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Editorial

Cochrane systematic reviews: contributions and perspectives

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Approximately 2.5 million new scientific articles are published each year in 28,100 different scholarly, peer-reviewed English-language journals [1], which represents an increase of about 2.5% each year. Physicians, researchers, and decision makers cannot possibly keep up to date with all the primary research findings and apply updated evidence-based results to their decision-making.

Systematic review and meta-analysis, a critical appraisal and synthesis of research findings performed in a systematic manner, emerged in the late 1980s. It is now considered the cornerstone of the clinical decision-making process. It is also essential for research planning because it avoids planning redundant and useless clinical trials [2].

The number of publications of systematic reviews and meta-analyses has increased exponentially [3,4]. However, the planning, conduct and reporting of several systematic reviews (some of which are published in high impact factor journals) raise some issues [4–6]. The search strategy is not always comprehensive, and the assessment of the primary study methodological quality is frequently inconsistent. Publication bias is often ignored. The reporting lacks transparency. In addition, systematic reviews are rapidly out of date. Furthermore, the accuracy of systematic reviews and meta-analyses performed by pharmaceutical companies or researchers linked to these companies is questionable. Indeed, a systematic review comparing conclusions of meta-analyses performed by industry versus non-industry showed that financial ties to one drug company was the only characteristic statistically significantly associated with favorable conclusions [7].

The Cochrane Collaboration was founded in 1992 by Ian Chalmers and a group of 70 other international colleagues to overcome the lack of appropriate evidence synthesis. Cochrane currently consists of more than 37,000 contributors from 130 or more countries. Cochrane mission is to "promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesized research evidence". The Cochrane Musculo-Skeletal group (http://musculoskeletal.cochrane.org) is one of the largest groups, with more than 700 active members from 26 countries and almost 400 published systematic reviews and ongoing protocols. The group is producing reliable, up-to-date systematic reviews of interventions for the prevention, treatment or rehabilitation of musculoskeletal disorders. For example, the group published a series of network meta-analysis on biologics in people with rheumatoid arthritis [8–12]. The most recent publication [9] focused on the benefits and harms of biologics and small molecule tofacitinib versus methotrexate (MTX)/other DMARDs in people with rheumatoid arthritis who are naive to methotrexate. This NMA included 19 RCTs with 6485 participants and concluded that "biologic with MTX use in MTX-naive populations is beneficial and that there is little/inconclusive evidence of harms. However, more data are needed for tofacitinib, radiographic progression and harms in this patient population to fully assess comparative efficacy and safety".

Cochrane is internationally recognized for the quality of its reviews and its high standards in terms of comprehensiveness of the literature search, quality of data extraction, assessment of primary study reports, and assessment of the level of evidence by use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification. Cochrane also has a very strong policy regarding conflict of interest, with no commercial or conflicted funding studies accepted. To avoid bias and "cherry picking", Cochrane requires the submission, peer review and publication of a protocol. Further Cochrane protocols are automatically added to Prospero, an international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero). A comparison of Cochrane and non-Cochrane reviews showed that Cochrane reviews scored higher in terms of methodological quality and transparency than non-Cochrane reviews [13].

To favor uptake of review findings in clinical practice, Cochrane summarizes the results in "plain language summaries" that provide a clear, concise and jargon-free summary of the key questions and findings of the systematic review. These summaries are dedicated to all users, particularly patients. Also, when possible, systematic reviews are reported with Summary of Findings tables designed to present key findings in a concise format with a description of essential information such as effect estimates and the certainty of the evidence according to the GRADE classification.

One of the strengths of the Cochrane Collaboration is the very strong network of Methods groups that question the methods used in systematic reviews, explore new methods and concepts and develop new tools. For example, Cochrane has been at the forefront in developing its Risk of Bias tools for randomized controlled trials (RoB) and non-randomized studies (ROBINS) [14]. RoB is currently the tool most frequently used to assess the quality of studies included in Cochrane and non-Cochrane systematic reviews.

Cochrane has developed very strong guidance for the planning and conduct of systematic reviews. This guidance is also used as a

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model for meta analyses by researchers performing non Cochrane reviews which could increase the overall quality of systematic reviews. However, how systematic reviews are planned and conducted is evolving considerably, with new sources of data available, new methods and new paradigms.

1. From published data to multiple sources data

Systematic reviews and meta-analyses currently rely mainly on data extracted from published articles identified by screening a large number of citations retrieved from extensive searches in electronic bibliographic databases. However, about half of completed randomized controlled trials are not published, with clear evidence of publication bias.

