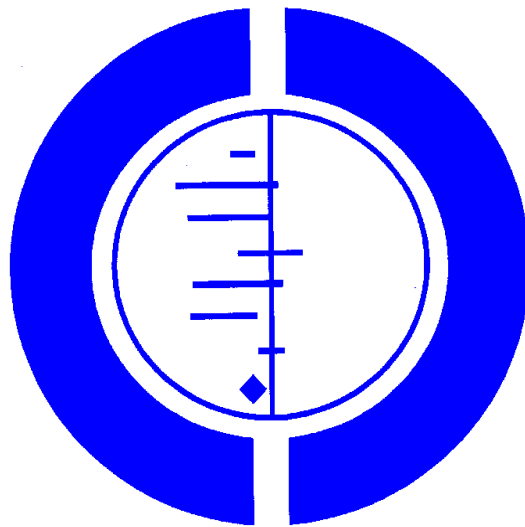


# The Cochrane Collaboration Methods Groups Newsletter

Volume 13 June 2009



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## PURPOSE OF THE NEWSLETTER

One of the primary roles of the Cochrane Collaboration's Methods Groups is to offer advice and support to other Cochrane entities. The main aims of this Newsletter are, therefore, to share information among Methods Groups and to inform others within The Cochrane Collaboration about their work. The target audience is primarily members of The Cochrane Collaboration Methods Groups but also includes other members of the Collaboration and people outside the Collaboration with an interest in methodological aspects of healthcare research.

The Newsletter is published once a year and this is the twelfth edition. Archive copies of the Newsletters are available from The Cochrane Collaboration website at: [www.cochrane.org/newslett/index.htm](http://www.cochrane.org/newslett/index.htm). Each issue contains relevant news from The Cochrane Collaboration, reports of recent methodological research (both within and outside the Collaboration), as well as recurrent topics such as details of forthcoming meetings, updates from individual Methods Groups and details of new Cochrane methodology reviews.

The opinions expressed in the Newsletter do not necessarily reflect the opinion of the editors, The Cochrane Collaboration, or anyone other than the authors of the individual articles. Contact details for all the Methods Groups and other contributors to the Newsletter, a guide to more information about The Cochrane Collaboration and details of Cochrane websites and Cochrane Centres can be found at the end of the Newsletter.

This Newsletter has been produced by the UK Cochrane Centre with resources from the National Institute for Health Research in the UK. The Newsletter is distributed to members of Methods Groups and all Cochrane entities. If you would like to suggest topics for future issues or to receive additional copies, please contact the UK Cochrane Centre.

## ABOUT THIS ISSUE

This year has seen a number of important new developments within The Cochrane Collaboration. Among the most important, and of particular relevance to Methods Groups, are the appointment of an Editor in Chief for *The Cochrane Library*, the outcome of The Cochrane Collaboration Strategic Review, instigation of a new Coordinating Editors Methods Working Group and the establishment of a Training Working Group. We include brief reports on each of these new initiatives as well as articles covering other challenging issues facing the methodology of Cochrane reviews and other types of systematic review.

As with previous years, this issue includes structured abstracts and commentaries on topical methodological issues. These include: a study comparing industry supported meta-analyses with those which received non-profit support or no support; an evaluation of the capture-mark-recapture technique as a stopping rule when searching for studies to include in systematic reviews; and research into a graphical presentation of information in diagnostic test accuracy reviews.

We are very grateful to the many people who have contributed to this Newsletter. We should welcome additional volunteers to help with the preparation of structured abstracts and commentaries for reports of methodology research. Suggestions for future themes or content of the Newsletter would be most appreciated.



## ARTICLES

### New Editor in Chief of *The Cochrane Library*

David Tovey

As I write this, I have completed two months in the role of Editor in Chief of *The Cochrane Library*. My initial task was to consult as widely as possible in order to learn more about the Collaboration from those working on the inside, and to identify key development issues. This culminated in the submission of my first report to the Steering Group for their half-year meeting in Copenhagen in April 2009. Whilst I have attempted to be as inclusive as possible, I fully recognise that to date I have spoken with only a tiny fraction of those involved in the Collaboration, so that the consultation will remain indefinitely an ongoing process.

It is important to record the very positive findings of my consultations to date. As the Strategic Review has identified, the Collaboration benefits from the extraordinary expertise and commitment of those that make up its vast and diverse networks. Cochrane insiders are also remarkable in demonstrating a desire to develop and improve *The Cochrane Library*, and to improve global health-related decision-making at all levels.

Perhaps the main reason for the Collaboration deciding to go down the path of appointing an Editor in Chief was to address concerns about variability in quality of reviews. Cochrane reviews are generally considered to be of higher quality than non-Cochrane reviews, a finding that was supported by a paper by David Moher and colleagues in 2007.<sup>1</sup> The Collaboration can also take much credit for its role in the methodological development of systematic reviews generally. The *Cochrane Handbook for Systematic*



*Reviews of Interventions*<sup>2</sup> exemplifies the concentration on quality as the key feature that distinguishes Cochrane reviews. Another example of this commitment to quality and one that also preceded my appointment is the development of the Co-ordinating Editors Methods Working Group, which aims to ensure good communication between the Cochrane Review Groups and methodologists, and to improve implementation of future methodological improvements across the Collaboration.

Two of the most important principles that will guide the work of my Editorial office will be firstly to build on the excellent work already taking place across the Collaboration, and secondly always to see *The Cochrane Library* through the eyes of end users, whether they are consumers, health professionals, managers or policy makers. This means that from my perspective quality is broader than validity, and crucially important that this is, in that it also reflects the relevance and breadth of coverage of *The Cochrane Library*, and the quality of the presentation of content to users. However, I recognise the importance that Methods Groups rightly attach to validity and reduction of bias, and am developing recommendations that I will present to stakeholders over the next few months, and aim to implement within 12 months. These will concentrate on building on best available evidence to draw up minimum standards for Cochrane reviews at key stages in their journey,<sup>3</sup> and also to encourage Cochrane Review Groups to undertake regular self audit aimed at improving accountability and sharing expertise.

#### References:

1. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. *PLoS Medicine* 2007; 4(3):e78.
2. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
3. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007; 7:10.

## The Cochrane Collaboration Strategic Review

Jeremy Grimshaw and Mary Ellen Schaafsma

In 2008, The Cochrane Collaboration began a Strategic Review of itself, which was led by Jeremy Grimshaw and supported by a team of three. The Review was intended to examine the Collaboration as a whole, in its internal and external environmental context. It was structured around seven 'Dialogues':

- Purpose;

- Brand and glue (external and internal coherence);
- Competition (external environment);
- Financial viability;
- Accountability and decision-making;
- Structures and processes; and
- Communication, advocacy and engagement with external stakeholders.

The Review team took a very consultative approach, and interviewed, surveyed and engaged more than 3000 people, via a specially developed website and a booth at the Cochrane Colloquium in Freiburg. These people represented every type of entity and role within the Collaboration and it also included 28 external stakeholders - from funders to guideline developers to other synthesis producers.

The overarching theme that came out of the Review from which all the other recommendations cascade is that The Cochrane Collaboration needs to integrate strategic thinking into all its activities and structures at every level. Until now, as the organization grew, plans were made and new activities undertaken based on interest and goodwill - which is appropriately aligned with the ethos of The Cochrane Collaboration. This is not an ethos that should be lost. However, in the evidence-based decision-making environment in which the Collaboration exists and now competes, having a more strategic approach is necessary in order to stay strong.

The 26 recommendations of the report ([www.cochrane.org/ccsg/review](http://www.cochrane.org/ccsg/review)) highlight specific areas in which strategic thinking and investment of resources (be they human, time or financial) should be considered. These recommendations are important to all entity types in the Collaboration - because what each group chooses to spend their time and resources on has an impact on the rest of the Collaboration and how well it functions.

## The Co-ordinating Editors Methods Working Group: a new interface between review production and methods

Julian Higgins and Jonathan Craig

The new *Cochrane Handbook for Systematic Reviews of Interventions* has presented the Collaboration with a number of challenges, particularly around the implementation of the Risk of bias tool and Summary of findings tables. Some have found these helpful and straightforward to implement; others have not; and some have expressed concern at the way in which they were developed and adopted by the Collaboration. The Steering Group meeting in Vellore in April 2008 identified the need for a partnership between Cochrane Review Groups (CRGs) and those developing methodology, to address some of the strategic issues associated with improving methodological quality. The end result is a small working group involving the Editor in Chief and some key individuals from CRGs, Methods Groups, the



Handbook Advisory Group and the Training Working Group.

The group is known as the Co-Eds Methods Working Group, and its three main aims are:

- To identify strategies to assist CRGs to implement the advice in the Handbook, principally through consultation between the Working Group and CRGs.
- To monitor methodological quality and set priorities for improving it, principally through consultation between the Working Group and Methods Groups.
- To serve as a forum for discussing implementation of future methodological developments and their impact on CRGs.

In the immediate term, the main focus will be on the first of these aims, and initial membership reflects priorities in implementing the main new methods in the Handbook. Work started with a survey of Co-ordinating Editors and Review Group Co-ordinators (now called Managing Editors) about the opportunities and barriers in implementing these methods. The group is investigating how Summary of findings tables can best be introduced into as many reviews as possible, and is compiling possible projects to improve methodological quality. The Working Group will provide a focus for discussions of surveys and research projects on aspects of methodological quality, which commonly reveal inadequacies in Cochrane reviews. In the future, the Working Group will discuss at an early stage any major new methodological developments that are being considered for Cochrane reviews, to enable better input from Cochrane Review Groups and planning for their dissemination.

The current membership of the Co-Eds Methods Working Group includes: Doug Altman, Sally Bell-Syer, Rachel Churchill, Jonathan Craig, Jon Deeks, Sally Green, Julian Higgins, Sophie Hill, Steve McDonald, Holger Schünemann, Roger Soll and David Tovey.

## Cochrane Training Working Group

Steve McDonald and Phil Wiffen

Providing high standards of training and support to authors and editorial teams is critical for maintaining and improving the quality of Cochrane reviews. Arising from the challenges identified in rolling out the revised *Cochrane Handbook for Systematic Reviews of Interventions* and RevMan 5 during 2008, a new Training Working Group (TWG) has been established to serve as the focal point for training issues in the Collaboration.

The TWG aims to develop strategies to meet the training and support needs of those who are actively involved in preparing and maintaining Cochrane reviews, including review authors, editors and members of editorial bases. An early priority will be to develop and maintain a core set of

training and support materials, developed with the Methods Groups and accessible via [www.cochrane.org](http://www.cochrane.org). The resulting training collection will ensure the consistency of training materials across the Collaboration, provide a mechanism for involving Methods Groups in developing materials, provide integrated access to a range of training initiatives in development across the Collaboration, and expand substantially the availability of online materials for authors.

The co-convenors of the TWG are Steve McDonald (Australasian Cochrane Centre) and Phil Wiffen (UK Cochrane Centre). An executive group has been formed to establish the work plan, co-ordinate activities and communicate on behalf of the TWG. Key groups such as Centre trainers, Methods Groups, Cochrane Review Groups and the Collaboration's Web Team are represented. General membership of the TWG is open to those actively involved in training and support in the Collaboration, and the group is eager to connect with those involved in existing training and support initiatives within the Collaboration. It is anticipated that *ad hoc* project groups will form as work gets under way, so there will be plenty of opportunity to be actively involved. If you would like to be involved or to find out more, contact Steve McDonald ([steve.mcdonald@med.monash.edu.au](mailto:steve.mcdonald@med.monash.edu.au)) or Phil Wiffen ([pwiffen@cochrane.ac.uk](mailto:pwiffen@cochrane.ac.uk)).

## Cochrane Methodology reviews – an undervalued asset in *The Cochrane Library*

Gerd Antes

Preparing, maintaining and disseminating systematic reviews of health care is the core business of The Cochrane Collaboration. Starting from scratch, the last 17 years have been a success story to set up an organization and a structure to ultimately achieve a complete overview of all comparative clinical trials, summarized in systematic reviews.

However, the notion of systematic reviews is almost exclusively linked to healthcare interventions. A different type of review, summarizing the methodological knowledge essential for systematic reviewing (see scope of the Methodology Review Group), is unknown to most users of Cochrane reviews and even not very familiar within the Collaboration. The largely hidden existence of methodology reviews is detrimental by because their results are not used. It also contributes to the lack of cognition of the methodological work which has been initiated and conducted by the Collaboration.

Currently, methodology reviews are only known to insiders within the Collaboration. Even for them they are difficult to find because they are part of the Cochrane Database of Systematic Reviews (CDSR). Methodology reviews were displayed as a separate section until two years ago but were moved into CDSR to achieve a unique status for different types of reviews. This was necessary to integrate



methodology reviews fully into the calculation of the impact factor for CDSR and to give the credit of the impact factor also to authors of those reviews. The price for it is that they are now buried under the 6000 normal reviews and widely neglected.

Methodology reviews (currently 11 protocols and 14 reviews) can be displayed in *The Cochrane Library* by clicking on “Browse by review group”, where they are listed under the Cochrane Methodology Review Group ([www.mrw.interscience.wiley.com/cochrane/cochrane\\_cls/srev\\_crglist\\_fs.html](http://www.mrw.interscience.wiley.com/cochrane/cochrane_cls/srev_crglist_fs.html)). An alternative access is to type in the code “HM-method” in the advanced search window, producing a list in the familiar format.

To improve the cognition of methodology reviews their number has to be increased considerably. The priorities among the large number of methodological questions which deserve and require a systematic review are listed ([www.mrw.interscience.wiley.com/cochrane/cochrane\\_cls/srev\\_crglist\\_fs.html](http://www.mrw.interscience.wiley.com/cochrane/cochrane_cls/srev_crglist_fs.html)). More authors are needed to choose an item from this list to prepare a high quality methodology review.

Finally, the existence of these reviews should be emphasized by displaying them as a specific category on the entry page to *The Cochrane Library* (similar to the position two years ago), as has been suggested to the Cochrane Collaboration Steering Group recently.

### **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)**

David Moher, Doug Altman, Alessandro Liberati and Jennifer Tetzlaff

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement is a reporting guideline to assist systematic review authors to report accurately, clearly, and transparently systematic reviews and/or meta-analyses of randomized trials and other study designs, such as quasi-experimental studies, evaluating healthcare interventions. The PRISMA Statement is a substantive update and expansion of the QUOROM (Quality of Reporting of Meta-analyses) Statement, published ten years ago. Improved reporting enables readers to make meaningful judgments about the reliability and validity of published research.

The development of PRISMA was motivated by several conceptual, methodological, and practical factors including: a large increase in the evidence base underpinning the conduct and reporting of systematic reviews; the emerging importance of and evidence about reporting biases; the development of outcome level assessment of risk of bias, such as the reliability and validity of specific outcomes included in a systematic review; the intertwined relationship between conduct and reporting of systematic reviews; and the iterative nature of completing a systematic review.

