Cochrane Scientific Committee

Should Cochrane apply error-adjustment methods when conducting repeated meta-analyses?

Document initially prepared by Christopher Schmid and Jackie Chandler

Edits by Panel Members

Expert Panel Recommendation and guidance points

Introduction

The Cochrane Scientific Committee (CSC) was asked to consider whether Cochrane should implement, and routinely adopt, sequential statistical methods for its Reviews.

Sequential methods have been proposed for the purpose of managing the probability of Type I (false positive) and Type II (false negative) errors arising when meta-analyses are updated because data from new trials are available. Sequential methods are motivated because of the opportunity to perform a new test of the null hypothesis of no difference between the experimental and comparator interventions each time a meta-analysis is updated, and the concern that p-values and confidence intervals arising from these tests require adjustment for multiple looks at the data. When tests are performed multiple times, the chance of incorrectly rejecting the null hypothesis at least once is greater than the nominal level. Sequential methods suggest adjustments that account for the number of tests performed.

Cochrane evaluated several sequential methods in a project supported by its Methods Innovation Fund (led by Mark Simmonds). Based on simulation studies, the project concluded that the sequential approaches proposed by Wetterslev et al (2008) – often known as "Trial Sequential Analysis" – and by Higgins et al (2011) were equivalent in their ability to control error across repeated meta-analyses (Simmonds, 2017).

It is core Cochrane policy that Cochrane Reviews should be updated regularly. Furthermore, a new approach to maintaining systematic reviews, the 'living systematic review', entails frequent monitoring and updating of the evidence. Concerns about updating meta-analyses in Cochrane Reviews, particularly in the context of a living systematic review, led the CSC to seek an Expert Panel view of whether sequential methods are necessary to avoid making incorrect inferences following an update and, if so, which method is most appropriate. The panel included both those familiar with Cochrane practice, and those with an independent perspective. Members of the CSC helped to identify relevant panel members. The panel met twice, chaired by a CSC member who had not been actively involved in development of the methods (Christopher Schmid).

The Expert Panel reached a consensus for review authors and editorial teams considering these methods when preparing Cochrane evidence.

Expert panel consensus statement

The Expert Panel recommends against the use of sequential methods for updated meta-analyses in most circumstances within the Cochrane context. They should not be used for the main analyses, or to draw main conclusions.

The Panel's recommendation is based on the following considerations.

1. The Panel believes that Cochrane Reviews should provide the best summary of the evidence to date. The results of each meta-analysis, conducted at any point in time, indicate the current best evidence of the estimated intervention effect and its accompanying uncertainty. These results need to stand on their own merit. Decision makers should use the currently available evidence, and their decisions should not be influenced by previous meta-analyses or plans for future updates.
2. Cochrane Review authors should interpret evidence on the basis of the estimated magnitude of the effect of intervention and its uncertainty (usually quantified using a confidence interval), rather than focusing primarily on the rejection of the null hypothesis of no treatment effect.
3. Cochrane Review authors should be discouraged from drawing binary interpretations of effect estimates as present or absent, based on defining results as 'significant' or 'non-significant'. This might require:
    - continued education and guidance, particularly around inappropriate interpretations of p-values and statistical significance;
    - training in use of language when describing and/or discussing results, particularly in implications for practice and research;
    - awareness of and emphasis of the caution needed when the accumulated number of trials, sample size or statistical information is small.
4. Sequential methods are commonly used to assist trial data monitoring boards who are charged with stopping a trial early if sufficient benefit is shown to render continuation of a trial unnecessary. The decision rules preserve the type I error probability while allowing the trial to be stopped at different predetermined time points if results cross a threshold established by the stopping rule. Typically, the decisions are driven by the estimated effect of intervention on a single pre-specified primary outcome and the decision is binding because it involves all parties concerned. The use of sequential methods for systematic reviews has been motivated by a similar concern that repeated updating of a meta-analysis without a corresponding decision rule might lead to a premature decision to declare the meta-analysis 'statistically significant', and stop updating the review further when statistical significance at the chosen threshold is reached. The panel concluded that several key differences between meta-analyses and clinical trials weakened the rationale for using sequential methods in meta-analysis.

