

The Cochrane Metabolic and Endocrine Disorders Review Group and its possible impact on the Spanish Society of Diabetes

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Abstract

Evidence based medicine means the integration of the best research evidence with clinical expertise and the patient's unique values and circumstances. Today, nobody seriously questions this concept anymore but strong counterforces try to distort or circumvent this momentum. The Cochrane Collaboration is one of the very few independent organisations of considerable size in medicine trying to establish high-quality systematic reviews and publish these in *The Cochrane Library*. The Cochrane Metabolic and Endocrine Disorders Group (CMED), one of more than 50 Cochrane Review Groups focuses on systematic reviews of the benefits and harms of healthcare interventions for metabolic and endocrine disorders. A Cochrane review is a formidable challenge but help is provided through all stages of review production by the CMED. More than 500 authors are currently actively participating in our group and helped to create the present impact factor of 5.182. Increased input to Cochrane reviews from a wider range of cultural and socio-economic sectors such as the 'Hispano side of the world' would be welcome to provide better information to patients globally.

Keywords: meta-analysis, systematic review, diabetes mellitus, Cochrane Review Group, evidence-based medicine.

Background

The momentum of evidence-based medicine (EBM) started more than a decade ago. Its current best definition is that EBM requires the integration of the best research evidence with clinical expertise and the patient's unique values and circumstances.¹ To some of the readers of this journal this may seem like an old hat. However, as Michael Berger, one of the pioneers of evidence-based diabetology, former president of the European Association for the Study of Diabetes and patient advocate put it: "the era of en-

lightment ends with the golden calf".² Michael Berger tried to emphasize that the enormous progress in the development of rationally justified medicine is time and again endangered especially by the tension between profit-oriented organisations and individuals and the rather weak appearing forces trying to establish something like a network of transparent patient-oriented research including new ways of informed decision making by concerned individuals. Not only scientific fraud and 'data dredging' or manipulations³ are of major concern but also conflicts of interest create a serious problem in the medical publishing industry. For example, a recent report on more than 200 guidelines (from various countries) established in 2004 with the US National Guideline Clearinghouse showed that "more than one third of the authors declared financial links to relevant drug companies, with around 70% of panels being affected".⁴ Moreover, almost half the guidelines provided no information about conflict of interest. Oppositional results from different panels investigating the same body of evidence are sometimes revealed, like in the example of the Canadian clinical practice guideline on insulin glargine.⁵ One has to think of this omnipresent environment to really appraise what happened after the Cochrane Collaboration came into operation.

Introduction to the Cochrane Collaboration

The Cochrane Collaboration is an international non-profit and especially independent organization, representing a global network of mostly devoted volunteers. The Cochrane Collaboration is dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. It produces, disseminates and constantly updates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions and diagnostic accuracy. The Cochrane Collaboration was founded in 1993 and named after the British epidemiologist Archie Cochrane.

The main product of the Collaboration is the Cochrane Database of Systematic Reviews which is published quarterly by Wiley-Blackwell as part of *The Cochrane Library*, an electronic publication on the internet or via DVD which currently is updated quarterly. Those who prepare the reviews are primarily healthcare professionals who volunteer to work in one of over 50 Co-

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Abbreviations:

CMED: Cochrane Metabolic and Endocrine Disorders Group; EBM: evidence-based medicine; IbCC: Iberoamerican Cochrane Centre.

chrane Review Groups, with editorial teams overseeing the preparation and maintenance of the reviews, as well as application of the rigorous quality standards for which Cochrane reviews stand for. The activities of the Collaboration are directed by an elected Steering Group and are supported by staff in so-called Cochrane Entities (for example Centres and Methods Groups) around the world. For more information the reader is advised to visit the Cochrane Collaboration's web site with a wealth of information and interesting links on 'www.cochrane.org'.

Moreover, in 1997 a Spanish Cochrane Centre was opened which expanded its scope to that of an Iberoamerican Cochrane Centre (IbCC) and is located at the Casa de Convalecencia del Hospital de la Santa Creu i Sant Pau, Barcelona – headed by its director Dr. Xavier Bonfill (for additional information please visit 'www.cochrane.es'). Various activities have been carried out since the registration of the IbCC in 2000. For instance, in Latin America many Cochrane workshops and institutional agreements have been arranged and an Iberoamerican Cochrane network has been established. Notably, there is a Spanish version of the Cochrane Library called 'La Biblioteca Cochrane Plus' (accessible on www.update-software.com).