A three-day consensus meeting involving 29 review authors, methodologists, clinicians, editors and a consumer was held in Ottawa, Canada, in 2005. After the meeting, the PRISMA executive drafted a checklist that was circulated to the meeting participants, and others, for further input and feedback. After 11 revisions, the PRISMA Statement was approved by them.

The PRISMA Statement consists of a 27-item checklist regarding the conduct of a systematic review using the IMRAD (Introduction, Methods, Results and Discussion) structure, and four-phase flow diagram, documenting the flow of records through the review process. The checklist is a minimum set of items deemed essential when reporting systematic reviews assessing healthcare interventions. A small group of participants attending the Ottawa meeting helped draft the PRISMA explanatory paper. This long in-depth article, modelled after the CONSORT (CONsolidated Standards Of Reporting Trials), STARD (Standards for the Reporting of Diagnostic accuracy studies), and STROBE (Strengthening The Reporting of OBServational studies in Epidemiology) explanatory papers, includes an exemplar of good reporting for each checklist item, along with a rationale and explanation as to why the item should be included in a report of a systematic review. Whenever possible, we included evidence to inform the inclusion of the checklist item. For maximum effect we recommend reading the explanatory document in conjunction with the short PRISMA Statement. We hope journals and international editorial groups will endorse PRISMA by modifying their ‘Instructions to Authors’. While endorsement is an important step it needs to be accompanied by adherence for effective improvements in the quality of reporting systematic reviews. PRISMA will be published in 2009.

### **Cochrane centralised updating project**

Julie Brown

The Cochrane Collaboration aims to provide up-to-date and timely research evidence. The main objectives of the updating project were to assess the feasibility of centralising the updating of Cochrane reviews and to identify and quantify the barriers to this process.

In 2008, the Menstrual Disorders and Subfertility Group in conjunction with the New Zealand branch of the Australasian Cochrane Centre facilitated a pilot centralised updating project.

At that time, we estimated that more than half of Cochrane reviews were out of date by two years or more. Inability to contact authors, lack of interest or time from authors, funding issues and RevMan 5 were cited as the main explanations for not updating.

Eight reviews were selected and seven had the content and methodology updated, risk of bias tables created and were



submitted to the editorial process. The average duration from search to editorial submission was 6.4 months (range: 3 to 11 months).

All participants in the project were asked for feedback. There was general consensus that the project had been successful and many Cochrane Review Groups reported that they would use an Updating Officer again but would spend more time in prioritising the review to put forward for updating. There were concerns that in centralising the process the Updating Officer may be unfamiliar with the clinical topic or Review Group's methods. There was an acknowledgement from all participants that there had been a lack of commitment by the contact author in several of the reviews and there was also an issue relating to authorship and subsequent updating requirements from the Updating Officer.

The successes of the project were that the team used experienced review authors who were able to complete the updates in a timely fashion and in doing so had strengthened the quality of the reviews.

As a result of the project, four models for updating were proposed to The Cochrane Collaboration. The first model was that of a 'centralised updating officer' - the model piloted in this project. Updating could also be undertaken within Cochrane Review Groups with targeted proportional funding linked to productivity. There could be a selected prioritised call for reviews with payment made on submission or a new entity could be created with the sole purpose of ensuring timely updates across all groups.

There are a number of issues pertinent to all models. These include prioritisation of the large number of reviews currently out of date, ensuring there are contractual agreements in place with the contact authors and Cochrane Review Groups, and of course staffing.

If you want further details regarding the updating project then please contact us at the Menstrual Disorders and Subfertility Group.

### Updating Cochrane reviews: a decision tool

Sally Hopewell, Kirsty Loudon, Mike Clarke, David Moher, Rob Scholten, Anne Eisinga and Simon French

The Cochrane Collaboration has a policy that Cochrane review authors should agree to update their review periodically following its initial publication. Current guidance states this should be done every two years, but there is limited evidence to suggest the ideal time for updating; too soon may introduce bias and, if too late, the end user may act on out-of-date or potentially misleading information.

Given the increasing workload of Cochrane Review Groups and review authors, a change to current procedures for

updating Cochrane reviews is needed to replace the *ad hoc* and arbitrary approach that currently exists. We aimed to develop and validate a decision tool to help assess the need and likely benefits of updating a Cochrane review.

In developing this updating tool we established an international Steering Committee to provide guidance and support to the project. The tool was developed building on existing empirical evidence on updating systematic reviews, guidance in the new *Cochrane Handbook for Systematic Reviews of Interventions* and Review Manager (RevMan) 5, work undertaken by the Cochrane Updating Working Group and existing checklists from various agencies, including Cochrane Review Groups. Formal piloting and input from users and experts involved in updating Cochrane reviews are being used to enhance and refine the tool.

The updating tool is in two parts. Step 1 is a decision tree to identify triggers for updating a Cochrane review. The most likely trigger is knowledge of the findings of a new study. However, other possible triggers or combinations of triggers might include: new information (e.g. information about new treatment regimes, population subgroups, harms, economic data, or outcome measures, including data from ongoing studies or previously missing data); new methodology (e.g. new statistical techniques, or changes in the *Cochrane Handbook for Systematic Reviews of Interventions* or RevMan); response to feedback from users of the review; or other factors (e.g. the age of the review or its use in policy decision-making or clinical practice guidelines).

If review authors decide that a trigger is likely to change the conclusions of their Cochrane review, Step 2 provides a checklist designed to help them consider which sections of their review require updating. It guides authors step by step through the review process using questions or triggers, which may or may not lead to action and the updating of specific sections of the review.

We hope that this updating tool will make it easier to identify Cochrane reviews which are ripe for updating and ensure that the decision-making process is made clearer and more transparent to the end user. If you are interested in the decision tool and would like to find out more please contact: [shopewell@cochrane.ac.uk](mailto:shopewell@cochrane.ac.uk).

This project was funded by the Cochrane Opportunities Fund in 2007.

### Systematic reviews of diagnostic test accuracy

Mariska Leeflang on behalf of the Cochrane Diagnostic Test Accuracy Working Group

More and more systematic reviews of diagnostic test accuracy studies are being published, but they can be methodologically challenging. In a recent paper,<sup>1</sup> we presented some of the recent developments in the methodology for conducting systematic reviews of



diagnostic test accuracy studies, by using our experience from the work on the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*.

Because diagnostic accuracy is not a fixed property of a test and can vary between patient subgroups, the review question should contain elements of clinical setting and disease spectrum. Also, review authors need to consider the possible role of the test or tests under evaluation. This may include the formulation of comparative questions, for example, can this test be used to replace an older or more invasive test? When retrieving potentially relevant studies for the review, the use of restrictive electronic search filters is discouraged. One of the reasons for this discouragement is that diagnostic studies are poorly indexed in bibliographic databases. When assessing the methodological quality of a diagnostic study, the Working Group recommends the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist.<sup>2</sup>

Methods for meta-analysis should take into account the paired nature of the estimates and their dependence on threshold. Therefore, sensitivity and specificity should not be pooled separately, but combined in one model. Authors of these reviews are advised to use the hierarchical summary receiver operating characteristic (SROC) or the bivariate model for the data analysis. The results of these models can be presented with curves or summary points (with confidence ellipses around them) in graphs of true positive fraction (sensitivity) versus false positive fraction (1-specificity). The interpretation of the curves differs from the interpretation of the summary points. When interpreting the results, the quality of the original studies, and setting and spectrum of the patients need to be taken into account. As accuracy does not directly reflect the outcome for the patient when the test is used or not, interpretation of diagnostic reviews remains challenging. Another challenge is the poor reporting of original diagnostic test accuracy studies. They need to report on patient characteristics, for example, in order to make interpretation of the results possible.

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1. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Annals of Internal Medicine* 2008; 149:889-97.
2. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003; 3:25.

## Multiplicity in systematic reviews

Ralf Bender



The higher the number of comparisons made by means of statistical significance tests or confidence intervals the more likely it is that some of these tests or confidence intervals will produce 'statistically significant' results by chance alone. This multiplicity problem occurs in clinical trials, epidemiology and public health research as well as in systematic reviews. However, in systematic reviews it is more difficult to deal with multiplicity than in individual studies. Additional problems associated with multiplicity in systematic reviews are given by selective reporting in the individual studies and the need for *a priori* planning of multiple test procedures because it is not known in advance, which outcomes and which effect measures will be available for systematic review.

No simple or completely satisfactory solution to the problem of multiple comparisons in systematic reviews is available. However, the *Cochrane Handbook for Systematic Reviews of Interventions* contains some general advice. The most important points are:

- In the protocol for the review, state which analyses and outcomes are of particular interest (the fewer the better). Outcomes should be classified in advance as primary and secondary outcomes. Main outcomes to appear in the 'Summary of findings' table should be pre-specified. If there is a clear key hypothesis, which could be tested by means of multiple significance tests, performing an adequate adjustment for multiple testing will lead to stronger confidence in any conclusions that are drawn.
- Do not select results for emphasis (e.g. in the abstract) on the basis of a statistically significant P value.
- If there is a choice of time points for an outcome, attempts should be made to present a summary effect over all time points, or to choose one time point that is the most appropriate one. Multiple testing of the effect at each of the time points should be avoided.
- Keep subgroup analyses to a minimum and interpret them cautiously.
- Interpret cautiously any findings that were not hypothesized in advance, even when they are 'statistically significant'.

A short description of the multiplicity problem in systematic reviews and the complete key recommendations are included in Chapter 16: Special topics in statistics, of the *Cochrane Handbook for Systematic Reviews of Interventions* ([www.cochrane-handbook.org](http://www.cochrane-handbook.org)). A more detailed discussion is given in a recent review article.<sup>1</sup>

#### Reference:

1. Bender R, Bunce C, Clarke M, Gates S, Lange S, Pace NL, Thorlund, K. Attention should be given to multiplicity issues in systematic reviews. *Journal of Clinical Epidemiology* 2008; 61: 857-65.



## PUBLISHED METHODOLOGICAL RESEARCH - structured abstracts and commentaries

### Industry-supported meta-analyses compared with meta-analyses with non-profit or no support: differences in methodological quality and conclusions

Jørgensen AW, Maric KL, Tendal B, Faurschou A, Gøtzsche PC. *BMC Medical Research Methodology* 2008; 8:60.

#### STRUCTURED ABSTRACT

**Background:** Studies have shown that industry-sponsored meta-analyses of drugs lack scientific rigour and have biased conclusions. However, these studies have been restricted to certain medical specialities.

**Objective:** To compare all industry-supported meta-analyses of drug versus drug comparisons with those without industry support.

**Design:** PubMed was searched for all meta-analyses that compared different drugs or classes of drugs published in 2004. Two authors assessed the meta-analyses and independently extracted data. A validated scale was used to judge methodological quality and a binary scale was used to judge the conclusions. The meta-analyses were divided according to the type of support in three categories: industry-supported, non-profit support or no support, and undeclared support.

**Main results:** Thirty nine meta-analyses were included, 10 had industry support, 18 non-profit or no support, and 11 undeclared support. On a 0 to 7 scale, the median quality score was six for meta-analyses with non-profit or no support and 2.5 for the industry-supported meta-analyses ( $P<0.01$ ). Compared with industry-supported meta-analyses, more meta-analyses with non-profit or no support avoided bias in the selection of studies ( $P=0.01$ ), more often stated the search methods used to find studies ( $P=0.02$ ), searched extensively ( $P<0.01$ ), reported criteria for assessing the validity of the studies ( $P=0.02$ ), used appropriate criteria ( $P=0.04$ ), described methods of allocation concealment ( $P=0.05$ ), described methods of blinding ( $P=0.05$ ), and described excluded patients ( $P=0.08$ ) and studies ( $P=0.15$ ). Forty per cent of the industry-supported meta-analyses recommended the experimental drug without reservations, compared with 22% of the meta-analyses with non-profit or no support ( $P=0.57$ ). In a sensitivity analysis, the authors of the meta-analyses with undeclared support were contacted; eight replied that they had not received industry funding. These were added to those with non-profit or no support,

and three who did not reply were added to those with industry support. This analysis did not change the results much.

**Conclusions:** Transparency is essential for readers to make their own judgment about medical interventions guided by the results of meta-analyses. We found that industry-supported meta-analyses are less transparent than meta-analyses with non-profit support or no support.

#### COMMENTARY

*Prepared by Joel Lexchin*

The finding by Jørgensen and colleagues that meta-analyses supported by pharmaceutical companies are less methodologically rigorous than those done with either non-profit support or no support should not come as any surprise. Yank et al<sup>1</sup> reported that industry support for meta-analyses of antihypertensive medications was strongly predictive of favourable conclusions about the study drug. The qualitative systematic review by Sisondo demonstrates that the positive bias in outcomes associated with industry funding extends beyond meta-analyses to include clinical trials and pharmacoeconomic studies, although in some cases there is no difference in the methodological quality between industry and non-industry supported research.<sup>2</sup>

In the past, critics of similar research have suggested that meta-analyses published as journal articles are more likely to have lower methodology scores because space limitations preclude a full methodological description. However, here Jørgensen cites work showing that Cochrane reviews published as journal articles achieve methodological scores equivalent to Cochrane reviews published in *The Cochrane Library*.

Jørgensen's work speaks to the validity of the criteria used in evaluating the quality of meta-analyses in general and specifically the reliability of the meta-analyses published in *The Cochrane Library*. The rating scale developed by Oxman and Guyatt has been validated and is widely accepted and used but some have suggested additional items should be considered such as whether double counting was avoided and whether values used were genuine or imputed.<sup>3</sup> Would these extra criteria improve the reporting of meta-analyses and the credibility of Cochrane reviews or would they just impose more work on the people who undertake them?

Finally, this meta-analysis still leaves some unanswered questions. Is any industry participation in the construction of meta-analyses too much or is there a level below which there is no detectable bias? If the latter is the case then perhaps The Cochrane Collaboration should relax its standards on industry involvement. If the former is the case, and I suspect that it is, then continued maintenance of the current restriction is not only prudent but wise.

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## Graphical presentation of diagnostic information

Whiting PF, Sterne JA, Westwood ME, Bachmann LM, Harbord R, Egger M, Deeks JJ. *BMC Medical Research Methodology* 2008; 8:20.

### STRUCTURED ABSTRACT

**Background:** Graphical displays of results allow researchers to summarise and communicate the key findings of their study. Diagnostic information should be presented in an easily interpretable way, which conveys both test characteristics (diagnostic accuracy) and the potential for use in clinical practice (predictive value).

**Objective:** To discuss the types of graphical display commonly encountered in diagnostic accuracy studies and systematic reviews of such studies, and to review how graphical displays are currently incorporated in studies of test performance.

**Design:** A systematic review was conducted to identify diagnostic accuracy studies published in 2004 and systematic reviews of diagnostic accuracy published in 2003. Studies were located by hand searching 12 general medical and speciality journals whilst systematic reviews were identified from DARE (Database of Abstracts of Reviews of Effects). Types of graphical display encountered in studies of diagnostic accuracy are presented.