5. The production of evidence included in retrospective meta-analyses is not under the control of the meta-analyst. Except in the case of a prospective meta-analysis, the meta-analyst has no control over designing or affecting trials that are eligible for the meta-analysis, so it would be impossible to construct a set of workable stopping rules which require a preplanned set of interim analyses. It would also be impossible to design a retrospective sequential program that would maintain desirable properties as new studies appeared erratically. Conversely, planned adjustments for future updates may be unnecessary if new evidence does not appear.
6. A meta-analysis will not usually relate to a single decision or single decision-maker, so that a sequential adjustment will not capture the complexity of the decision-making process. Systematic reviews may address effects of interventions on different outcomes and on different subgroups for benefits and harms. These will need to be integrated to make a final decision and will therefore involve multiple decision thresholds that sequential methods do not accommodate. Information from new trials may also continue to be informative to different aspects of a meta-analysis. For example, in network meta-analysis, the production of new data may continue to be informative for parts of a network even when some comparative effects are well-estimated. Cochrane also summarizes evidence for the benefit of multiple end users including patients, health professionals, decision makers and guideline developers who are independent of Cochrane. Different decision makers may choose to use the evidence differently and reach different decisions based on different priorities at different times. Any sequential adjustment procedure is necessarily based on a particular instance of the evolution of evidence that applies to a limited context and cannot satisfy the requirements of all decision makers.
7. Heterogeneity is prevalent in meta-analyses and random-effects models are commonly used when heterogeneity is present. Results of a random-effects meta-analysis depend on both the mean and the variation of true intervention effects across studies. Panel members considered sequential methods to have important methodological limitations when used prospectively in the presence of heterogeneity.

The Expert Panel concluded that Cochrane should support the decision maker and end user by providing the best and latest evidence, but that interpretation of that evidence should be left to the user to make within their own context. The priority is to ensure the decision maker is aware that the current estimate of the intervention effect may change as further information becomes available. Most decision makers are well aware of this. Unless the evidence is overwhelmingly convincing, any decision may change or be reversed over time.

Further notes

1. Formal decision analytic methods integrate effects of interventions estimated using meta-analyses and network meta-analyses with costs of the benefits and harm outcomes. Such methods are now available and are more informative for

decision makers than declarations of statistical significance (whether adjusted or not).

2. Cochrane Reviews may recommend that a meta-analysis is no longer updated for an individual outcome only when the result is convincing for benefit, or serious adverse effects are identified, and when neither further data nor future changes in clinical practice are likely to change these conclusions. In this situation, the work required to update a review is not justified. Not drawing such conclusions based on small amounts of evidence will avoid many of the early stopping issues to which sequential methods are addressed.
3. Sequential approaches to meta-analysis methods may be considered in Cochrane Reviews in the context of a prospectively planned meta-analysis of a series of clinical trials.

Agreed by:

Christopher Schmid (Chair)

Stephen Senn

Jonathan Sterne

Elena Kulinskaya

Martin Posch

Kit Roes

Jo McKenzie

References

Higgins JPT, Whitehead A, Simmonds M. (2011) Sequential Methods for random effects meta-analysis. *Statistics in Medicine*; 30 903–921

Simmonds M. (2017) Formal statistical methods for updating meta-analyses. Powerpoint presentation, Cochrane Meta-analysis project, Bristol Meeting, November 2017.

Wetterslev J, Thorlund K, Brok J, Gluud C. (2008) Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* ; 61:64e75.

Bibliography

1. Kulinskaya, E. and Wood, J. (2014) Trial sequential methods for meta-analysis. *Research Synthesis Methods*, **5**(3), 212-220. Article first published online: 28 NOV 2013 DOI: 10.1002/jrsm.1104
2. Kulinskaya, E., Huggins, R. and Dogo, S. (2015) Sequential biases in accumulating evidence. Research Synthesis Methods. Published online Dec 1, 2015 DOI: 10.1002/jrsm.1185. 2016 Sep;7(3):294-305

3. Samson Henry Dogo, Allan Clark, Elena Kulinskaya (2016) Sequential change detection and monitoring of temporal trends in random-effect meta-analysis; Research Synthesis Methods, First published: 8 December 2016, DOI: 10.1002/jrsm.1222
4. Lau J, Schmid CH and Chalmers TC. Cumulative Meta-Analysis of Clinical Trials Builds Evidence for Exemplary Medical Care. Journal of Clinical Epidemiology 48: 45-57, 1995.
5. Rice, K., Higgins, J., & Lumley, T. (2018). A re-evaluation of fixed effect (s) meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society). 181, Part 1, pp205-227.
6. Senn, S. J. (2000). The many modes of meta. Drug Information Journal, 34, 535-549.
7. Senn, S. J. (2014). A note regarding meta-analysis of sequential trials stopping for efficacy. Pharmaceutical Statistics; 13:371-375.
8. Committee for proprietary medicinal products (CPMP), Points to consider on application with 1. Meta-analysis, 2. One pivotal study. London 31st May 2001 (CPMP/EWP/2330/99). The European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use.
9. Yates, F., & Cochran, W. G. (1938). The analysis of groups of experiments. Journal of Agricultural Science, 28(4), 556-580.