

AGENDA

8th November 2018

Teleconference



DT – David Tovey, Editor in Chief, LD – Louisa Dunn, Methods Support Officer (minutes)

Committee members:

Corinna Dressler (CD)

Research Associate at the Division of Evidence-Based Medicine (dEBM) at the Charité – Universitätsmedizin Berlin, Germany

Donna Gilles (DG)

Senior Researcher, Clinical Performance Mental Health Network, Western Sydney, Australia and editor for both the Cochrane Developmental, Psychosocial and Learning Problems Group and Diagnostic Test Accuracy Review Group. Julian Higgins (JH)

Professor of Evidence Synthesis at the School of Social and Community Medicine, at the University of Bristol, Bristol, UK, and current Senior Scientific Editor of the *Cochrane Handbook of Systematic Reviews for Interventions*. AsbjØrn Hróbjartsson (AH)

Professor of Evidence-Based Medicine and Clinical Research Methodology at the University of Southern Denmark, and Head of Research for the Center for Evidence-Based Medicine at Odense University Hospital, which hosts the secretariat of the Cochrane Bias Methods Group.

Ana Marusic (AM)

Professor of Anatomy and Chair of the Department of Research in Biomedicine and Health at the University of Split School of Medicine, Split, Croatia and founder of Cochrane Croatia.

Jane Noyes (JN)

Professor of Health and Social Services Research and Child Health, Bangor University, Wales, UK, lead Convenor of the Cochrane Qualitative and Implementation Methods Group, and a UK Cochrane Fellow.

Tomas Pantoja (TP)

Associate Professor, Family Medicine Department, School of Medicine, Pontificia Universidad Católica de Chile and Editor of the Cochrane Effective Practice and Organisation of Care (EPOC) Group.

Philippe Ravaud (PR)

Professor of Epidemiology, Faculty of Medicine, Head of the Clinical

Epidemiology Centre, Hôtel-Dieu Hospital, Paris Descartes University, France and Director of Cochrane France.

Johannes Reitsma (JR)

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Associate Professor at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands and a member of both the Cochrane Diagnostic Test Accuracy Working Group and the Screening and Diagnostic Tests Methods Group.

Rebecca Ryan (RR)

Research Fellow at the School of Psychology and Public Health, La Trobe University, Australia and Deputy Co-ordinating Editor of the Cochrane Consumers and Communication Group.

Christopher Schmid (CS)

Professor of Biostatistics, founding member and Co-Director of the Center for Evidence Synthesis in Health, Brown School of Public Health, US, Fellow of the American Statistical Association (ASA) and Founding Co-Editor of *Research Synthesis Methods*.

Nicole Skoetz (NS)

Scientific Co-ordinator, Working Group Standard Operating Procedures of the Comprehensive Cancer Centers, Center of Integrative Oncology Köln Bonn, and Co-ordinating Editor Cochrane Haematological Malignancies Group, Department of Internal Medicine, University Hospital of Cologne.

Nichole Taske (NT)

Associate Director (Methodology), Centre for Guidelines, NICE, UK

AGENDA ITEM		Details and links to documents	Responsibility for item
1)	Welcome and apologies received		Chairs
2)	Approval of previous minutes	Minutes dated 5 th June (Paper 1)	Chairs
		Notes of informal meeting at Edinburgh Colloquium. (For information only) (Paper 2)	Chairs
3)	CSC Business matters	Krakow – full day meeting planned 31 st March 2018. Funding for travel/accommodation only when other sources of funding are not available.	
4)	Submissions	No further submissions	
5)	Methods for CSC Review	 a) Does the Scientific Committee think it should have a role in the approval of methods/guidance for relatively new review types (e.g. stand-alone reviews of qualitative evidence; reviews on prognosis)? b) Suggestions for future review 2019/2020 Two new tools in development: Risk of Bias due to Missing Evidence (RoB- ME), and Tool for Addressing Conflict of Interests in Trials (TACIT) Semi automation methods Prognosis methods 	CSC members
6)	Methods for CSC sign off and	Expert panel report on whether using	CSC members
	recommendation	sequential methods to adjust P values is	
		necessary in repeated meta-analyses. (Paper 3)	
		"Should Cochrane apply error-adjustment	
		methods when conducting repeated meta-	
		analyses?": Version 6 has been	