**Main results:** Fifty seven studies and 49 systematic reviews were identified. Fifty-six per cent of studies and 53% of systematic reviews used graphical displays to present results. Dot-plot or box-and-whisker plots were the most commonly used graph in studies and were included in 22 (39%) of these. Receiver operating characteristic (ROC) plots were the most common type of plot included in systematic reviews and were included in 22 (45%) reviews. One study and five systematic reviews included a probability-modifying plot.

**Conclusions:** Graphical displays are currently underused in diagnostic accuracy studies and systematic reviews of such studies. Diagnostic accuracy studies need to include multiple types of graphic in order to provide both a detailed

overview of the results (diagnostic accuracy) and to communicate information that can be used to inform clinical practice (predictive value). Work is required to improve graphical displays, to communicate better the utility of a test in clinical practice and the implications of test results for individual patients.

### COMMENTARY

*Prepared by Sue Mallett*

Graphical displays can greatly aid the communication of diagnostic information from diagnostic studies, with particular roles in the display of uncertainty (95% confidence intervals) for individual study results, and the heterogeneity of results from different studies.

Whiting and colleagues review the graphical displays of diagnostic accuracy results, through a systematic review of 56 studies and 49 systematic reviews published in 2004 from a mixture of major general medical and specialty journals typically read by clinicians.

The main results show only 57% of studies and 53% of systematic reviews used a graphical display. Details are provided on the use of different graphs. Particularly disappointing was that only one study published a STARD (Standards for the Reporting of Diagnostic accuracy studies) flow diagram, as recommended in the STARD guidelines published in January 2003.

Similar reviews of the use of graphics in randomized trials have been published<sup>1</sup> with some previous information on graphs used in systematic reviews of diagnostic studies.<sup>2,3</sup>

#### *Implications for practice and for Cochrane reviews*

This is a helpful review of the multiple roles of graphical displays and how these can be met by inclusion of several different graphical displays. For example, SROC graphs provide a good visual display of the variability (heterogeneity) of diagnostic accuracy results such as sensitivity and specificity of studies in a systematic review, as well as showing potential correlation of sensitivity and specificity (commonly as a result of threshold effects). However 95% confidence intervals for individual studies are more clearly displayed in separate forest plots of sensitivity and specificity, which lack the combined single display of sensitivity and specificity seen in SROC graphs. STARD flow diagrams provide a distinct function of allowing the flow of patients in a study to be clearly described.

The authors draw attention to the potential usefulness of predictive nomograms and probability modifying plots, allowing clinicians to understand how diagnostic tests alter the pre-test probability of disease to a post-test probability. The potential dangers of these predictive nomogram plots are highlighted, as they may tempt readers to apply diagnostic accuracy results to different prevalence settings, which may relate inappropriately to very different clinical populations. It could have been helpful to broaden the



discussion to include graphical displays of methodological quality, such as those recommended in Cochrane diagnostic test accuracy reviews.

#### *Implications for future methodological research*

The article cites research showing that clinicians frequently misinterpret clinical usefulness of diagnostic tests based on accuracy measures such as sensitivity and specificity. Graphical displays could play an important role in communicating the potential utility of tests in clinical practice, however more research is needed to find out which graphical displays might be the most effective.

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3. Mallett S, Deeks JJ, Halligan S, Hopewell S, Cornelius V, Altman DG. Systematic reviews of diagnostic tests in cancer: review of methods and reporting. *BMJ* 2006; 333:413.

### **Empirical comparison of subgroup effects in conventional and individual patient data meta-analyses**

Koopman L, van der Heijden GJ, Hoes AW, Grobbee DE, Rovers MM. *International Journal of Technology Assessment in Health Care* 2008; 24: 358-61.

#### STRUCTURED ABSTRACT

**Background:** Individual patient data (IPD) meta-analyses have been proposed as a major improvement in meta-analytic methods to study subgroup effects. Subgroup effects of conventional and IPD meta-analyses using identical data have not been compared.

**Objective:** To compare subgroup effects of conventional and IPD meta-analyses using data from trials on the effectiveness of antibiotics in children with acute otitis media.

**Design:** Using data from six trials (n=1643) from a previously conducted IPD meta-analysis, effect measures (relative risks, risk differences, and 95% confidence intervals) were calculated from: (i) conventional meta-analysis using summary statistics derived from published data; (ii) two-stage approach to IPD meta-analysis using summary statistics derived from IPD; (iii) one-stage approach to IPD meta-analysis where IPD is pooled into a single data set.

**Main results:** In the conventional meta-analysis, only two of the six studies were included, because only these reported on relevant subgroup effects. The conventional meta-analysis showed larger subgroup effects (in children less than two years) or smaller subgroup effects (in children aged two or more years) and wider confidence intervals than both IPD meta-analyses. The most important reason for these discrepant results is that the two studies included in the conventional meta-analysis reported outcomes that were different both from each other and from the IPD meta-analyses.

**Conclusions:** This empirical example shows that conventional meta-analyses do not allow proper subgroup analyses, whereas IPD meta-analyses produce more accurate estimates of effects in subgroups. It also found no differences between the one- and two-stage meta-analytic approaches.

#### COMMENTARY

*Prepared by Lesley Stewart*

Koopman and colleagues report empirical evidence supporting the view that conventional meta-analyses do not generally permit subgroup analyses, and that where such analyses are important in a systematic review, an individual patient data (IPD) meta-analysis is warranted.

Using data collected from six randomized trials (1643 children) for an IPD meta-analysis assessing the effectiveness of antibiotics in children with acute otitis media, the authors compared IPD subgroup results with corresponding analyses done using aggregate data extracted from trial publications.

The authors also compared a two-stage IPD approach (summary statistics calculated for each study and then combined) with a one-stage IPD approach (all data analysed together in a model incorporating a covariate for trials).

Only two out of six trials reported results by age and none reported results according to whether acute otitis media was unilateral or bilateral. Furthermore, the two trials reported outcomes that differed from each other and from that used in the IPD analyses (where data were translated into a single outcome - a composite of ear pain and fever).

The conventional meta-analysis suggested a larger effect in children under two years of age (relative risk (RR) 0.33 95% CI 0.16 to 0.68) than that obtained using IPD (RR 0.68 95% CI 0.55 to 0.84, stage two). In children aged two years or more, the results were similar for conventional (RR 0.62 95% CI 0.25 to 1.55) and IPD analysis (RR 0.64 95%CI 0.52 to 0.79). Results for one- and two-stage IPD approaches were almost identical in age and uni/bilateral subgroups.

Although conventional and IPD approaches gave different estimates in the under two years category, given the overlap in confidence intervals it could be argued that the



conclusions drawn from each approach should still be the same and that there is no strong evidence that the intervention has different effects in these age groupings, and that the most robust estimate of effectiveness is the overall estimate based on all individuals. Nonetheless, this study has demonstrated clearly that published reports seldom present sufficient data to allow meaningful subgroup analyses and that the findings of subgroup analyses in a conventional meta-analysis can differ from those obtained from the corresponding IPD. Further similar empirical comparisons will add to the debate.

### Improving the reporting of pragmatic trials: an extension of the CONSORT Statement

Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, Oxman AD, Moher D, for the CONSORT Group and Pragmatic Trials in HealthCare (Practihc) Group. *BMJ* 2008; 337:a2390.

#### STRUCTURED ABSTRACT

**Background:** The CONSORT Statement is intended to improve reporting of randomized trials and focuses on minimising the risk of bias (internal validity). The applicability of a trial's results (generalisability or external validity) is also important, particularly for pragmatic trials. A pragmatic trial can be broadly defined as a randomized trial whose purpose is to inform decisions about practice.

**Objective:** To extend the CONSORT Statement to provide guidance for the reporting of pragmatic trials and their applicability.

**Design:** Two two-day meetings were held in Toronto, Canada, in 2005 and 2008, to review the CONSORT Statement and its extensions, the literature on pragmatic trials and applicability, and the group's experiences in conducting pragmatic trials. Participants included people with experience in clinical care, commissioning research, healthcare financing, developing clinical practice guidelines, and trial methodology and reporting. Twenty-four people participated in 2005 and 42 in 2008, including members of the CONSORT and Pragmatic Randomized Controlled Trials in HealthCare (Practihc) groups.

**Main results:** The CONSORT extension for pragmatic trials builds upon the existing CONSORT checklist and gives specific guidance for eight of the 22 checklist items in relation to pragmatic trials. For each of the eight items the standard CONSORT text and additional guidance, an example of good reporting for the item, and an explanation of the issues are presented. Importantly, these suggestions should be seen as additional to the general guidance in the main CONSORT explanatory paper and, where relevant, other CONSORT guidance.

**Conclusions:** Adherence to these reporting criteria will make it easier for decision makers to judge how applicable

the results of randomized trials are to their own conditions. Empirical studies are needed to ascertain the usefulness and comprehensiveness of these CONSORT checklist item extensions. In the meantime, it is recommended that those who support, conduct, and report pragmatic trials should use this extension of the CONSORT Statement to facilitate the use of trial results in decisions about health care.

#### COMMENTARY

*Prepared by Sue Richards*

In determining the effectiveness of treatments, randomized trials are accepted as the most reliable method but theoretical and empirical research has demonstrated that there are aspects that affect their reliability. Their reporting can fail to make these important aspects clear, and can itself introduce bias. The original CONSORT Statement ([www.consort-statement.org](http://www.consort-statement.org)) and its later revisions, giving a checklist to be followed when reporting results, and the encouragement by journal editors for authors to use it, has made it easier for authors to ensure that they are providing the relevant information.

Zwarenstein and colleagues propose an extension to the CONSORT checklist when reporting trials whose purpose is to inform decisions about practice. The work was initiated at a meeting of experts and a draft report was revised after circulation and a further meeting.

Though apparently common sense, it is a shame that it is not so easy to provide evidence for most of the additions, rather than a statement that "participants felt that eight items needed additional text".

The additions are not as straightforward as the original checklist and so a set of examples and explanations has been given. Some readers may find the examples, taken out of context, difficult to follow. Perhaps the most controversial point is the request that "the numbers of participants approached..., the number eligible and reasons for non-participation should be reported". Here, even the example does not include reasons for non-participation other than a lack of agreement to participate.

Due to the necessarily less precise points made, it will be more difficult for journals and systematic review authors to assess the compliance of authors than it is for the standard CONSORT Statement.

Nevertheless, this checklist, with the additional features recommended to be reported for pragmatic trials clearly laid out in a table, should help to improve reporting. Authors should be strongly encouraged to use it. Systematic review authors should use it in their assessment of the quality of trials and the relevance of results to practice.



## Locating systematic reviews of test accuracy studies: how five specialist review databases measure up

Bayliss SE, Davenport C. *International Journal of Technology Assessment in Health Care* 2008; 24:403-11.

### STRUCTURED ABSTRACT

**Background:** Over recent years there has been a substantial increase in the volume of primary research concerned with test accuracy, as reflected in a growing number of systematic reviews in this area. Systematic reviews provide valuable summaries of existing knowledge about test accuracy for both practitioners and review authors. Specialist review databases provide an alternative and possibly more reliable means of identifying studies of test accuracy than general bibliographic databases.

**Objective:** To evaluate how five specialist review databases perform in locating systematic reviews of test accuracy in terms of overlap between databases, utility and currency, and epidemiology of reviews contained within the databases. The databases evaluated were: Health Technology Assessment (HTA) database and Database of Abstracts of Reviews of Effects (DARE) (Centre for Reviews and Dissemination, York), Medion (Meta-analyses van Diagnostisch Onderzoek, University of Maastricht), C-EBLM database (International Federation of Clinical Chemistry and Laboratory Medicine Committee for Evidence-based Laboratory Medicine), and the ARIF database (Aggressive Research Intelligence Facility, University of Birmingham).

**Design:** Searches for all systematic reviews of test accuracy were conducted for the period 1996 to 2006. Reviews were located using in-house diagnostic search filters and with help from database producers where databases were not confined to test accuracy reviews. References were coded by disease area, review purpose and test application. Ease of use, volume, overlap and content of databases were recorded.

**Main results:** There was considerable overlap between the databases. Medion contained the largest number (n=672) and largest number of unique (n=328) test accuracy references. A combination of three databases identified only 76% of test reviews. All databases were rated as easy to search but varied with respect to how often they are updated and compatibility with reference management software. Eighty-five per cent of reviews evaluated test accuracy but the HTA database had a larger proportion of cost-effectiveness and screening reviews and C-EBLM more reviews addressing early test development. Most reviews were conducted in secondary care settings.

**Conclusions:** Specialist review databases offer an essential addition to general bibliographic databases where application of diagnostic method filters can compromise

search sensitivity. Important differences exist between databases in ease of use and content.

### COMMENTARY

*Prepared by Ruth Mitchell*

This paper is really two papers combined into one. It is a cross-sectional study of five specialist review databases (as listed in the abstract, above), which compares the characteristics of each database in terms of ease of access and use, currency, and the overlap of records between them. In addition, Bayliss and colleagues have categorised the reviews retrieved from the databases as to their disease topic areas, their purpose i.e. type of test evaluation study (e.g. test accuracy, effectiveness, costs, cost-effectiveness) and the clinical setting, or likely origin of patients to be tested.

The comparison of these databases is useful for authors of Cochrane diagnostic test accuracy reviews. Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* recommends that searchers use these databases as reviews can be a useful source of extra studies.<sup>1</sup> These studies may also provide examples of Medical Subject Headings (MeSH) terms and text words for their search strategies.

The methods and results sections discussing the searches of DARE and the HTA database, both available via *The Cochrane Library*, are interesting for searchers, and show the difficulties of using methodological filters for finding articles relating to diagnostic test accuracy. However, I cannot agree with the authors' suggestion that "specialist review databases and in particular those devoted to reviews of test accuracy provide an alternative and possibly more reliable means of accessing these studies". The studies included in any systematic review are a direct result of the search methods used. Non-Cochrane reviews are often deficient in this area, or lack transparency in reporting the conduct of searches.<sup>2</sup> For Cochrane reviews, there is an explicit recommendation that authors should not use methodological filters.

The results of the searches are documented in a flow diagram in supplementary Figure 2 on the publisher's website. Here it would have been useful to have had the final figures for the number of records unique to each database, as well as the percentages, because Figure 1 (unique references according to database) does not give this information clearly, and its scale is too small to gauge it accurately.

It would also have been interesting to know how many of the 1620 reviews were indexed in MEDLINE, and whether a search of MEDLINE would have captured them. In other words, is it easier just to search MEDLINE for reviews (given that an author would be incorporating a test or target condition component, or both, in the search strategy) or to search across some or all of the five databases?



Since no database contained all the unique records, the authors have provided a useful analysis in supplementary Table 2 of the yield of the searches according to different combinations of databases searched. They also provide a series of algorithms in supplementary Table 3 to help authors in deciding which combination of databases to search, depending on the purpose of their search.

