

Cochrane Scientific Committee

Recommendation statement/report

Date: 28th February 2018

Relates to agenda item and meeting reference: 5.1

Priority: Medium

Open access/restricted: Open

INTERIM GUIDANCE ON HOW TO DECIDE WHETHER TO INCLUDE CLINICAL STUDY REPORTS AND OTHER REGULATORY DOCUMENTS INTO COCHRANE REVIEWS

Lead developers/investigators: Tom Jefferson, Peter Doshi, Lesley Stewart, Isabelle Boutron, Carol Lefebvre, Mark Jones, Su Golder and Alex Hodkinson

Abstract:

Aim & objective: To produce interim guidance on the circumstances under which clinical study reports and other regulatory documents should be considered for inclusion in Cochrane Reviews, either in addition to or instead of data from more traditional sources.

Methods for development: There is very little evidence on which to develop guidance and identify a rule for determining which reviews would most benefit from the inclusion of such data. Experts used their own experience and knowledge having surveyed the literature. They also undertook a survey of both Cochrane and non-Cochrane authors to ascertain current practice. The guidance focuses on clinical study reports and other regulatory documents relating to pharmaceuticals and biologics for which these documents generally exist. Authors admit, however, that non-pharmaceutical interventions (such as implantable devices, surgery, rehabilitation, behavioural interventions and diagnostics) are responsible for a large part of healthcare expenditure and that regulatory activity and transparency have been recently increasing in this area, at a slower pace, however, particularly the field of devices.

Results/Development: Table 1 (pp 8-11) in the guidance contains a selected and illustrative list of studies that have compared different sources of data for the same trial, such as publication vs. CSR or trial register entries vs. publications. Although this is not an exhaustive list of all such studies, it covers more than 50 different interventions and offers glimpses of the ways in which reporting bias affects the biomedical literature. Survey results on current review author practice from 160 respondents found 20/160 (13%) of the respondents had previously requested or used CSRs and other regulatory documents, 7/160 (4%) had considered it, and 133/160 (83%) had never considered it. Data sought by survey respondents were mainly from the EMA and/or the FDA (19 (40%) of the 47 requests made by those previously requesting CSRs in total) and/or directly from pharmaceutical companies (18/47 (38%)). 5/47 (11%) of the requests included non-regulatory data requests to authors of published trials. Amongst the 20 respondents that requested regulatory data, 12 (60%) involved CSRs, five obtained medical and statistical reviews

from the FDA and two European public assessment reports (EPARs). The main reasons for accessing CSRs were concerns about reporting biases 11/20 (55%), outcome reporting bias and publication bias (5/20 - 25%). Trigger criteria were developed (Table 3, p14) and tested on a survey of n=21 survey responders who had used such data, results are provided on level of importance in Figure 1, p15.

Final product: A report provides interim guidance on how to decide whether to include clinical study reports and other regulatory documents in to Cochrane Reviews, and includes a glossary of document types with definition and document image. This guidance does not address how to access, assess and extract regulatory data. Report authors conclude that Cochrane should consider making regulatory data a preferred source, primarily when the intervention in question is of potential high value and when there is evidence of reporting bias, or both. Cochrane should invest in its infrastructure to make this possible.

SUPPORTING DOCUMENTATION

Presentation: [link](#)

Editorial (received post meeting): Redefining the 'E' in EBM. Jefferson T, Jørgensen L. BMJ Evidence-Based Medicine. Epub ahead of print: 9 March 2018. doi:10.1136/bmjebm-2018-110918

CSC RECOMMENDATION

Highly recommended

Because

Recommended with provisions

Because

Optional/advisory (one among several options)

CSC members agreed this data was important in tackling reporting bias. Further development of methods and tools were required that identifies where more evidence is needed as well as where Cochrane should concentrate its energies. The report's findings were accepted in principle by the committee. However, further consideration of roll out and implementation within the main body of Cochrane required the input of both Governing Board (resources) and Editorial Board (implementation requirements).

Not recommended

Because

CSC STATEMENT

Summary statement

Following a presentation from Tom Jefferson and Peter Doshi (providing disclosures) raising their concerns on reporting bias in Cochrane Reviews they asked, as a matter of urgency, Cochrane starts to debate how and when it should expect Cochrane Reviews to look beyond published journal reports where other unpublished data is available for scrutiny. Tom provided a specific definition for the types of reviews this report covered:

Anything which is generated in the course of submission for a marketing organisation for a drug or biologic or a particularly invasive device. Excluded from this anything not going to market and interventions for which we have no clinical data, so no full reports.

Identification of the different types of documents and the basis on which the information is collated was a key objective to developing the glossary: CSRs were complete reports of trials, whereas medical officer reports were an individual's own report of peer review comments on the trial's original report. It was noted that all these documents were equally prone to error but they provided more complete information than published reports. Also, they are not always easy to read. The glossary tries to aid the navigation of these documents. They provide multiple sources of information to cross check data whereas typically Cochrane Reviews rely upon a single report that is not able to provide all the data and information collected during the trial. The Restoring Invisible and Abandoned Trials (RIAT) Support Center will support the interactive glossary.

CSC members agreed the problem existed and discussed primarily the best approach that Cochrane, given its resources, could take. The following key points were made:

- The Cochrane community needed to discuss its approach and support for using this type of data before mobilising funds and resources.
- The field is in its infancy.
- To move methods forward greater familiarity with these documents was required.
- Experimental or exemplar reviews needed to be undertaken to test Cochrane processes and infra-structure.
- Although, not on most people's radar and with confusion over terms used it was noted as a matter of principle Cochrane should use the most truthful report of the trial. An example of the discrepancy was that the compression of the original report into a journal article was in a ratio of 8000 pages to 1.
- Availability of data will vary by drug and regulator. Although some regulators e.g. EMA are now providing this data freely.
- Issues for authors are time to obtain these documents, risk of inexperience causing errors in synthesis by the reviewer, complex methods required.
- Need to clarify when it is sensible to undertake review of this data and the identify the resources to ensure it is conducted properly.
- Not required for every title, therefore we need prioritisation of which titles to support.
- Collaboration between Cochrane and regulatory bodies could be fruitful.
- Undertaking such high-profile reviews important reviews using these documents may impact on the number of overall reviews undertaken in Cochrane.

Credibility & validity: The issue of reporting bias with journal publications is well established.

Limitations/caveats: All data collated has limitations and scrutiny of the data requires authors able to identify any problems when reviewing these documents.

Areas of concern/uncertainty: Primarily development of methods and tools to aid authors.

Impact on Cochrane: Further internal discussions are required.

Cochrane resources needed: Feasibility and assessment of infra-structure developments is required before full scale roll out.