Cochrane Scientific Committee Agenda Meeting 8 th November 2018 OPEN ACCESS 4	
	agreed by the expert panel and is presented to the
	Committee for final recommendation.
	Data-based predictive distributions for between-
	study heterogeneity
	Following Rebecca Turner's presentation at the
	previous meeting the Committee is asked to sign
	off on the recommendation statement. (Paper 4)
7) Any Other Business	
8) Meeting schedule	List of meetings
	31 st March 2019 – full day Krakow.
	Further meetings to be scheduled.
	Colloquium 2019 – Santiago Chile. Informal
	meeting for those able to attend.
8) Meeting schedule	List of meetings 31 st March 2019 – full day Krakow. Further meetings to be scheduled. Colloquium 2019 – Santiago Chile. Informal meeting for those able to attend.

Teleconference 5th June 2018

Notes and abbreviations

Members of the CSC present		
Corinna Dressler (CD)	Present	
Donna Gilles (DG)	Apologies	
Julian Higgins (JH)	Present	
Asbjørn Hróbjartsson (AH)	Present	
Ana Marusic (AM)	Present	
Jane Noyes (JN)	Present	
Tomas Pantoja (TP)	Present	
Philippe Ravaud (PR)	Present	
Johannes Reitsma (JR)	Present	
Rebecca Ryan (RR)	Present	
Christopher Schmid (CS)	Present	
Nicole Skoetz (NS)	Present	
Nichole Taske (NT)	Apologies	
David Tovey (DT)	Present	
Other attendees		
Jackie Chandler	Minutes	
Rebecca Turner	Invited speaker	

AGENDA ITEM		Minutes
1)	Welcome and apologies received	Nicole Taske, Donna Gillies
2)	 Approval of Minutes dated 28th February 2018 (Paper 1) previous minutes 	
	a) Matters arising	5. (2) Expert panel report on whether using sequential methods to adjust P values is necessary in repeated meta-analyses. CS apologised for the delay in completing the position statement based on the outcome of the expert panel discussions. JH, not a panel member, reviewed the current version and proposed some amendments. CS will provide an updated version to the expert panel members to reach a final version to present the Committee for final
		recommendation. JH commented on the wording asking that the principle recommendation should shift its emphasis to an active recommendation, stating, the 'expert panel recommends against ' the use of sequential methods and he articulated six reasons, why:

- Cochrane Reviews should provide the best summary of current evidence
- 2) Cochrane advocates a preference for reporting confidence intervals, with exact P values, if desired. There is an inappropriate arbitrary division between what determines statistically significance or non-significance which is at the heart of these sequential approaches.
- 3) The meta-analysis context is not the same as the trial context
- 4) Decision makers using Cochrane Reviews may not agree with approach chosen by review authors.
- 5) There are technical problems with these methods.
- 6) Readers are unlikely to understand these methods.

If reviewers insist on using these techniques Cochrane must be clear on the context in which they can be used. They must not be used for primary analysis. It is permissible to use these methods for secondary analysis to provide an additional interpretation of the data from a specific perspective.