The section of the paper looking at the characteristics of the individual reviews suffers to some extent from a lack of clarity both in the methods and in the presentation of results, and in the definitions of categories for review purpose and clinical setting. The title and abstract of this paper refer to reviews of test accuracy, yet other kinds of test evaluation reviews were included in the final figure of included reviews. Under exclusion criteria the authors say that the focus was “systematic reviews concerned with assessment of test accuracy, either in isolation or as part of a broader evaluation of tests”. However, the exclusion criteria were only that a paper was not a review or not concerned with test evaluation, which implies that reviews of, say, cost-effectiveness, that did not also have a component of test accuracy, would be included. Assigning codes based on the title alone may also have resulted in inaccuracies.

The figures were not always easy to understand, particularly Figure 2, which is difficult to read. Some results in the text were presented as percentages, and other related results were given in numbers, making it difficult to compare them e.g. the comparison of the DARE and HTA searches by the authors and the database producers. The fact that the title alone was used to determine to which categories each review belonged would have contributed to the significant number of reviews coded as unclear for either review purpose or clinical setting. This makes the results for proportions of reviews falling under the different categories less reliable, though given the high proportion of reviews in the ‘test accuracy’ purpose category, and ‘secondary care’ and ‘screening’ categories, these are likely to be valid, and to provide guidance as to which databases are best searched for these types of reviews.

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## The capture-mark-recapture technique can be used as a stopping rule when searching in systematic reviews

Kastner M, Straus SE, McKibbin KA, Goldsmith CH.  
*Journal of Clinical Epidemiology* 2009; 62:149-57.

### STRUCTURED ABSTRACT

**Background:** An important challenge in conducting systematic reviews is to determine how extensive the search should be, particularly because it is unknown how much literature exists on a given topic. Unlike clinical trials, no empirically derived stopping rules exist for this purpose. A potential solution is offered by the capture-mark-recapture statistical modelling technique, commonly applied to problems where multiple samples of occurrence are conducted to estimate the whole population (entitled the Horizon Estimate).

**Objective:** To test a stopping strategy based on the capture-mark-recapture statistical modelling to estimate the total number of reports of randomized trials evaluating clinical decision support tools for osteoporosis disease management.

**Design:** A systematic review of the literature was conducted to identify studies published in any language from 1996 to 2006. Searches were conducted in four large databases (MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EBM (Evidence-Based Medicine) reviews). In addition, websites were searched for grey literature; reference lists and clinical practice guidelines were reviewed, and contact made with experts in the field. Two review authors conducted the selection of studies, data extraction and quality assessment. The size of the retrievals (i.e. the Horizon Estimate) was calculated at two levels of screening: title and abstract (1246 potentially relevant articles) and full text (42 potentially relevant articles).

**Main results:** The capture-mark-recapture model suggested that the total number of potential articles was 1838 for the first level of screening and 49 for the full text level. The four databases provided 68% of known articles for the first level of screening and 81% for full text screening.

**Conclusions:** The capture-mark-recapture technique can be used in systematic reviews to estimate the closeness to capturing the total body of literature on a given topic. More studies are needed to determine the usefulness of Horizon Estimates as a stopping rule strategy for systematic review searching.

### COMMENTARY

*Prepared by Phil Edwards*

Capture-mark-recapture is a method used in ecology to estimate population sizes. As a simple example, to estimate the total number of turtles (N) living in a lake we could



catch and mark a sample of turtles (M) and then release them back into the lake. After a few days, we return and catch a second sample of turtles (C) and count how many are marked (R). If we assume that the proportion marked in our second sample (R/C) equals the proportion marked in the population (M/N), we can estimate the population size as  $N = CM/R$ . For this method to produce reliable results several assumptions must be satisfied. We must assume that the population is fixed (i.e. no migration; no births or deaths), that samples are independent (i.e. inclusion in the first sample does not influence the probability of inclusion in any subsequent sample), and that the probability of inclusion in any sample is equal for all members of the population.

The capture-mark-recapture method has been used to estimate the proportion of studies eligible for inclusion in a systematic review that is missed when using only one, instead of two, observers to screen records from electronic searches.<sup>1</sup> We concluded that two observers should be used to screen records for eligibility whenever possible, in order to maximise the ascertainment of relevant studies.

Kastner and colleagues have proposed that the method can be used to estimate the population of eligible studies and provide instructions about how to use capture-mark-recapture as part of a stopping rule for systematic review searching. Their main idea is that in advance of any searching, authors set the proportion of all eligible studies that they aim to include in their review (e.g. 90% of studies). The next step is to search two databases from which the greatest yield of eligible studies is expected. After searching these two databases, capture-mark-recapture is used to estimate the total population of eligible studies, and the proportion that has been identified from the first two databases. If the proportion is less than that specified in advance, a search of a third database is required, and so on. Once the 95% confidence interval for the true proportion includes that set in advance, then searching can stop. The threshold 'stopping' proportion might refer only to included studies, or to potentially eligible full text reports, or to titles and abstracts of records of potentially eligible studies.

With two databases it would be possible to estimate the total number of eligible studies using the simple equation given above. With more than two databases, the estimation of population size may require help from a statistician. Kastner et al. tested their stopping rule by searching four databases for randomized trials evaluating clinical decision support tools for osteoporosis disease management. They estimated that searches of MEDLINE, EMBASE, CINAHL and EBM reviews yielded 81% of known articles for full-text screening.

Does this use of capture-mark-recapture satisfy the assumptions? The assumption of a fixed population seems reasonable, particularly if the database searches cover the same time periods. The assumption of independence of databases may be harder to justify. For example, might we expect that a study indexed in MEDLINE is more likely also

to be indexed in EMBASE than a study not indexed in MEDLINE? Similarly, the assumption that each study is equally likely to be included in each database would also appear dubious. Such dependence could lead to biased estimates of population size.<sup>2</sup>

The authors conclude by recommending that further research is needed, and ask: "is capturing 90%, 95% or 99% of studies enough?" But is this the right question?

There is no doubt that any development that can help to reduce the amount of time spent screening titles and abstracts for eligible studies will be welcomed. However, as omission of eligible studies can introduce bias, such developments must not impact negatively on the ascertainment and inclusion of relevant studies. Stopping rules are usually applied in clinical trials in populations where each participant carries equal weight in the analysis. However, study results do not all have equal weight in a meta-analysis and so studies cannot be treated equally in this way. Studies that are hardest to catch may be different in ways that are important in an overview of the evidence.

Further work in this area might therefore be informed by a 'value of information' analysis. For instance, how might healthcare decisions be influenced by the inclusion of the last 5% or 10% of studies identified in a systematic review? The decision about when to stop searching must depend on the costs and benefits of further searching, rather than achieving any arbitrary inclusion proportion. If resources are limited, it may be more important to ensure that an adequate assessment of study quality is made for all included studies than to conduct exhaustive searches.<sup>3</sup>

Other research using published Cochrane reviews could assess the reliability of the capture-mark-recapture method for estimating the total number of eligible studies. If the results from searching the first two databases in each review are used to estimate the total number of eligible studies, this could be compared with the number of studies actually included. It would be interesting to hear from authors of reviews how their total included studies compares with the total that would be estimated using the capture-mark-recapture method on the results of searching their first two databases.

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assessment of trial quality in systematic reviews? Empirical study. *Health Technology Assessment* 2003; 7(1):1-76.

### Systematic reviewers commonly contact study authors but do so with limited rigor

Mullan RJ, Flynn DN, Carlberg B, Tleyjeh IM, Kamath CC, LaBella ML, Erwin PJ, Guyatt GH, Montori VM. *Journal of Clinical Epidemiology* 2009; 62:138-42.

#### STRUCTURED ABSTRACT

**Background:** The quality of systematic reviews can be enhanced by contacting authors of studies to elicit missing data. Little is known about this practice.

**Objective:** To investigate the practice of author contact in recently published systematic reviews to characterise its prevalence, quality and results.

**Design:** A systematic review of systematic reviews of treatment efficacy published in 2005 to 2006 in the 25 journals with the highest impact factor publishing systematic reviews in clinical medicine or in the *Cochrane Database of Systematic Reviews*. MEDLINE, EMBASE and *The Cochrane Library* were searched. Reviews were included if they reported relevant data, had assessed the quality of eligible studies and included at least three randomized trials. Two review authors conducted the selection of reviews and data extraction. A survey of authors of included reviews was conducted to assess the accuracy of the data.

**Main results:** Forty-six (50%) of the 93 eligible reviews published in top journals and 46 (85%) of the 54 eligible Cochrane reviews reported contacting study authors. Most author contact was initiated to seek missing information: 40 (76%) clinical medicine reviews and 45 (98%) Cochrane reviews. One hundred and nine of 147 (74%) review authors responded to the survey and reported a higher rate of author contact than was apparent from the published record.

**Conclusions:** Author contact is not a universal feature of systematic reviews published in top journals and the ways in which it is reported needs improvement.

#### COMMENTARY

Prepared by Taryn Young

Despite guidelines for reporting of randomized trials,<sup>1</sup> data commonly missing from published papers include details of allocation concealment and blinding, information about loss to follow up and standard deviations. Standard systematic review methodology includes contacting authors of included studies for details about missing or inadequate data.<sup>2</sup> Not finding the required information results in incomplete risk of bias assessments and outcome reporting, and thus limits review conclusions.

Mullan and colleagues describe this practice of contacting authors for missing data: how often and why review authors seek to contact authors, to what extent these contacts are successful, how review authors report author contact procedures and their outcome in systematic reviews. They searched MEDLINE, EMBASE and *The Cochrane Library* for systematic reviews published from January 2005 to March 2006 in top medical journals, including *The Cochrane Library*. Eligibility criteria were clearly specified and review authors worked independently to select and extract data from eligible reviews. To assess the accuracy of the data abstracted, they also contacted authors of all the included systematic reviews to complete an online survey on whether all, some, or no authors of eligible studies were contacted; the purpose of author contact; the number of authors contacted; and reason(s) for not contacting authors. Mullan and colleagues found that most included reviews mentioned author contact. Furthermore, they found that review authors contacted authors of eligible studies more often than reported in the published record, most frequently for method clarification. Both Cochrane and journal reviews infrequently and incompletely report the results of author contact.

Authors of Cochrane reviews should include more detailed information on the frequency and results of contact with authors of included studies, and should do sensitivity analyses to assess its impact, in line with guidelines for reporting of systematic reviews.<sup>3</sup> The editorial teams of Cochrane Review Groups can play a role in monitoring reporting practices. Furthermore, trialists can improve the quality of their reporting by adhering to guidelines such as CONSORT to make it easier to assess the risk of bias assessment and improve the usability of their research.

#### References:

1. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement [editorial]. *BMJ* 1996; 313:570-1.
2. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
3. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354:1896-900.

### Developing and evaluating complex interventions: the new Medical Research Council guidance

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. *BMJ* 2008; 337:979-83.

#### STRUCTURED ABSTRACT



**Background:** Complex interventions are widely used in the health service, in public health practice, and in areas of social policy that have important health consequences, such as education, transport, and housing. They present various problems for evaluators, including practical and methodological difficulties. In 2000, the Medical Research Council (MRC) in the UK published a framework to help researchers and funders to recognise and adopt appropriate methods.

**Objective:** To update guidance provided in the 2000 MRC framework on the development, evaluation and implementation of complex interventions to improve health.

**Design:** A workshop was held by the MRC Population Health Sciences Research Network to consider whether and how the framework should be updated.

**Main results:** The updated guidelines provide more guidance on how to approach the development, reporting, and implementation of complex interventions, with greater attention to the contexts in which interventions take place. It also recommends consideration of alternatives to randomized trials, and of highly complex or non-health sector interventions to which biomedical methods may not be applicable. Evidence and examples to support and illustrate the recommendations are also provided. This article summarizes the issues that prompted the revision and the key messages of the new guidance, which has been incorporated into the MRC's guidance ([www.mrc.ac.uk/complexinterventionsguidance](http://www.mrc.ac.uk/complexinterventionsguidance)).

**Conclusions:** The revised guidance aims to help researchers, funders, and other decision-makers to make appropriate methodological and practical choices in the area of complex interventions.

#### COMMENTARY

*Prepared by Sasha Shepperd*

Nine years ago, the Medical Research Council (MRC) in the UK published guidance for researchers designing evaluations of complex interventions.<sup>1</sup> The guidance suggested distinct steps for researchers to consider when developing and evaluating complex interventions. The steps include a review of the evidence, defining the components of the complex intervention using a range of evidence and conducting an exploratory trial prior to proceeding to the main trial. The final phase examines the implementation of the intervention in practice. Over the intervening years the guidance stimulated much debate and comment, with some researchers using the guidance to underpin the evaluation of a complex intervention.

Eight years on, following a workshop held by the MRC Population Health Sciences Research Network, revised guidance, which has drawn on the experience of researchers using the guidance, has been published by Craig and colleagues.

*How does the new guidance differ from the original document?*

The new guidance confronts head on the political and practical reality that can constrain the methods used to evaluate complex interventions; and acknowledges that in some situations, randomization is not feasible. The tension between accounting for local context versus standardizing a complex intervention across settings is highlighted; and there is greater emphasis on the iterative nature of evaluation.

*How can the MRC guidance be applied to systematic reviews?*

The guidance can provide a broad conceptual framework that encourages review authors to seek additional information about the nature of a complex intervention and structure the review in a logical sequence. However, the degree to which this can be done is limited by the range of other factors that have to be considered, such as risk of bias, when commenting on an individual trial within a review.

#### References:

1. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, Tyrer P. Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000; 321:694-6.



## EMPIRICAL STUDIES WITHIN THE COLLABORATION

This section aims to highlight some of the current methodological research being carried out within The Cochrane Collaboration. To register ongoing methodological research within The Cochrane Collaboration please contact [shopewell@cochrane.co.uk](mailto:shopewell@cochrane.co.uk).

### Cochrane Review Group recommendations for assessing the risk of bias

Andreas Lundh and Peter C Gøtzsche

**Title:** Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies.

**Contact:** Peter C Gøtzsche, Nordic Cochrane Centre, Rigshospitalet Dept. 343, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: [pcg@cochrane.dk](mailto:pcg@cochrane.dk).

**Background:** Assessing the risk of bias in individual studies in a systematic review can be done by listing different methodological areas separately (component approach) or by summarizing the study quality in an overall



score (scale approach). A major problem with scales is that they often incorporate items that are more related to the quality of reporting, ethical issues or statistical issues than to bias.

**Objective:** To examine how the Cochrane Review Groups currently recommend assessment and handling of the risk of bias in studies, with a focus on the use of scales, and suggest possible improvements.

**Location:** Nordic Cochrane Centre, Denmark.

**Methods:** The instructions to authors of the 50 Cochrane Review Groups (CRGs) that focus on clinical interventions were examined for recommendations on methodological quality assessment of studies.

