The Cochrane Skin Group

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Abstract. Over the last 10 years, the advent of evidence-based medicine has caused a paradigm shift in medical thinking and clinical practice. The Cochrane Skin Group organizes, drafts, publishes, and updates systematic reviews of randomized clinical trials of therapeutic interventions in skin diseases to assist in evidence-based clinical decision making. This article provides background information on the history and operation of this group, including the process by which systematic reviews are prepared.

Key words: Cochrane Collaboration, systematic review, evidence-based dermatology.

The Need for Access to Reliable Scientific Information in Medicine

Due to the increasing amount of medical information that is becoming available, there is growing interest in access to valid and reliable information on the effects of different types of medical care. The difficulty of identifying the high-quality information that is required may have negative repercussions both in the decisions made by health care professionals and patients, and in the setting of priorities by managers and politicians. As a result, the use of health care interventions that are ineffective, or even harmful, leads to large-scale wastage of resources each year, while other effective interventions are often underused. However, it is unreasonable to expect all those who want reliable information on the effects of health care—such as clinicians, managers, and the patients themselves—to scrutinize all the existing evidence from original studies, as this information is too extensive and disparate to be of practical use. Most are obliged to place their faith in nonsystematic reviews of original research as a means of combating the information overload that faces them. In fact, it is surprising that many health care decisions are being taken without those involved having access to reliable reviews that have systematically evaluated and updated the available scientific evidence.¹

The Cochrane Collaboration

The Cochrane Collaboration is an international organization created to improve the access of physicians, researchers, and the general public to scientific information regarding the efficacy and safety of medical treatments and interventions. This organization takes its name from the British physician Archie Cochrane, who drew attention in the 1970s to the widespread lack of awareness regarding the effects of health care practices.² These ideas have received growing support, initially restricted to certain specialties such as obstetrics, and from the 1990s onwards, throughout the medical sciences.

The work of the Cochrane Collaboration is based on the identification and exhaustive collection of data arising from clinical research in order to undertake a scientifically rigorous and transparent critical analysis. Its main task is to prepare, update, and publish systematic reviews of clinical trials on
health care interventions and, when these are not available, reviews of the most reliable evidence from other sources in an effort to help individuals make well-informed medical decisions. The organization produces a quarterly electronic publication, The Cochrane Library, which constitutes one of the most complete sources of information on clinical trials and systematic reviews.

Achieving the goals of the Cochrane Collaboration represents a challenge of such magnitude that some have compared it to the Human Genome Project in terms of its potential implications for modern medicine and the huge efforts that are being invested to guarantee or even improve the quality of the Cochrane systematic reviews. Thousands of people in more than 50 countries are currently actively involved in this work, which is supported by more than 650 organizations worldwide, including health care providers, research organizations, health care departments, international organizations, industry, and universities. These global collaborative efforts are providing valuable information to guide current clinical practice and future research. A recently published study provided data demonstrating that, on average, the Cochrane reviews of topics in dermatology have a higher validity than other systematic reviews published in the major scientific journals. In fact, the main medical journals are willing to publish adapted versions of the Cochrane reviews, thereby recognizing the importance of providing readers with high-quality summaries of available scientific evidence.

The Cochrane Collaboration is made up of various entities with specific roles. It is organized into different topics or study areas and is supported by Cochrane Centers distributed throughout the world. These centers share the responsibility of helping to coordinate and provide training and research support to members of the Cochrane Collaboration in their particular geographic area. In Spain, these activities are the responsibility of the Iberamerican Cochrane Center located in Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, which in turn coordinates the Iberamerican Cochrane Network, which has centers in Spain and Latin America. The Cochrane Collaboration is also organized according to health care areas that extend beyond specific health problems, such as health care provision (e.g., primary care), patient group (e.g., elderly), or types of intervention (e.g., vaccination). The individuals who are linked to the different fields ensure that the priorities and perspectives in their areas of interest are reflected in the Collaborative Review Groups.

