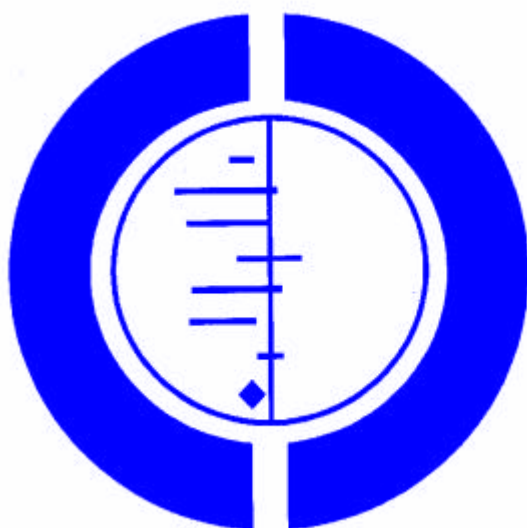


# The Cochrane Collaboration Methods Groups Newsletter

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## PURPOSE OF THE NEWSLETTER

One of the primary roles of 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 tenth 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 Health Service Research and Development Programme 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's Newsletter focuses on some of the challenging issues facing the methodology of Cochrane and other types of systematic reviews. This includes articles updating readers on the World Health Organization (WHO) International Clinical Trials Registry Platform, The Cochrane Collaboration's Working Group on updating Cochrane reviews and the Summary of Findings tables in Cochrane reviews project. It also describes a number of empirical research studies being conducted within The Cochrane Collaboration. For example, a report on a study investigating how the conclusions change when Cochrane reviews are updated and an examination of the Implications for Research section of Cochrane reviews.

As with previous years, this issue includes structured abstracts and commentaries on topical methodological issues. These include a study assessing how heterogeneity has been examined in systematic reviews of diagnostic test accuracy, and a study examining the problems of identifying research for systematic reviews of diagnostic test accuracy due to poor sensitivity and precision of the methodological filter and a lack of information available in the original abstracts. A further study reviews some of the methodological challenges for conducting systematic reviews that assess the harms of treatment interventions.

As ever, 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.

This is the tenth edition of the Cochrane Methods Groups Newsletter and to mark the occasion this year's Newsletter also includes a special supplementary issue containing an overview of systematic reviews of the design and conduct of randomized trials and systematic reviews of healthcare interventions. We hope that you will enjoy reading these!



## ARTICLES

### Update from the WHO International Clinical Trials Registry Platform

An-Wen Chan, Ida Sim, A. Metin Gülmezoglu, Patrick Unterlerchner, Ghassan Karam, and Tikki Pang

Selective reporting of clinical trial results is known to be widespread, and recent high-profile cases have demonstrated the potential impact of suppressing negative findings in healthcare. In order to restore public trust in clinical research, it is clear that transparency and accountability must be strengthened through trial registration and the reporting of results on public electronic databases.

The World Health Organization (WHO) established the International Clinical Trials Registry Platform in August 2005 with the primary objective of ensuring that all clinical trials worldwide are uniquely identifiable through a system of public registers, and that a minimum set of results is made publicly available. Current WHO Registry Platform policies are detailed at [www.who.int/ictip](http://www.who.int/ictip) and will be highlighted in this article.



Registry Platform policies apply to all research trials that prospectively assign humans to one or more interventions to examine their effects on health outcomes, regardless of specific trial design or intervention type. For a trial to be considered fully registered, all 20 items in the WHO Trial Registration Data Set (Version 1.0, see below) must be recorded prior to participant enrolment in a national, regional, or international Primary Register that meets acceptable standards for content, technical capabilities, quality assurance, and administration. A WHO Search Portal to identify trials across Primary Registers will be developed to meet the needs of patients, scientists, and other healthcare workers. WHO has no plans to administer its own trial register.

A larger number of Associate Registers, which automatically send their registration data to a designated Primary Register, will also be part of the WHO Registers Network. They can be either broadly-based or restricted to a specific disease, company, or institution. A trialist or sponsor need only register the trial once with either a Primary or Associate Register.

As a single trial might be registered more than once on the same or different registers, a reliable mechanism must be established to detect and 'de-duplicate' such entries. Use of a single data interchange standard would simplify the identification of duplicate entries across registers. A Universal Trial Reference Number will then be assigned to each globally unique trial.

Some stakeholders have argued against immediate disclosure of registered trial data to protect competitively sensitive information. A policy on the timing of public disclosure will be finalized in this year.

Finally, global compliance, oversight, and capacity building must be considered in WHO Registry Platform policies, which will be re-evaluated and refined periodically as the complex field of trial registration continues to evolve.