**Summary of main results:** Forty-one of the CRGs (82%) recommended quality assessment using components and nine using a scale. All groups recommending components recommended to assess concealment of allocation, compared to only two of the groups recommending scales ( $P < 0.0001$ ). Thirty-five groups (70%) recommended assessment of sequence generation and 21 groups (42%) recommended assessment of intention-to-treat analysis. Only 28 groups (56%) had specific recommendations for using the quality assessment of studies analytically in reviews, with sensitivity analysis, quality as an inclusion threshold and subgroup analysis being the most commonly recommended methods. The scales recommended had problems in the individual items and some of the groups recommending components recommended items not related to bias in their quality assessment.

**Conclusions:** Recommendations by some groups were not based on empirical evidence and many groups had no recommendations on how to use the quality assessment in reviews. It is suggested that all CRGs refer to the *Cochrane Handbook for Systematic Reviews of Interventions*, which is evidence based, in their instructions to authors and that their own guidelines are kept to a minimum and describe only how methodological topics that are specific to their fields should be handled.

**Reference:**

Lundh A, Gøtzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. *BMC Medical Research Methodology* 2008; 8:22.

### A retrospective cohort study of the life history of Cochrane protocols

Andrea Tricco, Jamie Brehaut, Maggie Chen and David Moher

**Title:** Following 411 Cochrane protocols to completion: a retrospective cohort study.

**Contact:** David Moher, Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada. E-mail: [dmoher@uottawa.ca](mailto:dmoher@uottawa.ca).

**Background:** Cochrane reviews are regarded as being scientifically rigorous and are increasingly used by a variety of stakeholders. However, factors predicting the publication of Cochrane reviews have not been reported. If a higher proportion of Cochrane protocols with certain characteristics (e.g., funding) are being published, this may lead to inaccurate decisions.

**Objective:** To examine the frequency of published and unpublished Cochrane reviews and protocol factors that predict the publication of Cochrane reviews.

**Location:** Chalmers Research Group, Canada.

**Methods:** Retrospective cohort study of Cochrane protocols published in 2000 (Issues 2 to 4) and 2001 (Issue 1). The publication status of these reviews was followed up to Issue 1, 2008 in *The Cochrane Library*. Survival analysis of the time from protocol publication to the first review publication, and protocol factors predicting the time to publication, was conducted.

**Summary of main results:** There were 411 new Cochrane protocols in the cohort. After excluding 39; 71/372 (19%) were unpublished and 301/372 (81%) were published as full Cochrane reviews at the time of study analysis (January 2008). The median time to publication was 2.4 years (range: 0.15 to 8.96). Multivariate analyses revealed that shorter time to publication was associated with the review subsequently being updated (hazard ratio, HR: 1.80 [95% confidence interval, CI: 1.39 to 2.33]) and longer time to publication was associated with the review having two published protocols, indicating changes to the review plan (HR: 0.33 [95% CI: 0.12 to 0.90]).

**Conclusions:** Only about 80% of Cochrane protocols were published as full reviews after more than eight years of follow-up. The median time to publication was 2.4 years and some reviews took much longer. Strategies to decrease time to publication should be considered, such as streamlining the review process, increased support for authors when protocol amendments occur, and better infrastructure for updating Cochrane reviews.

**Reference:**

Tricco AC, Brehaut J, Chen MH, Moher D. Following 411 Cochrane protocols to completion: a retrospective cohort study. *PLoS ONE* 2008; 3:e3684.

### Surveillance search techniques as triggers for updating systematic reviews

Margaret Sampson, Kaveh G Shojania, Jessie McGowan, Raymond Daniel, Tamara Rader, Alla E Iansavichene, Jun Ji, Mohammed T Ansari and David Moher



**Title:** Surveillance search techniques identified the need to update systematic reviews.

**Contact:** Margaret Sampson, Children's Hospital of Eastern Ontario Research Institute, Chalmers Research Group, 401 Smyth Road, Ottawa, Ontario K1H 8L1, Canada. E-mail: [msampson@cheo.on.ca](mailto:msampson@cheo.on.ca).

**Background:** Systematic review searches attempt to achieve high recall (i.e. to retrieve all relevant studies), but generally do so at the expense of precision (i.e. they retrieve many non-relevant studies). The low precision of the searches presents a barrier to ongoing monitoring of the literature for the purposes of updating.

**Objective:** To test literature surveillance methods to identify new evidence eligible for updating systematic reviews.

**Location:** Children's Hospital of Eastern Ontario Research Institute, Canada.

**Methods:** Five search strategies were employed to identify new studies in MEDLINE and CENTRAL (Cochrane Central Register of Controlled Trials) that would signal major or invalidating new evidence for 77 of 100 randomly selected systematic reviews of healthcare interventions for which newer reviews did not exist. The reviews were published from 1995 to 2005 and indexed in *ACP Journal Club*. Recall for each search approach was assessed as a proportion of a composite yield of relevant studies across all search approaches that were identified by that approach. Screening burden was the number of studies that would need to be reviewed to identify the evidence that would necessitate updating.

**Summary of main results:** No single method yielded consistently high recall of relevant new evidence, so combinations of the strategies were examined. A search algorithm based on PubMed's related article search in combination with subject searching using clinical queries was the most effective combination, retrieving all relevant new records in 68 cases. Screening burden was a median of 71 new records per review (inter-quartile range 42 to 161).

**Conclusions:** Surveillance for emerging evidence that signals the need to update systematic reviews is feasible using a combination of subject searching and searching based on PubMed's related article function.

**Reference:**

Sampson M, Shojania KG, McGowan J, Daniel R, Rader T, Iansavichene AE, Ji J, Ansari MT, Moher D. Surveillance search techniques identified the need to update systematic reviews. *Journal of Clinical Epidemiology* 2008; 61:755-62.

## Methods to prioritise the updating of systematic reviews

Alex Sutton, Sarah Donegan, Yemisi Takwoingi, Paul Garner, Carol Gamble and Alison Donald

**Title:** An encouraging assessment of methods to inform priorities for updating systematic reviews

**Contact:** Alex Sutton, Department of Health Sciences, University of Leicester, 2nd Floor (Room 214e), Adrian Building, University Road, Leicester LE1 7RH, UK. E-mail: [ajs22@le.ac.uk](mailto:ajs22@le.ac.uk).

**Background:** Updating a systematic review and producing the corresponding updated document is often a continual and a time-consuming process and resources are usually limited. Strategies such as updating all reviews according to a perpetual (unordered) rota may result in an inefficient use of resources in slowly developing fields or delayed incorporation of new knowledge in rapidly evolving fields.

**Objective:** To consider the use of statistical methods that aim to prioritize the updating of a collection of systematic reviews based on preliminary literature searches.

**Location:** University of Leicester, UK.

**Methods:** A new simulation-based method estimating statistical power and the ratio of the weights assigned to the predicted new and old evidence, and the existing Barrowman n approach was considered. Using only information on the numbers of subjects randomized in the 'new' trials, these were applied retrospectively, by removing recent studies, to existing systematic reviews from the Cochrane Infectious Diseases Group.

**Summary of main results:** Twelve systematic reviews were included. When the removed studies were reinstated, inferences changed in five of them. These reviews were ranked, in order of update priority, 1, 2, 3, 4, and 11 and 1, 2, 3, 4, and 12 by the Barrowman n and simulation-based power approaches, respectively. The low ranking of one significant meta-analysis by both methods was due to unexpectedly favourable results in the reinstated study.

**Conclusions:** This research demonstrates the feasibility of the use of analytical methods to inform update prioritization strategies. Under conditions of homogeneity, Barrowman's n and simulated power were in close agreement.

**Reference:**

Sutton AJ, Donegan S, Takwoingi Y, Garner P, Gamble C, Donald A. An encouraging assessment of methods to inform priorities for updating systematic reviews. *Journal of Clinical Epidemiology* 2009; 62: 241-51.



## Estimating and presenting baseline risks: recommendations for Summary of findings tables

Jill Hayden, George Tomlinson, Maurits van Tulder and Doug Altman

**Title:** Approaches to estimate and present baseline risks: recommendations for Cochrane review Summary of findings (SoF) tables.

**Contact:** Jill Hayden, Dept. of Community Health and Epidemiology, Dalhousie University, 5790 University Avenue, Room 222, Halifax, Nova Scotia, B3H 1V7, Canada. E-mail: [JHayden@Dal.ca](mailto:JHayden@Dal.ca).

**Background:** The SoF table presents an absolute measure of effect, using a measure of baseline risk to convert relative effect sizes. Current recommendations are to estimate baseline risk from the control group rate of included trials. This may not provide a valid estimate as participants in trials represent a select group of people, and it may not adequately address the real heterogeneity in patient populations. Alternatives are available, but there are trade-offs between validity, feasibility, and comprehensibility of estimates.

**Objective:** This project will: summarize the methodological literature relevant to estimating baseline risk; compare and identify issues with different approaches to estimate baseline risk in available systematic review databases (of randomized trials and prognosis studies); conduct a discussion workshop among key Cochrane stakeholders to identify additional issues, debate, and attempt to reach consensus on appropriate recommendations for estimation and presentation of baseline risk.

**Location:** Halifax, Nova Scotia, Canada (Prognosis Methodology Resource Group, a new subgroup of the Prognosis Methods Group; Dalhousie University Network Site of the Canadian Cochrane Network and Centre).

**Methods:** We will explore several approaches using different data sources (trials and prognosis studies, with or without clinical judgment) and measures (central tendency, subgroups and risk groups, with or without probability distributions). We will compare and identify issues with each approach to estimate baseline risk using existing data from a Cochrane review that included a Bayesian hierarchical meta-regression analysis, available independent patient data from included trials, a completed review of the prognosis literature, and consultation with clinical experts. This will be followed by a process to allow input from different Cochrane Review Groups and relevant Methods Groups.

**Summary of main results:** Ongoing. A summary of the methodological literature and results of the exploratory analyses will be compiled, presented, and discussed with

key Cochrane stakeholders in pre-workshop and workshop activities. The planned outcome of this project will be recommendations to the Collaboration regarding methods to estimate and present baseline risk.

**Conclusions:** To be determined.

This study was funded by the Cochrane Opportunities Fund in 2008.



## Thomas C Chalmers M.D. Award - 2008

The Thomas C Chalmers M.D. prize is awarded annually for the best oral and poster presentations at the Cochrane Colloquium. In 2008 in Freiburg, Germany, the prize was shared between Richard Riley, Susanna Dodd, Jean Craig and Paula Williamson for their study entitled 'Meta-analysis of diagnostic test studies using individual patient data and aggregate data', Judith Anzures-Cabrera and Julian Higgins for their study entitled 'Expressing meta-analyses of continuous outcomes in terms of risks', and Britta Tendal, Peter Jüni, Julian Higgins, Asbjørn Hróbjartsson, Anders Jørgensen, Sven Trelle, Simon Wandel, Eveline Nüesch, Katarina Gesser, Søren Ilsoe-Kristensen and Peter Gøtzsche for their study entitled 'The data extraction challenge: observer variation when extracting data for the calculation of a standardised mean difference'.

## Meta-analysis of diagnostic test studies using individual patient data and aggregate data

Richard Riley, Susanna Dodd, Jean Craig and Paula Williamson

**Contact:** Richard Riley, Centre for Medical Statistics and Health Evaluation, Shelley's Cottage, University of Liverpool, Brownlow Street, Liverpool L69 3GS, UK. E-mail: [Richard.riley@liv.ac.uk](mailto:Richard.riley@liv.ac.uk).

**Background:** A meta-analysis of diagnostic test studies provides evidence-based results regarding the accuracy of a particular test and usually involves synthesizing aggregate data (AD) from each study, such as the two-by-two tables of diagnostic accuracy. A bivariate random-effects meta-analysis (BRMA) can appropriately synthesize these tables and leads to clinical results such as the mean sensitivity and mean specificity across studies. However, translating such results into practice may be limited by between-study heterogeneity and the fact that they relate to some 'average' patients across studies.

**Objective:** To describe how the meta-analysis of individual patient data (IPD) from diagnostic studies can lead to more



clinically meaningful results tailored to the individual patient.

**Location:** Centre for Medical Statistics and Health Evaluation, University of Liverpool, UK.

**Methods:** We present IPD models that extend the BRMA framework to include study-level covariates, which help explain the between-study heterogeneity, and also patient-level covariates, which allow the interaction between test accuracy and patient characteristics to be assessed.

**Summary of main results and conclusions:** We show how the inclusion of patient-level covariates requires careful separation of within-study and across-study accuracy-covariate interactions, as the latter are particularly prone to confounding. Our models are assessed through simulation and are extended to allow IPD studies to be combined with AD studies, as IPD are not always available for all studies. Application is made to 23 studies assessing the accuracy of ear temperature for diagnosing fever in children, with 16 IPD and 7 AD studies. The models revealed that between-study heterogeneity is partly explained by the use of different measurement devices and that there is no evidence that individual age modifies diagnostic accuracy.

**References:**

Riley RD, Dodd SR, Craig JV, Williamson PR. Meta-analysis of diagnostic test studies using individual patient data and aggregate data [abstract]. 16<sup>th</sup> Cochrane Colloquium: Evidence in the era of globalisation; 2008 Oct 3-7; Freiburg, Germany. *Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen* 2008;102 (Suppl VI):28.

Riley RD, Dodd SR, Craig JV, Thompson JR, Williamson PR. Meta-analysis of diagnostic test studies using individual patient data and aggregate data. *Statistics in Medicine* 2008; 27:6111-36.

## Expressing meta-analyses of continuous outcomes in terms of risks

Judith Anzures-Cabrera and Julian Higgins

**Contact:** Judith Anzures-Cabrera, MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Robinson Way, Cambridge, CB2 2SR, UK. E-mail: [judith.anzures-cabrera@mrc-bsu.cam.ac.uk](mailto:judith.anzures-cabrera@mrc-bsu.cam.ac.uk).

**Background:** Meta-analyses dealing with continuous outcome data usually report the effect of an intervention by using either mean difference (MD) or standardized mean difference (SMD). These two effect sizes often have a difficult clinical interpretation. Re-expressing the intervention effect in terms of risks may facilitate understanding and applicability, particularly in the context of a 'Summary of findings' table. For primary studies, researchers can easily determine odds ratios or relative risks

for a given cut-point, but in meta-analysis, this is not straightforward when the only available information are means and standard deviations for the two intervention groups.

**Objective:** To review, develop and compare methods for transformations that enable meta-analyses of continuous outcomes to be presented as risks.

**Location:** MRC Biostatistics Unit, Cambridge, UK.

**Methods:** We compared four methods in different applications and in a series of simulation studies. Two involve direct transformation of the SMD to an odds ratio (OR). The two others involve estimation of risks for a specific cut-point, one that can be applied to meta-analysis of MDs by specifying a typical control group mean and SD. To evaluate the methods, we simulated continuous outcome data for a single, two-group study, according to various distributions, different sample sizes and control group risks.