The Collaborative Review Groups are international multidisciplinary teams whose members (researchers, clinicians, health care professionals, service users, etc) share an interest in documenting scientific evidence that is relevant, reliable, and up to date on the prevention and treatment of health problems in their specific area of interest. The review groups all share the highly efficient and rigorous working methods employed by the Cochrane Collaboration, as well as the principles on which it is based. These are essentially a spirit of enthusiastic collaboration that is open to the participation of individuals with distinct but complementary visions, the evaluation of relevant results that are of interest to decision makers, avoidance of unnecessary duplication of effort through good coordination of work, and guaranteed methodological rigor, transparency, and periodic update of reviews of clinical research.

The activity of the different members of the review group is supported by an editorial team—designated by the group itself—that coordinates, organizes, and supervises or assesses the activities of the group, thereby guaranteeing that the systematic reviews that are produced are of sufficient quality to be published in the Cochrane Library. One of these groups is the Cochrane Skin Group (CSG), which is made up of multiple international collaborators committed to the preparation of systematic reviews of clinical trials related to dermatology.

The Cochrane Skin Group

The CSG prepares systematic reviews of randomized clinical trials of any aspect of the management of skin disease that could be of use either for professionals or for the general public. Its contribution to the practice of dermatology is clear from the growing number of completed systematic reviews and review protocols in progress.

The areas covered by the CSG include interventions for the prevention, treatment, and management of skin diseases, as well as the effectiveness of different health care models. Sexually transmitted diseases, although commonly managed by dermatologists, are covered by a different review group. From a practical point of view, its activities may improve dermatological care by identifying the scientific basis of clinical decisions in dermatology. The process is initiated when a group of individuals jointly raises a question of clinical importance. A search for clinical trials, both published and unpublished, is then initiated, a critical evaluation carried out, and the information summarized rigorously and transparently in such a way that it can be understood both by health care professionals and by service users and administrators. To prepare a systematic review as comprehensively as possible it is necessary to identify and consider all randomized clinical trials on the subject. Consequently, the work of the CSG also involves a manual search for articles on clinical trials in printed journals (handsearching) and the development of an international register of clinical trials.

The editorial base that offers technical and statistical support to the reviewers during the development of protocols and reviews is closely linked to the Dermato-Epidemiology Unit of Queens Medical Centre at the University of...
Nottingham in the United Kingdom.\textsuperscript{11} The CSG was registered as a Cochrane entity in 1997, and since then it has become increasingly international and multidisciplinary, with notable patient participation.\textsuperscript{12}

**Patient Participation**

Patients and service users are actively involved in the CSG as authors of systematic reviews, external reviewers of protocols and reviews prepared by other authors, and as translators and handsearchers of clinical trials.\textsuperscript{13} They may also participate in the initial phase of deciding on a topic or proposing questions to be considered in a review. Thus, the topics chosen are of relevance and interest to patients and their families, and are not limited to aspects that might be of interest only to researchers and clinicians. For instance, a review and a protocol published by the CSG (on vitiligo and alopecia areata) have been led by patients.\textsuperscript{14-15} The participation of patients or service users in the reviews ensures that they are written in a way that is accessible to the general public. As a result, Cochrane reviews are easily understandable, since simplicity and clarity are essential to facilitating reading.

Consumers are also active participants in the annual meeting of the CSG and in the annual symposia of the Cochrane Collaboration. Also, the Cochrane Consumer Network provides information and acts as a forum to link patients and users participating in the Cochrane Collaboration and health care systems around the world.

**Cochrane Systematic Reviews**

Reviews of the literature occupy a key position in the chain linking the results of clinical research with the knowledge employed in health care. However, many reviews published in textbooks and journals (referred to as narrative since they are based on the opinion of the author) do not employ sufficient rigor and respect for the principles of scientific method, and their conclusions carry the serious risk of being biased, and as a result, their credibility compromised. Consequently, the use of narrative reviews, which often reach wide audiences due to the prestige of the author or of the book or journal in which they are published, commonly are of little or no use in making well-informed decisions. Only regularly updated systematically prepared reviews in which explicit criteria have been employed and scientific principles respected can provide objective, reliable, and accurate information on which to better base health care decisions.\textsuperscript{16} However, such systematic reviews are not easy to prepare as a result of the rigor and effort they require. Consequently, the efforts that have come to fruition remain few and limited, particularly if we take into account the challenge of answering all of the relevant doubts that arise on a daily basis and for which clear answers are unavailable.