A Cochrane Diabetes Group was registered as early as 1994 and started with much enthusiasm. Unfortunately, in 1998 its activities had to be terminated due to lack of funding. Revival efforts by Michael Berger and Bernd Richter led not only to a continuation of the work of the old group but also to an expansion of its scope to that of a Cochrane Metabolic and Endocrine Disorders Group (CMED), officially registered in February 2000. Since then the CMED has been preparing systematic reviews on the benefits and harms of healthcare interventions for metabolic and endocrine disorders, particularly diabetes mellitus and obesity. The Editorial Base is located at the Department of General Practice at the University Hospital Duesseldorf, Germany (Heinrich-Heine University) and is led by Bernd Richter.

The CMED is primarily concerned with the evaluation of randomised controlled trials and other controlled health care interventions relevant to the prevention, treatment or management, and rehabilitation of metabolic, nutritional and endocrine disorders (such as diabetes mellitus, obesity and thyroid diseases). The CMED primarily focuses on systematic reviews which evaluate patient-orientated outcome measures, like death from any cause and disease specific mortality, morbidity and complications, health-related quality of life, functioning and wellbeing, resource utilisation and costs, and adverse effects. Authors who wish to analyse surrogate outcomes like laboratory parameters may do so but always have to also investigate a standard set of patient-orientated endpoints.

How the Cochrane Metabolic and Endocrine Disorders review group functions

The work of the CMED is supported by editors, peer referees and administrative staff. The editors and referees provide feedback on protocols, reviews and review updates and help the editorial team develop policies and guidelines for the group. The CMED

is currently funding itself through health-technology assessment contract work.

The workflow of a Cochrane review undergoes several life cycles, starting with an author's creative idea (figure 1). The first thing potential new reviewers should do is to inspect the CMED's web site ('www.endoc.cochrane.org') to familiarize themselves with what is expected from Cochrane authors and to find out whether somebody else in the world is already working on this topic. Furthermore, it is strongly encouraged that novices in systematic reviews should participate in training workshops arranged by the IbCC making their life much easier.

A good overview of almost all registered titles, published protocols and reviews can be inspected at the CMED's web site under 'Our reviews'. Thereafter, authors should download the so-called title registration form from the CMED's web site (see 'Prospective authors'), fill this in and send it to CMED's Managing Editor. Within usually two weeks this title registration form is checked and –provided all requirements all fulfilled– the title is registered for the respective author. This means that the contact person for the review team (consisting of at least two persons) has the right but also the duty to work on this project and publish its results in *The Cochrane Library*. No 'very important person' can step in and take away this review from the registered authors. However, certain timeframes from title registration to the finished review apply and a title might be deregistered any time if authors do not work on it over a longer period.

After registration the CMED will provide the author team with a protocol template together with a wealth of information (for example have a look at the CMED web site's 'CMED resources for reviewers'). Determined authors should be able to formulate a good protocol draft within rather short time building on this template. The protocol step is an important one for a high-quality Cochrane review since it determines major steps in the review production –it is the foundation of a good house. On the other side, review production is a flexible process and amendments are always possible as long as they are reported in a transparent way.

Cochrane protocols and reviews are handled through the Collaboration's Review Manager (RevMan) software which is a mixture of a word-processor, spreadsheet and sophisticated statistical package. This software is freely available and a must for everybody wanting to embark on a Cochrane review project. Protocols and reviews are transferred with the help of the Collaboration's Information and Management System ('Archie') where registered authors as well as editors may check in and out protocols and reviews to work on them.

