Systematic reviews and meta-analyses: black boxes of medical literature?

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Essentially, a systematic review uses systematic and explicit methods to identify, select and critically appraise relevant research to answer a clearly formulated question. It collects and analyses data from the studies that are included in the review [1]. A meta-analysis aims to combine the quantitative results of these studies by statistical methods. Its purpose is to provide a summarized and thereby more precise effect of the results. Thus, a good systematic review is essential for a good meta-analysis [2].

That sounds quite dry. But why do we consider systematic reviews and meta-analyses that important? Because they matter! Meta-analyses and systematic reviews are a pivotal foundation for evidenced-based decision-making on diagnostic or therapeutic procedures. Physicians rely on this comprehensive knowledge and trust that they do the best possible for the patient by observing the messages. In addition, many clinical guidelines are based on systematic reviews and meta-analyses. This is the reason why our journal is committed to highest quality of this publication type, too. Further, systematic reviews and meta-analyses are valuable tools for health authorities, insurance providers and other public institutions to manage and to advance public health.

However, systematic reviews and meta-analyses serve also other purposes. Knowledge of the relevant publications helps to avoid unnecessary clinical trials, when the outcome is already clear from cumulated data. ‘Unnecessary’ applies to the risk for participants, who are denied the best treatment, as well as to spending of manifold resources. Furthermore, it is not consistent with good scientific and clinical practice to ignore results of previous research. Internationally recognized guidelines for set-up and reporting of clinical trials, the SPIRIT and CONSORT Statements [3, 4], request accounting for the current knowledge, the evidence. This includes checking for up-to-date systematic reviews and meta-analyses.

A systematic review requires five steps:

(i) framing of the question,
(ii) systematic search for and selection of relevant trials,
(iii) evaluation of the trials with specific consideration of the risks of biases,
(iv) analysis and summarization of results (with or without statistical synthesis of data) and
(v) interpretation of results.

The question is subject to the PICO rule: Patient, Intervention, Comparison and Outcome. That is, does a specific event (O) occur in patients with a specific problem (P) when one specific intervention (I) or a control intervention (C) is applied?

 Afterwards, performing a systematic review requires precise and diligent working. The scientific and non-scientific literature has to be searched as completely as possible. Major sources are the biomedical databases Medline, Cochrane Library and Embase. Searching trials registers and checking references of included studies and any relevant systematic reviews are also mandatory. Further sources are national, regional and subject-specific bibliographic databases, reports, dissertations, thesis databases, abstracts presented at conferences and journals that are not listed in the electronic databases. Contacting relevant entities (e.g. industry) for information on unpublished or ongoing studies is not any less important. Search strategies have to be carefully documented to allow for repetition [5].

Following the selection of relevant publications, biases of the reports have to be accounted for. Biases can be classified as

(i) selection bias due to differences between the baseline characteristics of the groups,
(ii) performance bias due to differences between other factors than the intervention including blinding,
(iii) detection bias due to differences in the determination of outcomes,
(iv) attrition bias due to differences in withdrawals resulting in incomplete data and
(v) reporting bias due to selective outcome reporting, in specific non-reporting of findings [5].

The next step is the statistical synthesis that is the meta-analysis proper. Firstly, data for outcome measurements of each study are recently published [6, 7]. Secondly, the
average of effects across all studies is calculated. Studies are weighted for samples size and/or variance of their results [5].

A thorough interpretation is to follow. It is the basis for transfer of the results to clinical practice. Therefore, this step necessitates again critical discussion not only of the results but of the whole working process and must allow the reader to appraise the limitations of the message with regard to her/his own patients. Of note, meta-analyses are not suited to reveal causative relations but only describe associations.

To sum up, drafting systematic reviews and meta-analyses requires competences in several areas. An interdisciplinary team that unites experts for each topic is necessary. To cite an article in JAMA: ‘It is relatively easy to create a mediocre or poor quality meta-analysis: an inexpert literature search and data extraction requires few resources and little training, and contemporary statistical packages (including those that are free) make it possible to complete an entire study quickly. This makes meta-analysis attractive to researchers with limited training or mentoring and has led to a plethora of such publications.’ [8]

But how can users of systematic reviews and meta-analyses find out if a paper is applicable to their patients and whether the quality is good enough to rely on it in practice? The Centre for Evidence-Based Medicine (CEBM) based in Oxford has published a set of Critical Appraisal tools [9] for systematic reviews including meta-analyses and for some types of clinical trials. The worksheets can be applied by any interested reader and are also recommended to peer-reviewers of manuscripts.

In the last years, prospective registration of randomized, controlled trials in approved databases and reporting according to the CONSORT Statement [4] have become standard, mainly due to the consensus of scientific journals to request both measures for publication. Correspondingly, systematic reviews and meta-analyses are to be reported according to the PRISMA Statement [1]. As a further effort to improve transparency, the register PROSPERO was launched in February 2011 as an international database for prospective registration of systematic reviews and meta-analyses at initial stage [10]. The purpose is to provide a permanent record of work in progress in order to guard against non-publication of ‘negative’ results and to avoid duplication of efforts. Prospective registration of protocols for systematic reviews and meta-analyses will become part of good scientific practice and a precondition for publication. EJCTS and ICVTS will implement the request in our policy.

Conflict of interest: Anette Blümle is an employee of Cochrane Germany, an entity of Cochrane whose handbook is cited in the paper. See http://www.cochrane.de/welcome for aims and scopes of the institution.

REFERENCES