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EDITORIAL

Noblesse oblige: critical issues at the highest level of clinical evidence

1. Noblesse oblige

Systematic reviews and meta-analyses are considered to represent the highest level of clinical evidence, especially when it comes to the assessment of all available research data on the efficacy and effectiveness of interventions. This of course requires that the evaluated research is relevant for the question under study, and that the reviews and meta-analyses meet essential criteria of methodological quality, reproducibility and objectivity. Also, independence and impartiality are crucial. Preferably avoidance of—but at least appropriately and transparently managing—any potential conflicts of interest so that these cannot influence the results, must be guaranteed. This also implies that systematic review authors should not be engaged in public interest groups or other activities related to their topic that may undermine their credibility when making reviews or updates. Beyond providing well balanced information based on the available data, they must not be involved in public and political debates; engaging in advocacy risks the perceived objectivity and thus the credibility of the original review, as well as updates when new studies are to be evaluated and integrated. In other words, the roles of independent systematic review author and advocate should be clearly separated. This may also imply that systematic review authors should not work for too long on the same topic, in order to keep fresh and non judgmental toward what they have to evaluate.

At the same time, it is preferable that systematic review authors have substantial experience with empirical work in primary studies in the clinical or public health field in which they do their reviews. Without such experience, it is difficult to make an appropriate and fair judgment on what can be considered the best possible and achievable evidence in the field of interest, and on what the related findings should imply for practice. Having only literature-based experience can be insufficient.

Meeting all these requirements in combination—in order to avoid not only manipulation bot also unconscious bias—is not easy. It has to be safeguarded by responsible professional networks and organizations with full public accountability, support from protocols, and strict and transparent review processes. In this context, networks as the Cochrane Collaboration [1] and the Campbell Collaboration [2] and institutions as the Agency for Healthcare Research and Quality [3], have huge responsibilities and must seek continuous self-evaluation, external review and ongoing improvement.

2. Good systematic review practice

Such safeguards are crucial since often critical decisions must be made at the key steps in the conduct of a systematic review: defining a clear research question and literature search strategy, selecting relevant studies, assessing methodological quality or risk of bias, abstracting relevant data, synthesizing results, and reporting findings [4].

In this context, Robson c.s. considered that, while much research has been conducted on optimal literature search strategies, developing tools for assessing risk of bias, and assessing the quality of reporting, there is much less information to support current standards on how to select studies for inclusion in systematic reviews, abstract their data, and appraise their quality. They therefore conducted a systematic review to determine the accuracy, reliability, impact, and efficiency of different methods for study selection, data abstraction, and quality appraisal. Of 5,600 screened titles and abstracts and 245 full-text articles, 37 studies were included. Based on their findings they make recommendations for: screening of titles and abstracts (e.g., using reviewers with content expertise and two independent reviewers), for data abstraction (e.g., using data abstractors with experience conducting reviews, and contacting authors for additional data when needed) and for quality appraisal (e.g., intensive training, providing decision rules for studies reporting insufficient detail, and contacting authors for details regarding quality assessment). Also, recommendations are made on how to act if the available resources preclude the application of the optimal approach. As the authors conclude, while few studies documenting common systematic review practices exist, these few studies do provide useful support for good systematic review practices. In addition, their results provide an updated evidence-base for current knowledge synthesis guidelines and methods requiring further research. The authors propose to update guidelines for systematic and rapid reviews, particularly on how to optimally and consistently deal with limited resources for the review.

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But availability of guidelines does not guarantee that these are appropriately implemented. Propadalo et al. studied whether and to what extent in Cochrane reviews risk of bias assessments for allocation concealment were in line with recommendations from the Cochrane's Handbook guidance. For this purpose, they analyzed judgments and comments of 721 Cochrane systematic review, covering 10,280 randomized controlled trials, and found that judgments for allocation concealment were discrepant for 29% of the trials. Their findings are an important signal, since if judgments of risk of bias are erroneous, the conclusions of reviews, and therefore the evidence input for clinical guidelines and clinical practice, may be misleading. The authors therefore conclude that interventions for improving judgments of allocation concealment in Cochrane reviews are warranted.