DT raised the issue regarding review sample size and whether enough information is provided, another rationale for using these methods. P value adjustment results in a GRADE downgrading decision, when the review provides sufficient data and confidence in the result if the P value is not adjusted. The EMD (CEU) is addressing a major dispute on this matter with a Review Group who routinely use Trial Sequential Analysis to which they link to the downgrading decisions in GRADE for imprecision/sparse data. Cochrane regard this as inappropriate but it is difficult to convince the Review Group. JH responded that this is covered by the first of the rationales in that meta-analyses should be based around existing evidence. He agreed to add a note to the position statement to clarify further. The Committee agreed that the guidance should be about the management of effects in relation to uncertainty not the other way around. The Committee's decision on the use of these methods will be final and will be published on the Cochrane Methods website. To enable the community to respond the Committee discussed publishing a Cochrane Editorial or external paper. At this stage the discussion document is to remain within the Scientific Committee and not be widely shared.

Action: DT to send CS a note detailing the sample size issue. JH will make amendments to point 3 to reflect this discussion.

8. Any other business

JH raised an item regarding scientific misconduct and whether there was an expectation to actively search for any errors or misconduct in study reports rather than respond to items that, opportunistically, come to light.

Action: JH to circulate draft section to AM and DT

JC has discussed with Bryony Urquhart the development of a broad misconduct policy for both author and reviewer. This is in development and should be available by the end of 2018. BU has commented on a draft from a new section in the Handbook. The EPPR will include a specific section on misconduct. AM believes that all linked documents should be examined and cross checked. The Committee should decide what procedures for detecting misconduct should be mandatory and, if reviewers find errors and plagiarism, how they deal with it. If it becomes mandatory, then a tool needs to be provided for reviewers to ensure consistency across reviews.

ACTION: AM will submit her recommendations in writing to the Committee.

3)	CSC Business	None	
	matters		
4)	Submissions	No further submissions	
5)	Methods for CSC	Data-based predictive distributions for between-study	
	Review	heterogeneity	
		In small meta-analyses, a conventional random-effects meta-	
		analysis is problematic because between-study heterogeneity is	
		imprecisely estimated, and this imprecision is not taken into	
		account. A Bayesian meta-analysis allows researchers to incorporate	
		external evidence on the likely extent of between-study	
		heterogeneity in their particular research setting.	
		Rebecca Turner will attend and present at the meeting. (Paper 2)	
		Following a presentation by Rebecca Turner the Committee had a	
		detailed discussion about the application of Bayesian meta-analysis	
		in Cochrane Reviews which included the following issues:	
		• Although this work was based on a set of data from 2008 it is	
		still relevant and cannot be repeated with an updated	
		dataset as the Cochrane Library stores its data differently now.	
		• Rebecca would advocate that specific priors from the initial	
		paper are used based on the nature of the meta-analysis i.e. narrow vs broad settings	
		 The priors in the initial paper can be used for any sized 	
		meta-analysis not just for those with 5 studies or fewer but	
		the recommendation would be that the cut-off be 10 or	
		 It was agreed that in a small number of studies the estimates are poor as most use the DerSimmonian- Laird technique. 	
		Given that 75% of Cochrane Reviews have fewer than 5	
		studies the Committee should recommend which technique	
		to use.	

		 The QIMG are very interested in Bayesian meta-analysis in relation to Qualitative Evidence Syntheses. Asking authors to add Bayesian meta-analysis alongside traditional syntheses may be a good compromise to compare the techniques. The current Cochrane Handbook is clear that Bayesian meta-analysis can be used although it is not included in RevMan so this presents a huge implementation challenge. The new updated Handbook addresses alternatives to DerSimmonian-Laird for random effects analyses. There are better methods available than in RevMan and this needs to be made clear to authors to prevent a multiplicity of findings from the same data set.
		The Committee thanked RT and a summation of decisions will be sent. ACTION: The Committee recommends that Cochrane Reviewers are encouraged to add Bayesian meta-analysis alongside the traditional techniques included in RevMan to supplement and improve their review. Particularly where there is a very high or low heterogeneity estimate. Therefore, in these situations an additional Bayesian analysis will have the greatest impact. This will be included in the new updated Handbook chapter.
6)	Methods for CSC	None
	sign off and	
	recommendation	
()	Special items	Nege
	a) Research priorities and strategy	None
8)	Any Other Business	Further clarification is needed in the template wording to distinguish between recommendations. In particular, to include the "recommended against" option to be more definitive
		ACTION: JC will clarify the wording in the templates.
9)	Meeting schedule	List of meetings
		16 th September 2018 at 7.30am (Colloquium) informal and invite the Methods Executive (overlapping membership).
		8 th November 2018 at 11.00am UK GMT