In general, Cochrane systematic reviews are of a higher quality than those that have not employed the Cochrane methods. A study has been published examining 38 systematic reviews (17 Cochrane reviews published in the Cochrane Library, 11 Cochrane reviews published in journals, and 10 non-Cochrane reviews published in journals).\textsuperscript{4} The Cochrane reviews analyzed data on quality of life and adverse effects more often than the non-Cochrane reviews. Furthermore, the Cochrane reviews more often included the search strategies used, took measures to minimize bias in the selection of participants, and undertook an appropriate evaluation of the validity of all the clinical trials included.

In a comprehensive and reliable systematic review, every effort is made to identify all the clinical trials available on the subject studied, including those that do not support the researchers’ hypothesis or the product of the study sponsor. Publication bias refers to the tendency for selective publication of studies with favorable results. The dermatology literature is not devoid of such practices. For instance, in the United Kingdom a systematic review funded by the government with an unfavorable conclusion regarding the use of evening primrose oil for atopic dermatitis included 20 clinical trials, 8 of which, while influencing the final result, had not been published in the public domain.\textsuperscript{17} Duplicate publication is another way to overemphasize the results of a study. For instance, a systematic review of 278 clinical trials of treatments for atopic dermatitis found 8 cases of duplicate and 1 of triplicate publication.\textsuperscript{18} Some sponsors have applied significant pressure to suppress or delay the publication of valuable studies that yielded results that were unfavorable for their product.\textsuperscript{19}

Systematic Cochrane reviews have contributed significantly to improving health care and use of effective, simple, and inexpensive interventions. For instance, they provided evidence regarding the efficacy of treatment with corticosteroids in pregnant women at risk of premature birth.\textsuperscript{20} Furthermore, they have questioned the widespread use of some interventions that have been proven to be ineffective or even harmful, such as the use of albumin for hypovolemic shock in critical patients.\textsuperscript{21} In addition, they have contributed to identifying areas in which no evidence is available regarding the effect of important interventions, and this has led to new lines of research. For instance, a review of the use of anticonvulsant therapy in women with eclampsia revealed a serious lack of evidence in an area where there was little agreement between experts, leading to the realization of a large international study\textsuperscript{22} that was considered the most important clinical trial undertaken in obstetrics during the 20th century.
The Cochrane Library

Through the electronic publication of the Cochrane Collaboration, the Cochrane Library, it is possible to consult one of the largest databases of clinical trials and systematic reviews available. There is an electronic edition in Spanish—known as Cochrane Library Plus (Biblioteca Cochrane Plus)—that is freely available without charge throughout Spain and some countries of Central and South America.23 It is published quarterly in CD-ROM format and on the Internet and includes the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), critical evaluations and structured summaries of systematic reviews published elsewhere, a register of clinical trials and their bibliographic references, and other sources of information on methods and evidence-based medicine.

The Systematic Review Process

The Cochrane Collaboration has a manual (The Cochrane Manual) that provides a practical description of the process and knowledge necessary to prepare a Cochrane systematic review.24 The Iberoamerican Cochrane Center also offers periodic interactive courses—that allow step-by-step learning and application of the knowledge and basic skills necessary to prepare a systematic review, including use of the free Cochrane Collaboration software RevMan for the preparation of reviews.25

The title of the review must be formally registered with the CSG by sending a registration form to the editorial base, which will decide on whether or not it is accepted. It is essential to determine beforehand whether other authors are already carrying out the same review by consulting the webpage where the titles of all Cochrane reviews are listed,26 including those that are not yet published in the Cochrane Library, to identify possible duplications or other expressions of interest to join the review group. A standard format is used to write the title according to the following basic formula: [intervention] FOR [disease or health problem]; eg, antibiotics for acne vulgaris. When the population of patients studied is explicitly mentioned the format is as follows: [intervention] FOR [disease or health problem] IN [type of patient]; eg, systemic treatments for tinea capitis in children. Once the title of the review has been registered, the editorial team of the CSG will contact the lead author and offer help in developing the search strategy for the protocol, including use of the free Cochrane Collaboration software RevMan for the preparation of reviews.25

The Cochrane Systematic Review Method

The method used for Cochrane systematic reviews is based on identifying and using the best scientific evidence available for patient care.28

Search Strategy and Access to Databases

Once the title of the review has been registered, the editorial team of the CSG will contact the lead author and offer help in developing the search strategy for the protocol, including access to databases if this is not available to authors in their own institutions. The authors can also make use of resources available on the website of the CSG.12

To identify the studies, a search is carried out in the databases described below, using terms for the disease combined with the interventions or interest and a sensitive strategy to identify randomized clinical trials, as described in the Cochrane Manual.