When reviews, and overview of reviews, have been conducted an important next step is to present the results in such way that they quickly find their way to where and when they are needed to improve clinical guidelines and patient care. In order to achieve this, excellent abstracts are crucial. For overviews of systematic reviews (OoSRs) Bougioukas and coauthors worked to offer guidelines to promote transparent and sufficient reporting in abstracts of OoSRs of health care interventions in a newly developed instrument: ''Preferred Reporting Items for OoSRs abstracts'' (PRIO for abstracts). Relevant items were developed by combining key features from abstracts of OoSRs, PRISMA for abstracts, and published reporting guidelines for OoSRs. The initial version was reviewed by experts who gave feedback, followed by pilot testing by a group of researchers. The refined checklist was applied in a sample of abstracts by two reviewers independently. The mean inter-rater reliability was 0.87. The authors provide an explanation and at least one published example of good reporting per item. They expect that this instrument will assist authors in writing transparent and informative abstracts for OoSRs and can be adopted by journals publishing such overviews.

3. Better input from primary studies needed

For allowing systematic reviews to make both unbiased and useful contributions to clinical guidelines and practice, non-selectively reported and patient-relevant outcomes are required. However, obtaining these from primary studies is still challenging. Aggarwal and Oremus reviewed randomized controlled trials of lung cancer immunotherapies and assessed the frequency of trial registration, reporting of trial registration numbers, prospective registration, and compliance with CONSORT guidelines [5]. They found that that selective outcome reporting is present and conclude that the use of trial registries in cancer immunotherapy is inconsistent, emphasizing the concern with this type of publication bias in this field. In another systematic review, Dorsey-Treviño et al., assessed the types of outcomes in randomized controlled trials of endocrine-related illnesses published in top endocrinology journals. Patient-important outcomes as primary outcomes were included in only one out of every 10 trials, and only 30% of the trials assessed patient-important outcomes at all. This finding was observed in all fields of endocrinology irrespective of study size, design, and funding. The authors conclude that at least for endocrinology treatment decisions of patients and clinicians are, in most cases, not based on what matters most to both of them. This threatens patient-centered care and the trustworthiness of the evidence that is guiding clinical decisions and practice guidelines.

Sharing individual patient data from primary research is an important way to make reviews and meta-analyses more topical and more directly connected to the original data. This is obviously a step further than contacting authors of primary studies for additional data when needed in the context of a review of already published data. In such cases, the willingness of investigators to share information or even all their data is crucial. We have previously highlighted this issue of research data as a public good, and made suggestions for positive incentives for sharing data [6]. Polanin and Terzian now address one of the paradoxes faced by those trying to encourage this: while sharing individual participant data among researchers is an ethical and responsible practice, primary study authors are often unwilling to share individual patient data for use in a meta-analysis. They evaluated whether a data-sharing agreement helps to increase researchers' willingness to share such data, using a randomized controlled trial design in conjunction with a web-based survey. Of more than 1,200 primary study authors of studies included in recent meta-analyses, 247 participated. Based on the survey, identified issues and concerns of participants were specifically addressed in a data-sharing agreement newly developed by the authors, for example, by adding statements like: ''The Primary Researcher (you) is under no obligation to modify, edit, update, or reanalyze the primary study dataset. Please provide, however, any documentation available that may be useful to the meta-analysis.''; ''The Primary Researcher (you) has the right to provide input and consultation to the project.''; The 'Right to Collaboration' statement addressing coauthorship', and, although financial compensation was not a significant concern, a statement addressing financial reimbursement. The participants who received a data-sharing agreement were indeed more willing to share their data set than control participants. The authors conclude that data-sharing attitudes can be improved by preemptively addressing researchers' concerns, and recommend that meta-analysts who communicate with primary study authors should send a data-sharing agreement along with the email asking for the data set.

In summary, as systematic reviews and meta-analyses are considered the highest level of clinical evidence, they

must also meet the highest possible standards of quality, independence and credibility. There is still much room for improvement in order to promote good review practice and the availability of valid, patient-relevant primary data.

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