Members of the CSC present		
Corinna Dressler (CD)	Present	
Donna Gilles (DG)	Present	
Julian Higgins (JH)	Present	
Asbjørn Hróbjartsson (AH)	Apologies	
Ana Marusic (AM)	Present	
Jane Noyes (JN)	Present	
Tomas Pantoja (TP)	Present	
Philippe Ravaud (PR)	Present	
Johannes Reitsma (JR)	Present	
Rebecca Ryan (RR)	Apologies	
Christopher Schmid (CS)	Present	
Nicole Skoetz (NS)	Present	
Nichole Taske (NT)	Apologies	
David Tovey (DT)	Apologies	
Other attendees		
Jackie Chandler	Methods Co-ordinator	
Louisa Dunn	Methods Support Officer (notes)	

Informal Meeting – Edinburgh Colloquium 15th September 2018

 Further clarity on how Cochrane decision making processes work, if required. Review Groups and individuals may submit items to be considered by the Scientific Committee. These can be submitted through the online form or through a Cochrane Review Group. The Methods Executive will review each submission and escalate to the Scientific Committee for further discussion if necessary. This threshold for escalation to the Scientific Committee requires further definition and clarification.

The Scientific Committee may set up an expert panel to consider the technique which could include members external to Cochrane in order to ensure a balanced view of whether a methodological technique is fit for purpose. This will be especially relevant when considering the new types of review under development such as Rapid Reviews, Qualitative Evidence Synthesis and Prognosis Reviews.

The Scientific Committee will ensure that methods being used are appropriate in the Cochrane model. After consideration of a method the Committee will produce a statement which will be submitted to the Editorial Board and Editor in Chief. The Scientific Committee is advisory and not decision making, it does not play a role in the implementation of methods. This is the remit of the Editorial Board. Any conflicts of interest will be dealt with as described in the Scientific Committee Terms of Reference.

- Scientific Committee meetings to date: How well are they going? Any suggestions? Request to recirculate the meeting etiquette document to improve the sound quality of the meetings. Presentations to the Committee are of a high standard. ACTION: Louisa will circulate along with agenda for next meeting.
- 3. Feedback from the expert panel on the position statement for sequential methods for updated meta-analyses. Chris Schmid & Julian Higgins The draft report has been circulated to the members of the expert panel for comment. The expert panel needs to reach a consensus so that the report can be distributed to the Committee before the next meeting. This will allow the Scientific Committee to endorse the report on 8th November 2018 and make a clear recommendation to the Editorial Board/Editor in Chief which will be disseminated as appropriate.
- Full day meeting planned 31st March 2019 in Krakow, Poland: Developing the agenda and further information about Cochrane Mid-year Governance meetings.
 Methods for consideration at further meetings: Qualitative Evidence Synthesis; Risk of Bias due to Missing Evidence (RoB-ME); Semi-automation and Methods for Prognosis.

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 Wettislev 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 metaanalyses 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.

- 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 prespecified 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 decisionmaker, 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 metaanalysis 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 possibly combined with an existing meta-analysis.

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.

Wettislev 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

- 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
- 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

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- 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) metaanalysis. *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.
- 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.