Once the final protocol draft together with a pre-submission checklist is checked in and submitted to the CMED, Archie automatically informs the editorial base and the regular peer review process starts. A Cochrane compared to a paper journal peer review usually is much more elaborate and accurate since it involves content experts, methodological and statistical experts and 'consumers' (like patients, concerned individuals, people working in health care) and others. As a result, comments from

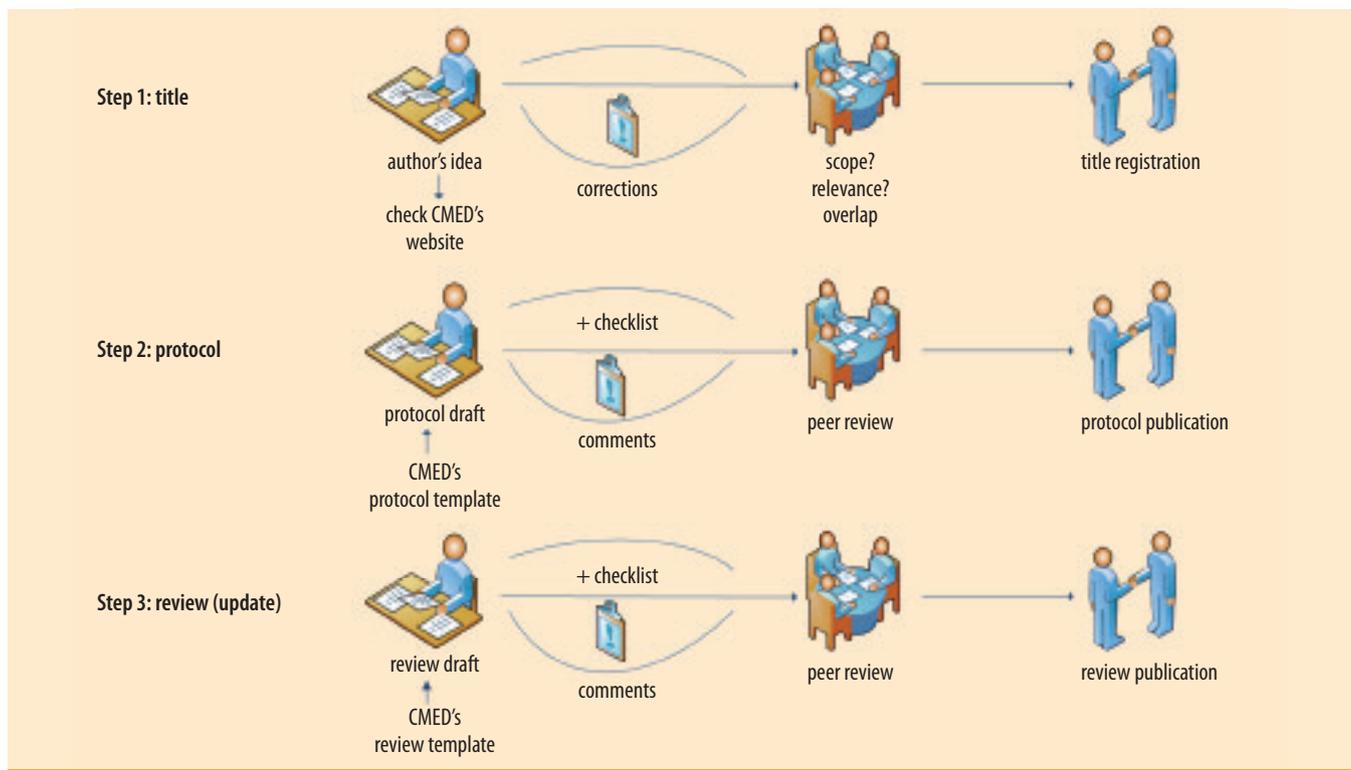


Figure 1. Workflow of reviews within the Cochrane Metabolic and Endocrine Disorders Group

the editorial base, CMED's editorial board and external peer referees are collated and sent to the authors. If everything works fine (sometimes after several rounds depending on authors' experiences), the protocol is published in the next version of *The Cochrane Library*. In principal, the third and last step resembles the protocol cycle. Review drafts together with pre-submission checklists are submitted and subjected to peer review. This also applies to updates of reviews which should be performed approximately every two years.

This may sound complicated and in fact readers should be aware that a Cochrane review is a prime scientific endeavour comparable to realising a high-quality randomized controlled clinical trial. The big difference however is that authors receive help and support at all stages of their review production from the CMED. For example, search strategies for various databases to detect primary studies for a systematic review are always quality assured by the CMED's information scientist, called Trials Search Coordinator and coordinated efforts to optimize these strategies are standard. Detailed help on statistical issues is a matter of course, as is the ever growing information material on the web site.