**Summary of main results:** Methods based on direct transformation of SMD to OR have reasonable properties for symmetrically distributed data when applied to risks near 0.5, but are biased for extreme risks. When the standard deviations are different across the two groups, these methods suffer from serious biases. One of the methods that estimate risks for the two groups has good properties for normally distributed data and large sample sizes, but is problematic for small sample sizes, when both bias and imprecision can occur.

**Conclusions:** Methods for expressing meta-analyses results from continuous outcome data are sensitive to underlying distributions, sample sizes and cut-points. We are not able to recommend a method for widespread application in 'Summary of findings' tables. We offer suggestions for situations in which the various methods may safely be applied.

**Reference:**

Anzures J, Higgins J. Expressing meta-analyses of continuous outcomes in terms of risks [abstract]. 16<sup>th</sup> Cochrane Colloquium: Evidence in the era of globalisation; 2008 Oct 3-7; Freiburg, Germany. *Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen* 2008;102 (Suppl VI):20.

## Data extraction challenge: observer variation when extracting data for the calculation of a standardised mean difference

Britta Tendal, Peter Jüni, Julian Higgins, Asbjørn Hróbjartsson, Anders Jørgensen, Sven Trelle, Simon Wandel, Eveline Nüesch, Katarina Gesser, Søren Ilse-Kristensen and Peter Gøtzsche



**Contact:** Britta Tendal, The Nordic Cochrane Centre, Rigshospitalet, 9 Blegdamsvej, 3343, 2100 Copenhagen, Denmark. E-mail: [bt@cochrane.dk](mailto:bt@cochrane.dk).

**Background:** Outcomes measured on ranking scales and continuous scales can be challenging for meta-analysts. We have previously reported a high rate of data extraction errors in meta-analyses using the standardized mean difference (SMD).

**Objective:** To study the inter-observer variation when several independent observers extracted the same type of data and the reasons for disagreements.

**Location:** The Nordic Cochrane Centre, Copenhagen, Denmark.

**Methods:** We selected a random sample of 10 recent Cochrane reviews that presented a result as an SMD and retrieved the trial reports (n = 45) that corresponded to the first SMD result in each review and the protocols for the reviews. Ten observers (five experienced methodologists and five PhD students) independently extracted the necessary data from the trial reports for calculation of the SMD. The observers did not have access to the original review and were only given the review protocols and the trial reports as pdf files. In the protocols, an additional researcher had highlighted the relevant outcome and other important factors. Based on the extracted data, this researcher calculated the SMDs. Agreement was defined as SMDs that differed less than 0.1 in their point estimates or confidence intervals.

**Summary of main results:** The results were analysed at two levels, meta-analysis and trial level, pairing the observers in all possible ways (45 pairs). Thus, the 10 meta-analyses yielded a total of 450 pairs, and the 45 trials yielded 2025 pairs for agreement analysis. The agreement was 30.4% (137/450) at the meta-analysis level and 52.8% (1070/2025) at the trial level. Important reasons for disagreement were calculation errors, oversights, and differences in selection of time points, scales, control groups, and type of calculations.

**Conclusions:** There was considerable disagreement between observers. Despite the limitations of this study due to its experimental design, it is clear that the multiplicity of data in trial reports calls for more detailed review protocols. The potential for error highlights the need for more than one observer and statistical knowledge or help from a statistician.

**Reference:**

Tendal B, Jüni P, Higgins JPT, Hróbjartsson A, Jørgensen A, Trelle S, Wandel S, Nüesch E, Gesser K, Ilsøe-Kristensen S, Gøtzsche PC. The data extraction challenge: observer variation when extracting data for the calculation of a standardised mean difference [abstract]. 16<sup>th</sup> Cochrane Colloquium: Evidence in the era of globalisation; 2008 Oct 3-7; Freiburg, Germany. *Zeitschrift für Evidenz,*

*Fortbildung und Qualität im Gesundheitswesen* 2008;102 (Suppl VI):90.



## Cochrane Methodology Review Group

Elizabeth Paulsen

The Cochrane Methodology Review Group (CMRG) editorial team is co-ordinated by Mike Clarke and Andy Oxman. The other editors are Philippa Middleton, Peter Gøtzsche, Karen Robinson, Paul Glasziou, Peter Jüni and Gordon Guyatt (Criticism Editor). Other members of the editorial team based in Oslo are Marit Johansen (Trials Search Co-ordinator), Jan Ødegaard-Jensen (Statistician), and Elizabeth Paulsen (Managing Editor, formerly called Review Group Co-ordinator).

The Cochrane Methodology Register (CMR) is maintained by Sally Hopewell and Anne Eisinga at the UK Cochrane Centre. Currently, the register contains more than 11,000 references to methodology studies.

At the start of 2009, 11 protocols and 14 full methodology reviews were published in *The Cochrane Library* (Issue 2, 2009).

We are trying to increase the involvement of people from low- and middle-income countries in developing and preparing Cochrane methodology reviews. For more information on how you can participate, contact the Managing Editor ([elizabeth.paulsen@nokc.no](mailto:elizabeth.paulsen@nokc.no)).

The next meeting of the CMRG editorial team will be in October 2009 at the Cochrane Colloquium in Singapore.

The abstract of the most recent Cochrane methodology review is presented below:

### Publication bias in clinical trials due to statistical significance or direction of trial results

Sally Hopewell, Kirsty Loudon, Mike Clarke, Andy Oxman and Kay Dickersin

**Background:** The tendency for authors to submit, and of journals to accept, manuscripts for publication based on the direction or strength of the study findings has been termed publication bias.

**Objective:** To assess the extent to which publication of a cohort of clinical trials is influenced by the statistical significance, perceived importance, or direction of their results.



**Search strategy:** We searched the Cochrane Methodology Register (*The Cochrane Library [Online]* Issue 2, 2007), MEDLINE (1950 to March Week 2 2007), EMBASE (1980 to Week 11 2007) and *Ovid MEDLINE In-Process & Other Non-Indexed Citations* (March 21 2007). We also searched the Science Citation Index (April 2007), checked reference lists of relevant articles and contacted researchers to identify additional studies.

**Selection criteria:** Studies containing analyses of the association between publication and the statistical significance or direction of the results (trial findings), for a cohort of registered clinical trials.

**Data collection and analysis:** Two authors independently extracted data. We classified findings as either positive (defined as results classified by the investigators as statistically significant ( $P < 0.05$ ), or perceived as striking or important, or showing a positive direction of effect) or negative (findings that were not statistically significant ( $P \geq 0.05$ ), or perceived as unimportant, or showing a negative or null direction in effect). We extracted information on other potential risk factors for failure to publish, when these data were available.

**Main results:** Five studies were included. Trials with positive findings were more likely to be published than trials with negative or null findings (odds ratio 3.90; 95% confidence interval (CI) 2.68 to 5.68). This corresponds to a risk ratio of 1.78 (95% CI 1.58 to 1.95), assuming that 41% of negative trials are published (the median among the included studies, range 11% to 85%). In absolute terms, this means that if 41% of negative trials are published, we would expect that 73% of positive trials would be published.

Two studies assessed time to publication and showed that trials with positive findings tended to be published after four to five years compared to those with negative findings, which were published after six to eight years. Three studies found no statistically significant association between sample size and publication. One study found no significant association between funding mechanism, investigator rank or sex, and publication.

**Authors' conclusions:** Trials with positive findings are published more often, and more quickly, than trials with negative findings.

#### Reference:

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: MR000006. DOI: 10.1002/14651858.MR000006.pub3.



## INFORMATION FROM THE METHODS GROUPS

### News from the Steering Group

There are 13 registered Methods Groups. Reports from these Groups are given below.

#### Registered groups

- Adverse Effects
- Applicability and Recommendations
- Bias
- Economics
- Individual Patient Data Meta-analysis
- Information Retrieval
- Non-Randomised Studies
- Patient Reported Outcomes
- Prognosis
- Prospective Meta-analysis
- Qualitative Research
- Screening and Diagnostic Tests
- Statistical Methods

## REGISTERED GROUPS

### Cochrane Adverse Effects Methods Group

Yoon Loke, Andrew Herxheimer and Su Golder

This has been a busy year for the Adverse Effects Methods Group. We had workshops in Milan, Freiburg, Amsterdam (thanks to Rob Scholten), and Edinburgh. These were excellent opportunities to help review authors in tackling adverse effects. Further workshops will be held in May 2009 at the Danube University in Krems (Austria) and in October at the Cochrane Colloquium in Singapore.

Andrew Herxheimer spoke on Adverse Effects at the US Cochrane Center conference on Prioritising Systematic Reviews. A podcast is available from: <http://apps1.jhsph.edu/cochrane/NSvideopodcastol.htm> Su Golder (MRC Fellow in Health Services Research) has also spearheaded important methodological work in the adverse effects arena. One overview looked for evidence of biased reporting of adverse effects data in pharmaceutical industry-funded studies.<sup>1</sup> Su and Yoon concluded that the raw data were adequate, but had serious concerns about the subjective interpretation of the safety data, which could potentially be biased to favour the sponsor's drug.

Identifying adverse effects data is a particular challenge, and Su and Yoon's recently published overview<sup>2</sup> in the *Journal of the Medical Library Association* describes the pros and cons of various strategies that can be used. Sad to say (and perhaps not unexpectedly), they conclude that no



single strategy covers all angles, and the time and resources available will determine the most appropriate choice.

We welcome questions from review authors or editors; please e-mail Yoon Loke ([Y.Loke@uea.ac.uk](mailto:Y.Loke@uea.ac.uk)) or Andrew Herxheimer ([a.herxheimer@ntlworld.com](mailto:a.herxheimer@ntlworld.com)). (Su is currently on maternity leave).

#### References:

1. Golder S, Loke YK. Is there evidence for biased reporting of published adverse effects data in pharmaceutical industry-funded studies. *British Journal of Clinical Pharmacology* 2008; 66:767-73.

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## Cochrane Applicability and Recommendations Methods Group

Holger Schünemann and Gordon Guyatt

Professional societies have recognized the need to use more rigorous processes to ensure that healthcare recommendations are informed by the best available research evidence. In 2007, members of more than 40 professional societies and other organizations, including The Cochrane Collaboration, participated in a workshop 'Integrating and co-ordinating efforts in guideline development: Chronic Obstructive Pulmonary Disease (COPD) as a case in point' organized by the American Thoracic Society (ATS) and the European Respiratory Society (ERS). COPD is the fourth leading cause of death worldwide with a prevalence that is projected to increase over the next 20 years. COPD served as an example for this workshop because there are multiple existing, overlapping and sometimes conflicting COPD guidelines. One of the products of this workshop, a vision statement published in *The Lancet*,<sup>1</sup> described the principles for designing a new model for COPD guidelines that can serve as a template to assist the efforts of guideline developers for other respiratory and non-respiratory conditions. One of the agreed principles is the use of systematic reviews and GRADE (Grades of Recommendation Assessment, Development and Evaluation) evidence profiles or Summary of findings tables to guide the development of guidelines. Thus, efforts such as this may lead to increased use and application of Cochrane reviews in the development of guidelines.

On 30 and 31 March 2009, leadership from selected organizations that participated in the workshop, including The Cochrane Collaboration, ATS, ERS, and the World Health Organization met in Geneva, Switzerland, to discuss the contributions that can be made by individual organizations to implement the vision statement. A decision was made to begin with a demonstration project that will include evaluating existing systematic reviews for their

usefulness in the process of practice guideline development. We will report on updates periodically.

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## Cochrane Bias Methods Group

Laura Weeks, David Moher, Jonathan Sterne and Doug Altman

The Bias Methods Group (BMG) continues to raise awareness of bias and to offer guidance on how to identify and deal with bias in individual studies and systematic reviews. In 2008, the BMG held training workshops, gave presentations, and conducted related methodology research, including methods reviews. The BMG currently has 88 members from over 15 countries who share an interest in the issue of bias in systematic reviews.

The focus of BMG training in 2008 was to help Cochrane review authors to implement the new Cochrane Risk of bias tool in their reviews. BMG convenors facilitated several workshops on this topic for review authors and also for future trainers, through two 'train-the-trainer' sessions in Ottawa, Canada and Cambridge, UK. The BMG also continues to offer both general and advanced workshops related to bias, for example 'Investigating and dealing with bias in systematic reviews' and 'Identifying and assessing the impact of outcome reporting bias in meta-analysis'.

Current Cochrane methodology reviews by BMG members (published or in progress) include:

- Checking reference lists to find additional studies for systematic reviews (Tanya Horsley).
- Publication bias in clinical trials due to statistical significance or direction of trial results (Sally Hopewell).
- When and how to update systematic reviews (David Moher).
- Comparison of protocols to published articles for randomized controlled trials (Rebecca Smyth).
- Blinded versus unblinded assessments of risk-of-bias in studies included in a systematic review (David Moher).
- Technical editing of research reports in biomedical journals (Elizabeth Wager).

Furthermore, BMG members are active in research related to bias in individual studies, for example 'Bias in Randomized AND Observational studies' (BRANDO) and 'Outcome Reporting Bias in Trials' (ORBIT).

The BMG is involved in several recent initiatives related to the reporting of health research. Without adequate reporting, it is impossible to identify and assess risk of bias in primary studies. Our convenors have offered numerous workshops



on this topic and are among the founders of the EQUATOR network (Enhancing the QUALity and Transparency Of health Research) that seeks to improve the quality of scientific publications by promoting transparent and accurate reporting of health research ([www.equator-network.org](http://www.equator-network.org)). Our members have also been integral to the development of updates and dissemination of the CONSORT (CONsolidated Standards Of Reporting Trials) and PRISMA Statements (Preferred Reporting Items for Systematic reviews and Meta-Analyses; previously QUOROM – Quality of Reporting of Meta-analyses).

The BMG will host a meeting at the Cochrane Colloquium in Singapore in October 2009 and invites all those interested to join us. We are thankful to our funders, the Canadian Institutes of Health Research and the Canadian Agency for Drugs and Technologies in Health, without whose support our continued progress would not be possible. For further information please visit [www.chalmersresearch.com/bmg](http://www.chalmersresearch.com/bmg).

### Campbell and Cochrane Economics Methods Group

Ian Shemilt and Miranda Mugford

Economics is the study of the optimal allocation of limited resources for the production of benefit to society. The Campbell and Cochrane Economics Methods Group (CCEMG) focuses on approaches to evidence synthesis that combine economics and systematic review methods - both the role of economics concepts and methods in the evidence review and synthesis process, and the role of evidence review and synthesis concepts and methods in economic evaluation.

For Cochrane and Campbell reviews, we advocate that authors should at least comment on economic aspects of interventions and if possible evaluate included evidence from an economic perspective. We also support systematic approaches to incorporating searches for, and critical summaries of, evidence on resource use, costs and cost-effectiveness into reviews, alongside evidence on beneficial and harmful effects. The primary objective here is not to synthesize estimates of costs or cost-effectiveness, but to explore potential economic trade-offs and present data to inform new economic analyses - in other words, to facilitate the use of evidence for economic decisions.