The Specialist Register of the Cochrane Skin Group

Authors can search the specialized CSG database of the Cochrane Library, containing references to all clinical trials in dermatology included in the Cochrane Library, obtained by handsearching, those published in specialist conferences, completed but unpublished clinical trials,29 and those that
are in progress. An example unique in dermatology is the CSG clinical trials register, which obliges registration of all clinical trials before they are initiated. This mechanism does not guarantee that all clinical trials are published but it does at least alert researchers to what has happened in studies that were carried out but not published. Although major criticisms have been raised regarding the limitations of the clinical trials published in dermatology,30 it appears that little has changed in the last 20 years.31,32 Selective publication of only certain clinical trials skews interpretation of the true effect of medical interventions, leading to a loss of time on the part of physicians and patients, spending of public money, and possibly serious harm.33

The Cochrane Central Register of Controlled Trials (CENTRAL)

The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library currently contains more than 489,000 references and represents the best database on clinical trials that is currently available. These are identified thanks to a coordinated worldwide effort that includes handsearching of more than 1700 biomedical journals in various languages, electronic searching of databases, and joint efforts with the pharmaceutical industry and other groups to ensure that access is available to all identified clinical trials in order to avoid publication or selection bias, which could ultimately lead to biased estimates of the effects of medical interventions.

MEDLINE

The “preliminary” search strategy for MEDLINE using the terms for the disease and the interventions is used as a basis for the development of search strategies in other databases. All references to clinical trials in MEDLINE up to 2002 have been transferred to CENTRAL. Consequently, MEDLINE need only be searched from 2003 to date.

EMBASE

EMBASE is a biomedical database containing information on pharmacology, medical research, and toxicology. It includes references from some European journals that are not included in other databases. All clinical trials held in EMBASE from 1974 to 2004 (some 73 million clinical trials that are not present in MEDLINE) have now been incorporated in CENTRAL.

LILACS and Other Databases

LILACS is a Latin American and Caribbean database of information in the health sciences that uses disease and intervention terminology in Spanish and Portuguese.34 There may be other databases that contain information relevant to a particular review, such as PsycINFO (psychology) and AMED (alternative and complementary medicine).

The CSG also recommends the following sources of information on clinical trials be included in the search strategy: the references contained in the studies identified in the search and in narrative reviews, contact with authors of clinical trials and participating centers, and meta-registries of clinical trials (www.controlled-trials.com and www.clinicaltrials.gov). Conference proceedings and posters are also explored in the search for clinical trials. The CSG may have included in its registry searches of certain conferences or meetings, and it is therefore useful to consult this information on its webpage.
To assess the effect of interventions it is also important to investigate their possible adverse effects. Although Cochrane reviews already contain information concerning the side effects described in each clinical trial, this type of study is not the best way to identify serious, rare, or long-term adverse effects. For these types of side effects it is necessary to carry out a more extensive literature search and prepare a qualitative summary of the information obtained. The Cochrane Manual contains a section on inclusion of adverse effects in systematic reviews.

Selection of Studies

The most reliable scientific evidence comes from well-designed randomized clinical trials and, consequently, only these form the basis for Cochrane systematic reviews. The authors of the review evaluate each study identified in the search to determine whether it meets the predefined criteria for inclusion related to both the study design and the characteristics of the participants, interventions, and results. However, it is also important to evaluate all information arising from clinical research and in particular controlled clinical trials (quasi-randomized), where allocation is carried out using nonrandom methods (e.g., those based on characteristics such as date of birth, name, or history number) that can be mentioned but not assessed more extensively in Cochrane reviews. Other types of evidence such as that derived from case-control studies are used in questions regarding adverse events and are described qualitatively.