For a smooth review process good coordination of the mutual expectations and obligations is necessary. From the CMED's side a perfect team of review authors would consist of people with content and methodological background, an information scientist or librarian and a statistician. Since the CMED's resources are limited and on average around 100 Cochrane review projects

have to be mentored at the same time, some prioritization has to come into effect. Currently, the CMED's authors should always evaluate patient-oriented parameters and formulate rather broad but not absolutely specific questions of as much public health relevance as possible. This sure cannot be regulated mechanically and very much depends on context.

Key elements of (Cochrane) systematic reviews & meta-analyses

Space restrictions demand to focus on some essential elements in the attempt to achieve a high-quality systematic review. A systematic review tries to assemble all empirical evidence according to pre-specified eligibility criteria to answer a specific research question (often formulated with the PICOS approach, that is, Population or disease being addressed, Intervention or exposure, Comparator intervention or exposure, Outcome or endpoint and Study design chosen). Distinct and systematic methods to minimize bias should be employed to present reliable findings from which conclusions can be drawn and decisions made. Key elements consist of: (1) a clearly stated set of objectives with a distinct reproducible methodology; (2) a systematic research to recognize studies meeting the in- and exclusion criteria; (3) an evaluation of the validity of the results of the included studies; (4) a systematic presentation and synthesis of the characteristics and findings of the included studies. A systematic review always forms the backbone of a Cochrane review. If possible and feasible, meta-analysis might be applied to provide more precise esti-

mates of the effects of health care compared to individual study results included in the review. Meta-analysis uses statistical techniques to integrate and summarize the results of the included studies.

A very important first step and good start is to thoroughly study the *Cochrane Handbook for Systematic Reviews of Interventions*.⁶ The 'Handbook' is also available as a hardcover. Various excellent individuals of the Cochrane Collaboration invested great efforts to provide this guidance for Cochrane review authors and systematic reviewers in general. Therefore, if readers seriously consider beginning a Cochrane review project they should definitely take advantage of this wonderful resource and success is almost guaranteed! In the near future the CMED will also register titles of systematic reviews of diagnostic accuracy studies. Additional information and some chapters of a handbook on this area are available.⁷

The establishment of an adequate search strategy and managing of references is an often neglected but vital part of every systematic review. The best search strategy cannot replace the 'human interface' meaning that even with the best efforts, searches for systematic reviews have to be sensitive, quite often confronting authors with thousands of abstracts/titles downloaded from various databases. Therefore, as a minimum two authors should check the detected references because the danger of missing important information after spending tiring hours of scanning references is big and should be limited by the safeguard of additional monitors. Information lost at this stage of sifting the literature might never be detected again. As a matter of course an adequate search has to cover other systematic reviews, meta-analyses and health-technology assessment reports as well. Reference lists of included publications should be scrutinized and key publications used for identifying additional trials by means of Science Citation Databases (cited reference searching through, for example the ISI Web of Knowledge).

Another important step in the preparation of a Cochrane review is the transparent process of data extraction and reporting. As a minimum data should be extracted by one author and independently checked against the original publication by another. The CMED provides data extraction templates and also expects authors to publish their data extraction forms as appendices of the review. As mentioned above authors should report whether patient-oriented outcomes were investigated and provide an overview of all (as stated in the publication) investigated primary, secondary and other outcomes.

Furthermore, when carrying out a systematic review authors should distinguish between quality and risk of bias and focus on analysing and reporting the latter. It is a good exercise to a-priori think about what methodological and clinical risk of bias might influence the results of the systematic review. The Cochrane Collaboration discourages scales and the like and advocates a component approach by using the new Cochrane risk of bias tool which is part of the software RevMan. The reader should be aware that risk of bias consists of several levels. Most people would instantly think of study design features. However, it is of

great importance to investigate risk of bias at the outcome level. For example, a specific bias like blinding might be important for an outcome like health-related quality of life evaluated by questionnaires but less relevant for all-cause mortality.