Furthermore, publications are not a trustful reflection of how the trial was planned, conducted and analyzed. For example, systematic comparisons of outcomes listed in protocols or in trial registries and outcomes reported in publications showed that about one third of primary outcomes are deleted, modified or switched to a secondary outcome. This situation is a major threat to the interpretation of systematic reviews and meta-analyses [15].

Important initiatives were implemented to improve this situation. Editors require prospective clinical trial registration. The US law requires results from clinical trials of US Food and Drug Administration-approved drugs to be posted at ClinicalTrials.gov within 1 year after trial completion. Searching trial registries is now an essential step to identify both published and unpublished trials and to obtain outcome data. A systematic assessment of a sample of systematic reviews of randomized controlled trials showed that additional trials could be identified in trial registries in 43% of the reviews, with results available in the registry for half of them [16]. Furthermore, a study showed that reporting, particularly for serious adverse events, is significantly more complete at ClinicalTrials.gov than in the published article [17]. Nevertheless, only one third of non-Cochrane reviews reported searching trial registries [16].

Other sources of data are becoming accessible. Some pharmaceutical companies have also decided to release their data and for industry-funded trials, have set up a platform (https://www.clinicalstudydatarequest.com) for investigators to access all information from the protocols to the clinical study report and raw data [18]. Other initiatives such as the Yale University Open Data Access Project (http://yoda.yale.edu) aims to increase access to clinical research data and to promote its use to generate new knowledge. In 2016, the European Medicines Agency (EMA) became the first regulatory authority to give open access to clinical data submitted by companies in support of their marketing authorization applications. Researchers can now access these data at a specific website (https://clinicaldata.ema.europa.eu/web/cdp/home). Only clinical study reports are currently available, but the EMA is planning to give access to individual patient data.

Clinical Study Reports (CSRs) are dedicated to regulators. These documents provide detailed descriptions of the methods, conduct and results of a clinical trial. There is some evidence that CSRs contain more complete and accurate information about the trial than published articles [19]. However, other issues relate to the logistics of wading through all this information (a CSR contains a median of 600 pages), how to link all the information for a single trial (protocol, publications, registry, data management plan, CSR, raw data, etc.) and how to manage discrepancies between the various documents [20].

2. From meta-analysis to network meta-analysis (NMA)

Traditionally, systematic review and meta-analysis provides effect estimates for pairwise direct comparisons between two treatments. However, patients, physicians, and decision makers are more interested in a holistic approach considering all available treatments. NMA is a new analytic method that allows for evaluating the comparative effectiveness of many interventions for a specific clinical indication by gathering evidence from both direct and indirect comparisons. NMA provides effect estimates for all possible comparisons and can rank the treatments. This new method was rapidly embraced by academic and non-academic institutions, with an explosion of publications notably in journals with high impact factors.

However, such techniques rely on complex methods and should follow the same rigorous process as for systematic reviews. Nevertheless, a systematic assessment of published NMAs showed that they did not follow an appropriate process and were poorly reported [21,22]. Indeed, one third of NMA reports did not identify the primary outcome, half did not assess the risk of bias of primary studies and 85% did not explore publication bias. Overall, 72% were rated at low quality [21,22]. Cochrane, through its Methods group dedicated to “Comparing Multiple Interventions”, created in 2010, developed guidance for performing and interpreting these reviews, and several NMAs were published by the Cochrane musculoskeletal group [23–26].

3. Living network meta-analysis. A new paradigm

Another major issue with systematic reviews is that they become out of date almost as soon as they are published. Cochrane has been working to identify triggers to decide when to update a systematic review. However, these methods are questionable. Indeed, stakeholders expect to have access to all evidence when making a decision. Unfortunately, this situation is far from the case. A study of lung cancer sequentially compared the amount of evidence included in systematic reviews to the randomized evidence available for inclusion each year. No more than 60% of treatments, treatment comparisons and trials with available results were included in published systematic reviews [27]. Ravaud and colleagues proposed a new paradigm based on a living network meta-analysis, with the network meta-analysis updated as soon as a new evidence is available [27,28]. A recent study showed that such methods could facilitate timely recommendations and reduce waste in research [29]. However, this method requires rethinking the planning and conduct of systematic reviews and the dissemination of results.

In conclusion, systematic review and meta-analysis is indispensable for clinical decision making and for the planning of future primary research. However, results of systematic reviews could be misleading if they are not performed under a strict process. Cochrane is essential for providing trusted evidence synthesis and for exploring new methods for evidence synthesis.

Disclosure of interest

Isabelle Boutron is deputy director of Cochrane France, co-convenor of the Bias Methods group and editor of the Cochrane musculoskeletal group.

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