The CCEMG looks forward to several initiatives over the next year, including the publication of a new book in association with Wiley-Blackwell, to profile the latest methodological developments, proposals and controversies in our field (April 2010). We also aim to launch new tools for economics components of reviews, training workshops and web-based learning materials based on the *Cochrane Handbook for Systematic Reviews of Interventions* guidance on economics methods (Part 3, Chapter 15), and to promote expert economics input to Cochrane and Campbell reviews. We continue to seek funds to secure the future of the

CCEMG beyond September 2010 through grant applications to support our infrastructure and core work programme and the needed methodological research.

For further details of these and other activities and outputs, please contact our Research Co-ordinator Ian Shemilt ([i.shemilt@uea.ac.uk](mailto:i.shemilt@uea.ac.uk)) or visit [www.c-cemg.org](http://www.c-cemg.org).

### Cochrane Individual Patient Data Meta-analysis Methods Group

Larysa Rydzewska, Jayne Tierney, Lesley Stewart, Mike Clarke and Maroeska Rovers

We are pleased to welcome Maroeska Rovers as a new co-convenor for the Group. Maroeska has been an active member of the Group since 2005 and is an Associate Professor in Clinical Epidemiology at the Julius Center, University Medical Center, Utrecht in The Netherlands.

The Individual Patient Data (IPD) Meta-analysis Methods Group currently has 72 members (32 active) from 17 countries, with interests spanning a wide range of healthcare areas (e.g. cancer, stroke, perinatal care, and malaria). If you would like to join the Methods Group or are interested in finding out more, please contact Larysa Rydzewska ([lhr@ctu.mrc.ac.uk](mailto:lhr@ctu.mrc.ac.uk)) or visit [www.ctu.mrc.ac.uk/cochrane/ipdmg](http://www.ctu.mrc.ac.uk/cochrane/ipdmg). The website also contains searchable databases of both completed and ongoing IPD meta-analyses and methodology research projects, as well as general information about IPD meta-analyses, resource materials and a frequently asked questions section for anyone planning an IPD project or wanting to learn more about them. It provides an easy way for Cochrane Review Groups to contact the Methods Group for advice and allows people to check whether a topic being proposed for a Cochrane review has already been covered by an IPD review.

At the Colloquium in Freiburg in October 2008 and the UK and Ireland Contributors to The Cochrane Collaboration Meeting in March 2009, we ran training workshops, led by Richard Riley, on statistical methods for the analysis of IPD. We covered methods for modelling IPD, combining IPD and aggregate data, and estimating treatment-covariate interactions. We will also offer a training workshop on the use of IPD in systematic reviews at the Colloquium in Singapore in October 2009. This workshop should enable review authors to decide whether an IPD approach is appropriate to their own review question and circumstances, and provide practical guidance on all aspects of the IPD approach.

The Methods Group had a productive meeting at the Colloquium in Freiburg, attended by many of our new members. One of the main issues discussed was the difficulty in obtaining funding for IPD projects. We are now compiling a list of both frequent criticisms and positive feedback from funders, which might be helpful in future



funding applications. We are also looking to see whether applications which include methodological projects alongside the main IPD review have been more successful at securing funding. Although there are well-established advantages of collecting IPD for systematic reviews, this is not always apparent to funders. Also, for some newer types of systematic review, such as those of prognostic studies, the collection of IPD may be the only way to perform reliable meta-analyses. Therefore, we are also planning a 'position' paper for publication in a journal, which will give an up-to-date view on the value and importance of collecting IPD and could be cited in future funding applications.

## Cochrane Information Retrieval Methods Group

Carol Lefebvre, Jessie McGowan, Alison Weightman and Bernadette Cole

There are currently 170 members of the Information Retrieval Methods Group (IRMG), many of whom have been active in a number of the projects outlined below.

The co-convenors and members of the IRMG have continued to serve on various Cochrane Collaboration advisory groups relevant to information retrieval including the Handbook Advisory Group, the Publishing Policy Group, the Quality Advisory Group, the Trials Search Co-ordinators Working Group and the more recently-established Trials Search Co-ordinators Executive.

One of the co-convenors (CL) led the work on the new chapter on 'Searching for Studies' in the *Cochrane Handbook for Systematic Reviews of Interventions*, together with two other members of the IRMG and they continue to update this chapter, which was first published online in February 2008, then updated in September 2008.<sup>1</sup> It was also published in hard copy by Wiley-Blackwell in October 2008<sup>2</sup> and a revised edition is in preparation. All members of the IRMG were invited to contribute to the chapter and will be asked for further input at the next major updating stage, expected to be late 2009. The new chapter contains Collaboration policy on study identification for Cochrane reviews and information on search methods and sources to search, together with revised versions of the Cochrane Highly Sensitive Search Strategies for identifying reports of randomized trials in MEDLINE.

One of the co-convenors (CL) was invited to attend a three-day Cochrane Collaboration Steering Group funded meeting in Cambridge in July 2008, to explore approaches and identify solutions to meet the training and support requirements across the Collaboration. The meeting was attended by representatives from Centres, Review Groups, the Information Management System Group and Methods Groups. It is hoped that the IRMG, in light of its responsibility with respect to Collaboration policy in study identification issues and in particular the relevant section

(Chapter 6) of the *Cochrane Handbook for Systematic Reviews of Interventions*, will continue to be closely involved in the Training Working Group which arose from this meeting.

The PRESS project (Peer Review of Electronic Search Strategies), previously known as EHTAS (Evaluating HTA Searches), led by one of the co-convenors (JM) together with other IRMG members, to develop a checklist for search strategies for systematic reviews has been published as a report by the Canadian Agency for Drugs and Technologies in Health (CADTH).<sup>3</sup> A manuscript including an evidence-based practice guideline for peer-reviewing search strategies is available as an 'ahead of print' publication.<sup>4</sup> All members of the IRMG were invited to contribute to the survey that underpinned this project.

Two of the co-convenors (CL and JM) have recently submitted a funding application to undertake an audit of search strategies in new and / or updated Cochrane reviews, using the evidence-based practice guideline for peer-reviewing search strategies discussed above, with a view to improving the quality of search strategies in Cochrane Reviews.

Filters for importing records from *The Cochrane Library* into ProCite, Reference Manager and EndNote continue to be updated on our website ([www.irmg.cochrane.org/en/newPage1.html](http://www.irmg.cochrane.org/en/newPage1.html)). Development of this website is on hold pending plans by the Trials Search Co-ordinators to develop a website for filters for a range of databases / service providers (including *The Cochrane Library*), which will be accessible to others in the Collaboration.

Work on expanding and updating the web resource of search filters compiled by the InterTASC Information Specialists' Sub-Group (ISSG) continues ([www.york.ac.uk/inst/crd/intertasc/](http://www.york.ac.uk/inst/crd/intertasc/)). It currently records known search filters, filter design projects in progress, and research on the development and use of search filters. There are also critical appraisals for some of the filters, which have been carried out using an appraisal checklist developed by the ISSG<sup>5</sup>. The final stage of the project, which will involve IRMG members, will be to test the filters in practice where possible and record the results on the website.

Several members of the IRMG are involved in a project to build up the Specialized Register for the recently registered Cochrane Public Health Review Group (PHRG). In line with the underlying principles of public health, PHRG reviews will have a significant focus on equity and the specialized register will be developed so that equity-related studies can easily be identified. A particular effort will be made to identify studies for reviews that reflect the needs of low- and middle-income countries. The work is supported by the Welsh Assembly Government, Cardiff University, the EPPI (Evidence for Policy and Practice Information and Co-ordinating) Centre and the Review Group's editorial



base at the University of Melbourne and is led by one of the IRMG co-convenors (AW).

Other areas in which members of the IRMG have been active in developments within The Cochrane Collaboration include adverse events, diagnostic test accuracy and economic evaluations. Members of the Campbell IRMG continue to be members of the Cochrane IRMG, including Karianne Thune Hammerstrøm, the recently appointed Campbell IRMG Convenor, Hannah Rothstein and Anne Wade. Members attend each other's Colloquia and advise in areas of mutual interest or expertise. For example the 'Searching for Studies' chapter of the Cochrane Handbook is being used as the basis for the revised version of the Campbell Information Retrieval Policy Brief.

The IRMG discussion list is used to notify members of activities such as the annual IRMG meeting at Cochrane Colloquia and to circulate the minutes. It has been used to find possible collaborators in projects associated with information retrieval, including those listed above. To join the list, please contact Bernadette Coles ([colesbm@cardiff.ac.uk](mailto:colesbm@cardiff.ac.uk)).

Co-convenors and members of the IRMG conducted a number of workshops at the Cochrane Colloquium in Freiburg in 2008 and further workshops are planned for the Colloquium in Singapore in 2009, including an IRMG workshop on study identification. An open meeting of the IRMG was held during the Colloquium in Freiburg in 2008 and a further meeting is planned for the Singapore Colloquium in October 2009. Infrastructure support for the time of the co-convenors is provided by Cardiff University, the UK Cochrane Centre and the University of Ottawa. Support for the time of the Co-ordinator and administrative assistance is provided by Cardiff University.

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## Cochrane Non-Randomised Studies Methods Group

Barney Reeves

The debate about whether to include non-randomized studies (NRS) in reviews addressing questions about the benefits of healthcare interventions is one of the underlying tensions in the Collaboration. In several Cochrane Review Groups, there is a strong desire to use NRS when randomized trials are not available. It will be evident from Chapter 13 in the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>1</sup> that the Non-Randomised Studies Methods Group (NRSMG) is concerned about the validity of such studies and the risk that they may mislead more than they inform.

When thinking about the validity of NRS, attention is inevitably focused on confounding. However, in our experience, users of evidence (and authors of reviews) 'lower the bar' when appraising NRS - a tendency that, it is hoped, can be corrected by applying the risk of bias tool, at least to prospective NRS. The NRSMG is also keen that review authors consider reporting biases carefully. For example, given the complexity of the choices that can or need to be made when fitting models to 'adjust' for confounding, is there more opportunity than in randomized trials for researchers to report selectively those analyses that give the desired answer? Selective reporting of outcomes is becoming an important issue in trials;<sup>2</sup> how much worse may this risk be for NRS? I am reminded of the conclusions of a workshop on this topic - a review author really "can't tell" what the risk is without the study protocol or explicit statement in the paper, and it is very important to acknowledge this uncertainty.

The NRSMG has another important message about study design labels. Controlled before and after studies (CBA, "controlled cohort before and after studies"<sup>3</sup>) are 'cluster' studies, with study participants nested in some higher level unit such as a geographical area (town, administrative area) or organization (general practice, school). Just as for cluster-randomized trials, the potential strength of this design lies in the number of clusters studied. With only two clusters, one receiving a control intervention and the other an experimental intervention, the control and experimental



interventions are completely confounded with clusters. Moreover, the risk of a co-intervention affecting one or other cluster, coincident with the switch from the before to after phases of the study, is much higher. This analysis leads to a hypothesis that effect sizes in CBA studies with only two clusters will be more extreme (because of confounding, co-interventions and reporting biases) than CBA studies with more clusters. I wonder how cluster number is distributed across CBA studies included in Cochrane reviews?

The NRSMG is currently working on designing new workshops to explore some of these issues.

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## Cochrane Patient Reported Outcomes Methods Group

Gordon Guyatt and Donald Patrick

The Cochrane Patient Reported Outcomes (PRO) Methods Group met at the Cochrane Colloquium in Freiburg in 2008, and adopted a schedule of activities for 2009 to 2010. Based on the Chapter prepared by the co-convenors for the *Cochrane Handbook for Systematic Reviews of Interventions* and work by member Caroline Terwee, we are preparing systematic reviews of PROs that are available to each relevant Cochrane Review Group. These systematic reviews of PROs will also be available on the Cochrane PRO website: [www.cochrane-hrqol-mg.org](http://www.cochrane-hrqol-mg.org). Members of the PRO Methods Group will assist in providing consultation to Cochrane Review Groups on PROs in their ongoing and planned reviews. This includes how to search and evaluate PROs in particular areas of interest. Workshops are being planned for the Cochrane Colloquium in Singapore later this year, with emphasis on how to incorporate PROs into Cochrane reviews.

In collaboration with the Cochrane Applicability and Recommendations Methods Group, we are exploring

alternative methods for making the results of analysis of PROs more easily interpretable for consumers of Cochrane reviews. Interpretability represents a particular problem when patient level data from individual studies is unavailable to review authors (almost always the case) and when investigators have used different instruments to measure the same construct (often the case) and thus studies report results in different units.

Investigators can report results in standard deviation units using guidelines for small, medium and large effects. Limitations include possible differences in heterogeneity of populations in individual studies, and clinicians' unfamiliarity with standard deviation units. A second approach is to back translate these effect sizes into the natural units of the most popular of the measures used in the individual studies. A third approach translates results into the relative means of treatment and control. A fourth approach assumes a dichotomy (for instance, crossing a threshold of improvement) and reports the difference in proportions between groups and associated numbers needed to treat.

## Cochrane Prognosis Methods Group

Greta Ridley, Doug Altman, Riekie de Vet, Jill Hayden, Richard Riley, Katrina Williams and Susan Woolfenden

The Cochrane Prognosis Methods Group was registered in 2007. At this stage, prognosis systematic reviews cannot be undertaken within The Cochrane Collaboration, however, the Methods Group aims to establish appropriate and high quality methods for undertaking systematic reviews and meta-analyses of prognosis studies and to provide advice to review authors wishing to write prognosis systematic reviews or incorporate prognosis information into their intervention or diagnostic reviews. This information will be provided through Cochrane Newsletters, our website ([www.prognosismethods.cochrane.org/en/index.html](http://www.prognosismethods.cochrane.org/en/index.html)) and via e-mails to the Prognosis Review Network. If you are interested in joining this network or the Cochrane Prognosis Methods Group, or both, please contact Katy Sterling-Levis ([katy.sterling-levis@sesiahs.health.nsw.gov.au](mailto:katy.sterling-levis@sesiahs.health.nsw.gov.au)).

The Prognosis Methods Group met at the Cochrane Colloquium in Freiburg in October 2008. Key outcomes that were identified from these meetings are being used to:

1. Develop a research framework for the Prognosis Methods Group. This framework is currently being developed and will be available for viewing on the Prognosis website. The aim of the research framework is to identify research priorities for the Group and we encourage members of the Group to provide feedback on the framework.
2. Develop processes to inventory the needs of Cochrane Review Groups in relation to using prognosis information in diagnostic and intervention reviews. These processes will involve setting up lines of communication with Cochrane



Review Groups in the first instance. A similar approach will also be required in relation to establishing collaborations with other Methods Groups. Members of the Group are already involved with some Review Groups and establishing links between the Groups.