Recommendation statement/report

Date: 12th September 2018

Relates to agenda item and meeting reference: Item 5 5th June 2018

Priority: Low

Open access/restricted: Open

Data-based predictive distributions for between-study heterogeneity

Lead developers/investigators: Rebecca Turner and colleagues (including Julian Higgins)

Abstract:

In small meta-analyses, a conventional random-effects meta-analysis is problematic because between-study heterogeneity is imprecisely estimated, and this imprecision is not taken into account. A Bayesian meta-analysis allows researchers to incorporate external evidence on the likely extent of between-study heterogeneity in their particular research setting. Davey et al¹, found that 75% of meta-analyses reported in Cochrane Reviews included five or fewer studies.

Aim & objective: To assist with implementation of Bayesian meta-analysis, this project set out to provide empirical evidence on how much between-study heterogeneity could be expected in various healthcare settings.

Methods for development: Meta-analyses from the *Cochrane Database of Systematic Reviews* (Issue 1, 2008) were classified according to the type of outcome, type of intervention comparison and medical speciality. The impact of meta-analysis characteristics on the underlying between-study heterogeneity variance was investigated by modelling the study data from all meta-analyses simultaneously. Meta-analyses of binary outcomes and meta-analyses of continuous outcomes were modelled separately.

Predictive distributions were obtained for the between-study heterogeneity expected in future meta-analyses. These distributions can be used directly as data-based informative prior distributions for heterogeneity in Bayesian meta-analyses.

Results: Between-study heterogeneity was found to be strongly associated with the type of outcome measured in the meta-analysis and somewhat associated with the types of interventions compared. For example, between-study heterogeneity variances for meta-analyses in which the outcome was all-cause mortality were found to be on average 17% (95% CI 10% to 26%) of variances for other outcomes. In meta-analyses comparing two active pharmacological interventions, heterogeneity was on average 75% (95% CI 58% to 95%) of variances for non-pharmacological interventions.

We have published predictive distributions for heterogeneity for various settings, defined by type of outcome and type of intervention comparison, separately for meta-analyses of binary outcomes^{2,3} and for meta-analyses of continuous outcomes⁴. In addition, we have proposed

accessible methods for implementing Bayesian meta-analysis with informative priors, avoiding the need for specialist Bayesian software^{3, 5}.

Final product: Guidance will be incorporated into Version 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

SUPPORTING DOCUMENTATION

1. Davey J, Turner RM, Clarke MJ, Higgins JPT. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. *BMC Medical Research Methodology*; 2011; 11: 160.

2. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JPT. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology*; 2012; 41: 818-27.

3. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for betweenstudy heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in Medicine*; 2015; 34(6): 984-98.

4. Rhodes KR, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *Journal of Clinical Epidemiology* 2016; 68(1): 52-60.

5. Rhodes KM, Turner RM, White IR, Jackson D, Spiegelhalter DJ, Higgins JPT. Implementing informative priors for heterogeneity in meta-analysis using meta-regression and pseudo data. *Statistics in Medicine*; 2016; 35(29): 5495-511.

Key reference: Turner and colleagues: https://academic.oup.com/ije/article/41/3/818/834878

CSC RECOMMENDATION

Highly recommended Because

Recommended with provisions Because

Recommendation that method/tool etc. is not used Because

 Optional/advisory (one among several options)
 Because it provides an option to encourage review authors to consider how they should manage heterogeneity in meta-analyses of ten or fewer studies.
 Not recommended

Because

CSC STATEMENT

Summary statement

The Committee recommends that Cochrane Reviewers are encouraged to add Bayesian metaanalysis alongside the traditional techniques included in RevMan to supplement and improve their review. Particularly where there is a very high or low heterogeneity estimate therefore, in these situations an additional Bayesian analysis will have the greatest impact. This will be included in the new updated Handbook chapter.

Credibility & validity: -

Limitations/caveats: Methods should be used in specific circumstances and are not advised for all reviews.

Areas of concern/uncertainty: None noted

Impact on Cochrane: Low

Cochrane resources needed: No integration expected into RevMan at this point. Training for editors is a consideration. In addition, the Editorial & Methods Department might wish to consider whether any active encouragement is required or whether this is left to Reviewer judgement.