Deciding whether or not to combine data statistically by means of meta-analysis involves clinical, methodological and statistical considerations. All of these are influenced by the question the review is attempting to address. While statistical issues due to their technical nature most often have an evidence-base, clinical and methodological considerations very much depend on context. For any question there might not be a right or wrong choice concerning synthesis of data. As subjective elements are always involved authors should be transparent as to their decisions and characterize them for the readers. If authors are convinced that studies should be combined statistically, many additional issues have to be considered, like different effect measures of results, statistical models and methods for performing meta-analyses – all with specific assumptions and limitations.

Different studies are always expected to demonstrate some variation ('inconsistency') due to chance alone. Variability in access of that reflects true differences in the results of the studies and is termed 'heterogeneity'. When only a few trials are available for meta-analysis, as is often the case, results should be interpreted with great caution. If considerable heterogeneity is observed, pooled effect sizes should not naively be reported but possible reasons considered. When heterogeneity is found, potential reasons should be explored by examining individual study and subgroup characteristics as well as data extraction errors.⁸ Also, the robustness of the results should be tested by performing sensitivity analyses in order to explore the influence of particular factors on effect sizes. Standard sensitivity analyses especially include various risk of bias, diagnostic criteria, source of funding and different statistical models. This may sound as a strong word of caution to do any kind of meta-analysis. On the other side, if authors do not or cannot combine data quantitatively, the danger arises that eventually they may use quasi-quantitative rules of poor validity for interpreting results like vote counting of how many studies presented significant results. For guidance of reporting systematic reviews and meta-analyses the reader is advised to study the recently published PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.⁹

Concluding remarks

The task which the Cochrane Collaboration and the CMED, in particular, are undertaking is tremendous. It will be achieved as people of good will offer their skills and time, but also needs firm funding structures. Beyond author participation, there are many ways to get involved, for example as an editor, referee, consumer representative, methodology expert, hand searcher, translator, etc. In the end, all efforts are directed to contribute to improving patient care. The health of present and future generations depends on our ability to identify and apply affordable forms of health care that do more good than harm.

More influence and collaboration from the Iberoamerican area appears necessary: Currently the impact from 'Anglo-American' and other regions seems to dominate the systematic review environment, potentially undermining cultural and socio-economic characteristics of sectors which have to formulate their own priority questions of specific public-health relevance. Collaboration between the Spanish Society of Diabetes and the CMED could therefore materialize in several areas. For example, Cochrane reviews could be instrumented for the development of well-founded evidence-based guidelines and guidelines developers could feed back gaps of research evidence to stimulate further systematic reviews. Once relevant public health issues are dealt with, orientation for practising diabetologists could be facilitated on a national and international basis, especially when cultural, ethnic differences and distinguishing characteristics of several countries are taken into account.

Moreover, Cochrane reviews already are an important element for patient-informed decisions which will be an important factor in the evolvement of better doctor-patient communication. Years ago Michael Berger stated that the doctor-patient relationship reflects the role of the physician in society and has thus experienced substantial changes over time reflecting among other things the key element of professional competence as called for by the system of evidence-based medicine.¹⁰ Furthermore, a Cochrane review is an excellent opportunity for researchers to publish their high-quality investigations. Currently the impact factor is 5.182 and ranks 12th out of 107 in the ISI category Medicine, General & Internal. So, do not hesitate to join forces of more than 500 authors already actively working within the CMED. And the best is yet to come. The next but one Cochrane Colloquium in 2010 will take place in Madrid – this is a great conference to enter open discussions, make new friends and meet friendly experts, see you there! ■

Potential conflicts of interest

B. Richter and D. Mauricio are not aware of any conflicts of interest related to the subject of the article.

Practical considerations

- The Cochrane Metabolic and Endocrine Disorders Group (CMED) is one of more than 50 independent groups within the Cochrane Collaboration providing up-to-date and high-quality systematic reviews and meta-analyses on metabolic and endocrine diseases.
- Cochrane reviews mean a considerable challenge but help is provided at all stages of review production by the CMED which focuses on patient-oriented outcomes to better advise health care that should do more good than harm.
- Increased input to Cochrane reviews from a wider range of cultural and socio-economic sectors would be welcome to provide better information to patients globally.

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