3. Establish a database of prognosis systematic reviews and a methodological resource for the Prognosis Methods Group, and consider the development of a database of prognosis studies. As part of this initiative, Jill Hayden, a Convenor of the Prognosis Methods Group, was successful in receiving funding from the Nova Scotia Health Research Foundation in Canada ([www.nshrf.ca](http://www.nshrf.ca)) to form The Methodology Resource Group, a subgroup of the Prognosis Methods Group. This subgroup will help to co-ordinate and facilitate methodological research relevant to prognosis reviews. The subgroup aims to develop and maintain relevant databases and they will also support relevant training initiatives. Stay tuned for updates of projects and activities.

Following the Cochrane Colloquium, a satellite workshop was held on “Challenges in design, analysis and reporting of prognostic information and predictive marker research - from single studies to an EBM-based assessment”. This symposium was organized by Willi Sauerbrei and Doug Altman and presentations in relation to this symposium can be viewed on our website.

### **Cochrane Prospective Meta-analysis Methods Group**

Davina Gherzi, Jesse Berlin and Lisa Askie

With the help of resources provided to all Methods Groups by The Cochrane Collaboration, and matching funds provided by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre in Sydney, Australia, the Prospective Meta-analysis (PMA) Methods Group was able to employ a part-time research assistant (Henry Ko) to work with the convenors to develop a checklist of essential and desirable features of a prospective meta-analysis, and to apply this checklist to potential prospective meta-analyses identified through a systematic search. This work will result in a published tool that can be used to assist those wishing to critically appraise journal articles claiming to report results of prospective meta-analyses and will help establish a common definition of PMA. This project is still in progress.

The PMA Methods Group convenors meet bimonthly by teleconference. The convenors provide advice on request to those wanting to prepare a PMA protocol, including the editors of Cochrane Review Groups and the authors of these reviews. Advice is given by e-mail or telephone, or through participation in the advisory committees of several prospective meta-analyses (for example an ongoing PMA of neonatal oxygen levels). Other plans for the coming year

include establishing a PMA e-mail discussion forum and continuing to update the Group’s website.

For more information about the PMA Methods Group please visit [www.cochrane.org/docs/pma.htm](http://www.cochrane.org/docs/pma.htm).

### **Cochrane Qualitative Research Methods Group**

Angela Harden, Jane Noyes, Janet Harris, Karin Hannes, Andrew Booth, Craig Lockwood and Simon Lewin

Qualitative research can address many different questions including those around the appropriateness and implementation of interventions and patient and public perspectives. The integration of qualitative research within Cochrane reviews of the effects of interventions presents new challenges and opportunities for the Collaboration and the Cochrane Qualitative Research Methods Group (CQRMG) provides a network to advise on, debate and research solutions to these challenges.

A major activity of the group in the past year has been consolidation and expansion of our guidance on including qualitative research in systematic reviews. Following the publication of Chapter 20: ‘Qualitative research and Cochrane reviews’ in the new *Cochrane Handbook for Systematic Reviews of Interventions*, we convened a small working group to expand the chapter into a detailed resource with worked examples. This draft will form supplementary web-based guidance to complement the Handbook chapter. Members of the Group are also involved in developing books and journal articles that contribute to the wider literature on the synthesis of qualitative research.

The CQRMG has been running training events around the world to provide practical guidance on defining appropriate questions, devising search strategies, and extracting, appraising and synthesizing qualitative data. We ran fully booked workshops at the Cochrane Colloquium in Freiburg in 2008 and a well attended workshop at the UK and Ireland Contributors to The Cochrane Collaboration Meeting in Edinburgh in March 2009. Further afield we contributed sessions to the Oceania Regional Qualitative Synthesis Symposium in Adelaide in August 2008. Our next training events will be in Belgium, including one at the Continental European Cochrane Entities Meeting in June 2009, and Oslo at the Campbell Collaboration Colloquium in May 2009.

Our website at [www.joannabriggs.edu.au/cqrmg](http://www.joannabriggs.edu.au/cqrmg) is the main way for new and old members to keep up to date with activities and events and to contribute to the work of the Group. The systematic review and synthesis of qualitative work is a rapidly evolving and exciting field and there are plenty of opportunities to contribute. As well as information, the website houses a searchable register of methodological work and systematic reviews and a ‘toolkit’ made up of several presentations that can be used by



colleagues who are teaching in the area of qualitative evidence synthesis.

This past year has seen some change in membership and co-convenors. Firstly, we should like to offer sincere thanks to Professor Alan Pearson who has recently stepped down as co-convenor. Alan has made a huge contribution to the Group and we will miss his valuable insights. Finally, we would like to warmly welcome Angela Harden as a co-convenor and Simon Lewin as a key member of our methodological guidance group.

### **Cochrane Screening and Diagnostic Tests Methods Group**

Petra Macaskill, Constantine Gatsonis, Roger Harbord and Mariska Leeftang

The past year has again been busy and productive. In 2008 the number of co-convenors for our Group was expanded to four with the addition of Mariska Leeftang who is based in Amsterdam. Mariska also has the distinction of being the lead author on the first published Cochrane systematic review of diagnostic test accuracy. The publication of this review is a major milestone given the contributions over the years by many people in terms of methodology, software development and organization. More reviews are underway, and new titles are being registered.

Five workshops covering major aspects of a diagnostic test accuracy review were again offered at the Cochrane Colloquium in Freiburg under the umbrella of our Methods Group. These sessions were well attended and well received. Freiburg was also notable for the number of methodologists who attended the Colloquium. This led to many useful exchanges of ideas, and a large attendance at our business meeting.

The two existing support units (UK Support Unit (UKSU) based in Birmingham, and Continental Europe Support Unit (CESU) based in Amsterdam) have continued their training programmes for Cochrane Review Group editorial bases in the UK and Continental Europe. They have also had involvement in training in Australasia in conjunction with local methodologists and have undertaken a small amount of activity in the Americas. To date, 20 Cochrane Review Groups have been trained, with training scheduled for a further four before mid-2009, with 10 more Groups awaiting training dates. Seven Groups have no wish to be trained (often because they do not see questions of diagnosis as being relevant to their Group), and five have not clearly indicated their requirements.

Although the priority has been to provide training for Cochrane Review Group editorial teams, two-day training courses for review authors were run in Amsterdam in July 2007, June 2008 and June 2009. A training event for methodologists is scheduled in Birmingham for 6 – 8 July 2009, and each Cochrane Review Group and Centre has

been offered one free place. This special training event utilises the strong links between the support units and our Methods Group.

We would like to thank everyone who has contributed to the activities of our Methods Group over the past year, and we look forward to seeing many of you in Singapore.

### **Cochrane Statistical Methods Group**

Joanne McKenzie, Doug Altman, Joseph Beyene, Steff Lewis and Georgia Salanti

A joint meeting of the Statistical Methods Group (SMG) and the UK Meta-analysis in Medicine Group was held as a satellite event to the Colloquium in Freiburg on 3 October 2008. This included the four sessions: meta-analysis of continuous data; various topics; addressing risk of bias; when should meta-analyses be performed in Cochrane reviews? The meeting was well attended with over 50 registered participants. Details of titles of the presentations are available from the SMG website ([www.cochrane-smg.org](http://www.cochrane-smg.org)).

Many members of the SMG facilitated workshops at the Colloquium in Freiburg and at regional Contributors' meetings in 2008 and 2009.

The SMG will soon be undertaking a survey of statistical editors of Cochrane Review Groups to assess the statistical issues they commonly encounter and identify areas where they would value more discussion, training, and research. Information from this survey will be used to help the SMG to prioritise future research and target training.

A website for the SMG is available at [www.cochrane-smg.org](http://www.cochrane-smg.org). This website will be further developed to meet the needs of the SMG. Comments on how it can be improved or suggestions for additional content will be warmly received ([joanne.mckenzie@med.monash.edu.au](mailto:joanne.mckenzie@med.monash.edu.au)).

The SMG said farewell to Jon Deeks and Julian Higgins from their co-convenor roles in August 2008. Their long-standing contribution to the Group has been invaluable and we sincerely thank them for this. In particular, we thank them for all their hard work in co-ordinating the writing (and doing a lot of the writing themselves) of statistical sections of the *Cochrane Handbook for Systematic Reviews of Interventions*. The SMG welcomes Georgia Salanti (Ioannina, Greece) and Jo McKenzie (Melbourne, Australia) as new co-convenors.

We thank all those who have contributed to the SMG activities over the previous year and look forward to seeing many of you at the Colloquium in Singapore.





## CAMPBELL COLLABORATION METHODS CO-ORDINATING GROUP

The Campbell Methods Team

The Campbell Collaboration Methods Co-ordinating Group supports the production of Campbell Collaboration reviews by improving the methodology of research synthesis, and disseminating guidelines for state-of-the-art review methods.

The Methods Group has subgroups that play a key role in helping the editors to ensure the quality of Campbell's systematic reviews. The subgroups serve as forums for discussion on research models, and provide advice on specific topics of methodology and methods policy. They also provide training and support to review authors, editors, and those who wish to undertake a systematic review. Their topics are: economics, equity, information retrieval, process and implementation, statistics methods, and training.

This year's Campbell Collaboration Colloquium is scheduled from 18 - 20 May 2009. Policy makers, researchers, and practitioners will gather in Oslo, Norway to discuss legal, social welfare, and justice interventions. The draft agenda is as follows:

- Update on the proposal to adopt the *Cochrane Handbook for Systematic Reviews of Interventions* as the principal source of methods guidance for use in the preparation and maintenance of Campbell reviews.
- Discussion of the draft 'Guiding principles and policies for methods subgroups of The Campbell Collaboration' document prepared by the *ad hoc* working group convened by Ian Shemilt in July - August 2008.
- Clarification of the process by which the editor of the Campbell Methods Co-ordinating Group seeks specialist input to the peer review process from subgroups, for example when a new protocol or review includes an economics or equity component.

For more information about the Campbell Collaboration Methods Co-ordinating Group, please feel free to contact Erin Ueffing ([erin.ueffing@uottawa.ca](mailto:erin.ueffing@uottawa.ca)) or visit [www.campbellcollaboration.org](http://www.campbellcollaboration.org).



## FUTURE MEETINGS

## Seventeenth Cochrane Colloquium

Singapore  
11 to 14 October 2009

The first Cochrane Colloquium in Asia comes at a time of rapid growth in Cochrane activity and widespread interest among the region's policy makers in truly integrating evidence into healthcare decision-making.

This year's Colloquium will focus on the key challenges and opportunities both for the region and for The Cochrane Collaboration. In a city renowned for its cultural fusion, we will hear a range of perspectives and experiences to inform and enlighten our discussions. The scientific programme, like Singapore itself, will embrace the future while maintaining a healthy respect for the traditions of the past.

More information is available at [www.colloquium.info](http://www.colloquium.info).

## Sixth International Congress on Peer Review and Biomedical Publication

Vancouver, Canada  
10 to 12 September 2009

The Sixth International Congress on Peer Review and Biomedical Publication will be held from 10 to 12 September 2009 in Vancouver. As with the previous Congresses, the aim will be to improve the quality and credibility of biomedical peer review and publication and to help advance the efficiency, effectiveness, and equitability of the dissemination of biomedical information throughout the world.

More information is available at [www.jama-peer.org](http://www.jama-peer.org).



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## AVAILABILITY OF THE NEWSLETTER

Additional copies of the Methods Groups Newsletter may be obtained free of charge from the UK Cochrane Centre, which is based at:

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The Newsletter is also available from The Cochrane Collaboration website at [www.cochrane.org/newslett/index.htm](http://www.cochrane.org/newslett/index.htm)



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**APPENDIX****Previous structured abstracts and commentaries****Methods Groups Newsletter Volume 11, June 2008**

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## CURRENT STATUS OF COCHRANE METHODOLOGY REVIEWS

<b>Published reviews currently being updated</b>	
Edwards P, et al.	Methods to increase response rates to postal questionnaires
Kunz R, et al.	Randomisation to protect against selection bias in healthcare trials
<b>Published reviews updated 2008</b>	
Wager E, et al.	Technical editing of research reports in biomedical journals
Vist G, et al.	Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate
<b>All published reviews</b>	
Hopewell S, et al.	Publication bias in clinical trials due to statistical significance or direction of trial results (see page 22)
Rendell J, et al.	Incentives and disincentives to participation by clinicians in randomised controlled trials
Jefferson T, et al.	Editorial peer review for improving the quality of reports of biomedical studies
Hopewell S, et al.	Grey literature in meta-analyses of randomized trials of health care interventions
Hopewell S, et al.	Time to publication for results of clinical trials
Scherer R, et al.	Full publication of results initially presented in abstracts
Hopewell S, et al.	Handsearching versus electronic searching to identify reports of randomized trials
Mapstone J, et al.	Strategies to improve recruitment to research studies
Demicheli V, et al.	Peer review for improving the quality of grant applications
<b>Published reviews 2008</b>	
Moher D, et al.	When and how to update systematic reviews
<b>All published protocols</b>	
Hoile E, et al.	Methods to increase response rates for data collected by telephone (new in Issue 3, 2009)
Welch V, et al.	Equity assessment in systematic reviews (new in Issue 3, 2009)
Young T, et al.	Methods for obtaining unpublished data (new in Issue 2, 2009)
Horsley T, et al.	Checking reference lists to find additional studies for systematic reviews (new in Issue 1, 2009)
Moher D, et al.	Blinded versus unblinded assessments of risk-of-bias in studies included in a systematic review
Leeftang M, et al.	Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE
Soares H, et al.	New treatments compared to established treatments in randomized trials
Song F, et al.	Adjusted indirect comparison for estimating relative effects of competing healthcare interventions
McDonald S, et al.	Search strategies to identify reports of randomized trials in MEDLINE
Westby M, et al.	Masking reviewers at the study inclusion stage in a systematic review of health care interventions
Ghersi D, et al.	Impact of shared scientific or ethical review of multicentre clinical research on the quality of clinical research and the clinical research process
Edwards P, et al.	Methods to influence the completeness of response to self-administered questionnaires
Clarke M, et al.	Individual patient data meta-analyses compared with meta-analyses based on aggregate data
<b>Registered titles</b>	
Bero L, et al.	Pharmaceutical industry sponsorship and research outcome (new in 2008)
Hoile E, et al.	Strategies to increase the validity of self-reported behaviour (new in 2008)
Smyth R, et al.	Comparison of protocols to published articles for randomised controlled trials (new in 2008)
Sterne J, et al.	Tests for funnel plot asymmetry
Gesser K, et al.	Assessing the potential clinical significance of medication errors
Verbeek J, et al.	Reliability of sick leave as an outcome in intervention trials
Gates S, et al.	Methods for reducing data transcription errors
Olsen O, et al.	Response to mailed questionnaires versus telephone interviews (new in 2008)
Brueton V, et al.	Strategies to reduce attrition in randomized trials (new in 2009)
Moher D, et al.	Is using the consolidated standards of reporting trials (CONSORT) statement associated with improved quality of reporting of randomized controlled trials? (new in 2009)
Nasser M, et al.	Priority setting for comparative effectiveness research (new in 2009)



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