Assessment of Methodological Quality

Assessment of the quality of randomized clinical trials included in the systematic review requires evaluation of the following elements that can affect the final estimation of the effect of treatment:

Method Used to Generate the Randomization Sequence

In a randomized clinical trial, allocation of each patient to a particular group is unpredictable or random. The process involves the use of random-number tables, generally computer generated, although simpler methods such as flipping a coin can also be used.

Method Used to Conceal Allocation

Upon deciding whether a potential participant is eligible for inclusion in a clinical trial, the investigators may be aware of whether the individual is assigned to the treatment or control group. The method used to conceal allocation will be adequate if randomization is central, dispensing of the intervention is centralized in another area using numbered or coded containers, and the envelopes that contain the intervention code are numbered sequentially, opaque, and well sealed.

Blinding of the Investigators and the Participants Following Allocation

Blinding ensures that the intervention being administered is unknown (single or double blind) and prevents influencing or partial evaluation of the results. Blinding the investigator is particularly important, except in the case of easily observable outcomes such as death.

Loss to Follow-up

All participants are monitored and analyzed in the groups to which they were assigned on enrollment so as not to influence the results. When participants are lost it is important to indicate how many have been lost in each study arm. If the losses are counted as failed interventions it is known as intention-to-treat analysis.

Other Criteria

In addition to these general quality criteria, which are assessed in all studies, additional specific quality criteria can be used for each review: baseline comparison of the study groups (age, sex, duration and severity of disease), appropriate definition of the skin disease studied, specification of inclusion and exclusion criteria in the clinical trial, or adequate description of the interventions. It is important to differentiate between selection criteria and quality criteria. For instance, a review on bullous pemphigoid can specify that confirmation of all cases by immunofluorescence is required, when this is a criterion for inclusion. On the other hand, a different group of authors may wish to be more flexible in their definition of the disease and decide to include patients with a clinical diagnosis of bullous pemphigoid carried out by a dermatologist and specify immunofluorescence as an additional quality criterion.

Data Collection

It is desirable for data extraction from the clinical trial to be carried out by at least 2 authors. The review authors may contact the authors of the clinical trials to clarify or verify
Analysis and Synthesis of the Information

Different statistical models are used to assess the effect of treatment in each clinical trial. Dichotomous results (eg, cure vs no cure) are expressed with relative measures such as relative risk or risk ratio and the 95% confidence interval (CI), and if appropriate, also with absolute measures such as the number needed to treat and its CI. Continuous data are expressed as the weighted mean difference and CI. The results of multiple individual studies are combined in order to extract the most accurate estimates of the effects of treatment. A systematic review seeks to provide an overall estimate of the effect of an intervention based on the weighted mean of the results of all available individual studies with similar characteristics and quality. In this meta-analysis, the results of each study are generally weighted in such a way that greater weight in the final result is given to larger studies that provide more accurate estimates. Sometimes the weighting also takes into account the methodological quality of the studies.

When these statistical methods are used to combine the studies it is necessary to assess the heterogeneity between them. The source of the heterogeneity is explored in the sensitivity analysis. The reasons for the differences in the sensitivity analysis between the studies can be factors related to the participants (for instance, age, diagnosis, sex, or comorbidity), treatment (for instance, dosage or formulation), or the study itself (for instance, the quality of the information).

Application of the Results to Clinical Practice

The main aim of a Cochrane review is to provide the best information possible without offering advice or recommendations, and without making assumptions regarding the circumstances of clinical practice. The conclusions of the review are provided succinctly, such that the principal results are clearly and directly reflected. The implications for clinical practice tend to be clear and practical, focused on the evidence that has been reviewed and on the possible limitations of the information or the analysis. In this regard, it is important not to confuse “no evidence of efficacy” with “evidence of no efficacy.”

Cochrane reviews can help to establish whether an area of research is necessary, why, and the degree of urgency. They may also suggest the most important priorities for clinical trials in terms of future comparisons, improved design, and results.

Conclusion

Politicians, health-care managers, clinicians, and patients should base their decisions on scientific evidence. Despite there being numerous publications and controlled clinical trials in dermatology, many practices and policies in dermatology are not based on rigorous scientific data. To carry out all of the activities necessary for the development of evidence-based dermatology requires collective participation in a major effort that is only possible to achieve through the spirit of collaboration promoted by the CSG.

Conflicts of Interest

The author declares no conflicts of interest.

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