#### *WHO Trial Registration Data Set (Version 1.0)*

1. Primary Register and Trial ID number
2. Date of Registration in Primary Register
3. Secondary ID number(s)
4. Source(s) of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor(s)
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title
11. Countries of Recruitment
12. Health Condition(s) or Problem(s) Studied
13. Intervention(s)
14. Key Inclusion and Exclusion Criteria
15. Study Type
16. Date of First Enrolment
17. Target Sample Size

18. Recruitment Status
19. Primary Outcome(s)
20. Key Secondary Outcomes

### **Working group to look at updating reviews**

Rob Scholten

The current policy of The Cochrane Collaboration is that all Cochrane reviews should be updated at least every two years (or should have a note added to indicate why this has not been done). However, it appears that many Cochrane reviews have not been updated in the past two years. In October 2004, a working group was formed to look at methods to improve this situation. The Group began by exploring possible causes for the failure to update reviews, in order to try to identify possible solutions. We would like to highlight the following issues.

Review authors may be unable to update their review or not interested any more due to changes in their personal circumstances. Not much can be done about the latter, but encouragement to review authors to update might include incentives, such as improved academic recognition for updates (of any kind). We will work with our publisher Wiley to accomplish this. Another incentive might be to increase review authors' exposure through derivative publications, such as "Evidence-Based Child Health: a Cochrane review Journal". This is a new journal for publishing versions of Cochrane reviews relating to the health of children.

Cochrane Review Groups (CRGs) may not be able to deal adequately with updates due to the ever increasing workload they are facing. Many CRGs have developed their own methods to assist the updating process and we are in the process of collating and summarising these strategies. Our findings will be made available on the CRG resources page on [www.cochrane.org](http://www.cochrane.org).

Another way of dealing with the increasing updating workload is to prioritise reviews due to be updated. One of the CRGs that has developed this type of strategy is the Cochrane Infectious Diseases Group (CIDG). During this process they realised that some reviews no longer required a full update, perhaps because the intervention is no longer used or the evidence already in the review was so definite that the conclusions were stable. These reviews were labelled as "closed", which saved the CIDG editorial base and authors much unnecessary work. Several other CRGs are likely to adopt a strategy similar to that established by the CIDG.

We also considered centralising updating to reduce the workload of both CRGs and review authors. During their meeting in Khon Kaen in April 2006, the Cochrane Collaboration Steering Group awarded a grant for a pilot project to explore this course of action. The general idea is that a research fellow will be appointed centrally to work at



a Cochrane Entity (Centre, Field or CRG) for one year. This updating officer will assist with as many phases of the review as possible and feasible. We expect to start this pilot project in September 2006 and we will contact all CRGs to identify a few who would be willing to participate in this pilot phase.

We noted that the dates currently published in the citation of a Cochrane review, may lead to a situation where a review appears to be out of date, but may not be. A new date field "Date that review was last assessed as up to date" will be added to future citations in order to reflect more accurately the topicality of the review. Guidance on the use of this date will be added to the Cochrane Handbook for Systematic Reviews of Interventions.

We hope that our work will lead to a reduction in the number of Cochrane reviews that are, or appear to be, out of date and assist CRGs in their workload. We would welcome further suggestions on how to tackle this issue.

Members of the CCSG Working Group to look at updating reviews: Mike Clarke, Mark Davies, Davina Gherzi, Sally Green, Sonja Henderson, Sarah Hetrick, Harriet MacLehose, Jessie McGowan, David Moher, Phil Wiffen and Rob Scholten (Convenor).

## Database of Uncertainties about the Effects of Treatments – an update

Mark Fenton and Iain Chalmers

The *Database of Uncertainties about the Effects of Treatments* (DUETs) was established in early 2005, in conjunction with the James Lind Alliance. Information in DUETs aims to help those responsible for promoting and supporting research on the effects of treatments to base their priorities on the information needs of patients and clinicians. It identifies areas where up-to-date systematic reviews of existing evidence are not available and where research needs to generate additional evidence. Uncertainty is defined as questions about the effects of treatments which cannot currently be answered reliably by referring to up-to-date systematic reviews of existing research.

The development of DUETs has been guided by two working groups, the first of which looked at its development and structure as a database. The second focuses on reporting research recommendations generated from sources such as systematic reviews and clinical guidelines. This second group are currently drawing up recommendations to provide guiding principles to report continuing uncertainties about treatment and the effects of treatment following a systematic review. These uncertainties will be eligible for inclusion in DUETs.

