EDITORIAL

Regulatory agencies hold the key to improving Cochrane Reviews of drugs

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The perfect systematic review is an unachievable ideal. Conducting Cochrane Reviews is already time-consuming, and there is no lack of criticism of existing reviews and suggestions about what authors should have done. Cochrane should be applauded for being self-critical, but it is essential that recommendations to authors are feasible and that they improve the quality of the reviews.

The biggest threat to a systematic review's validity is its foundation. If the included trials are not a fair representation of all trials that exist, the results will be biased. That is why Cochrane contributors have spent thousands of hours handsearching journals and why authors screen thousands of abstracts to ensure that broad search strategies do not miss eligible studies. In spite of this, the problem of missing relevant data is far from solved. 'Negative findings' are less likely to be published, and this can seriously skew results from meta-analysis [1]. It was therefore not surprising that a recent study showed that including unpublished data from regulatory agencies changed the results of the original meta-analysis [2]. Initiatives such as ClinicalTrials.gov have tried to counter this problem by requiring registration of trials and publication of their results, so review authors can find out whether an unpublished trial exists. However, less than a quarter of trials on ClinicalTrials.gov have results published within the required time, and these were only the trials that were obliged by law to comply [3]. AllTrials, a major campaign endorsed by Cochrane, is attempting to rectify the problem of unreported data but admits there is a long way to go [4]. Unfortunately, publically available regulatory data are rarely used in Cochrane Reviews, even though this might be the least time-consuming source of unpublished data from drug trials [5]. Currently there is no guidance on searching regulatory data in the *Cochrane Handbook* [6], which may be the reason why so few review authors have included such data.

We found that almost all drug reports from the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA) for drugs approved in 2011 and 2012 contained enough efficacy data to be directly incorporated in a meta-analysis [7]. The two agencies complemented each other well, as FDA reports contained more data on harms whereas EMA reports were available on withdrawn and rejected drugs. The recent case of oseltamivir (Tamiflu) [8] has shown how fruitful incorporating data from clinical study reports can be, although the authors have shared that analysing the detailed data was labour-intensive and caused substantial delays in the review process. Publically available data from regulatory agencies is not as comprehensive as data from clinical study reports, but it is easy to find and sufficient for meta-analysis. Some, but not all, Cochrane Review Groups search ClinicalTrials.gov, but ClinicalTrials.gov is restricted to newer drugs as registration only became mandatory in 2007 and only for trials with at least one site in the United States. In the clinical study reports, pharmaceutical companies are required to submit all trials conducted on the specific indication. Thus, the list of trials provided to regulators should include all trials conducted to support the application for approval for a specific indication.

We therefore believe that searching regulatory data from the EMA and the FDA should be part of any Cochrane Review of drug interventions. These databases have some limitations. Less data will be available – and often in a less accessible form – for older drugs. Pairing published papers with the trials mentioned in the drug reports is not always easy as investigator names and ClinicalTrials.gov IDs are not mentioned. Only internal trial IDs are listed, but they are fortunately sometimes mentioned in published papers. Despite these limitations, searching and ensuring that all data mentioned in the regulatory documents that meet the criteria for the review are included is a fairly simple and quick process, unlike the process of dealing with clinical study reports.

Given that many reviewers find the regulatory databases difficult to navigate, it could make sense to create a support team for searching these databases for unpublished data. Such a team could develop strategies and give guidance on when and how to search for unpublished data and incorporate it into meta-analyses. This group could also develop a written guidance for the *Cochrane Handbook* and could expand and update the published guidance on searching the FDA website [9]. In sum, obtaining comprehensive data for Cochrane Reviews of drugs is worth the time and effort needed to search regulatory websites.

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Declarations of interest

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