An audit of UK based research funders involved in DUETs working group showed a variation in practice in the structure of records, with most using a Patient, Intervention,

Comparison and Outcome structure (PICO), and one using an Evidence, Patient, Intervention, Comparison, Outcome and Time (EPICOT) structure. Ongoing work has shown poor adherence to the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>1</sup> suggestions for writing research recommendations. However, the Cochrane Handbook gives no guidelines on how research recommendations should be structured.

Current sources of research recommendations, such as systematic reviews, clinical guidelines and BMJ Clinical Evidence are used by research commissioners to inform commissioning of future research. A recent snapshot of categorisations taken from Clinical Evidence (Issue 14, December 2005)<sup>2</sup> shows that almost one in two interventions are categorised as being of 'unknown effectiveness'. This means that, for these interventions no rigorous evidence of benefit, harm or likely ineffectiveness could be documented. As DUETs grows, more research recommendations will be entered, allowing patients and clinicians to identify their shared priorities in research, and research funders to commission research which has undergone a shared prioritisation.

### Reference

1. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. In: *The Cochrane Library*, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd.

2. How much do we know? [editorial] *Clinical Evidence* [online] London, UK: BMJ Publishing Group Ltd, Dec 2005. Available at:

[www.clinicalevidence.com/ceweb/about/knowledge.jsp](http://www.clinicalevidence.com/ceweb/about/knowledge.jsp) [Accessed 31 May 2006].

## Summary of findings tables in Cochrane reviews: a pilot study

Gunn Vist, Andy Oxman, Paul Glasziou, Julian Higgins and Holger Schünemann

To help readers of Cochrane reviews focus quickly on the essential results and navigate the review, Summary of Findings (SoF) tables have been suggested as a separate element of a Cochrane review to be located near the abstract. The SoF table includes information about each of the main outcomes for the main comparison in the review. The number of patients and trials, the control group risk, the effect size (relative and absolute), and the quality of the evidence are presented for each main outcome. Reviews with more than one main comparison require separate SoF tables for each comparison.

The aims of this pilot study were to inform decisions about the inclusion of SoF tables in Cochrane reviews, identify and address practical problems with reviewers preparing the



SoF tables and to assess and improve draft guidelines, software and specifications for preparing SoF tables.

We informed and invited all Cochrane Review Groups to participate in this project. The review authors who agreed to participate were provided with software (GRADEpro®) and instructions for preparing an SoF table. Additionally, each review author was allocated a contact person for support. These contact people had been involved with the GRADE Working Group for some time and were familiar with the methodology and software. The review authors themselves completed the SoF tables for their Cochrane reviews. Review authors were sent a brief questionnaire about their experiences and asked for suggestions for improvements of the SoF table and the software.

Summary of Findings tables based on 20 new or updated Cochrane reviews were completed and submitted to us during the period of the pilot study (June to September 2005). The included reviews were from 17 different Cochrane Review Groups. Thirteen review authors completed and returned the questionnaire to us. Two of the authors prepared SoF tables for more than one review.

How much time did it take? An additional four hours (range 2 to 40 hours) were required to complete the Summary of Findings table for each review. Most reviewers thought the SoF table was helpful in the preparation of their review and that it will be an aid to improve the accessibility of the results of the review. Most of the negative feedback was related to difficulties with using the software and instructions. The software, instructions and help files are currently being upgraded and improved with more definitions, explanations and examples.

We wish to thank all the review authors who prepared and helped to prepare SoF tables of their Cochrane reviews. We hope that all future reviews will be able to include a Summary of Findings table in the near future. If you are interested in more details please email Gunn at [gunn.vist@kunnskapssenteret.no](mailto:gunn.vist@kunnskapssenteret.no).



## PUBLISHED METHODOLOGICAL RESEARCH - structured abstracts and commentaries

### Meta-analysis of individual patient data from randomized trials: a review of methods used in practice

Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. *Clinical Trials* 2005; 2:209-217.

#### STRUCTURED ABSTRACT

*Prepared by the Cochrane Methodology Review Group*

**Background:** Meta-analyses based on individual patient data (IPD) are regarded as the gold standard for systematic reviews. However, the methods used for analysing and presenting results from IPD meta-analyses have received little discussion.

**Objective:** To review methods used for analysing and presenting results in IPD meta-analyses of randomized trials in health care.

**Design:** A cohort study.

**Data collection and analysis:** Forty-four IPD meta-analyses published during the years 1999-2001 were assessed. Data were extracted on whether meta-analysts obtained all the data they sought, what types of approaches were used in the analysis, including assumptions of common or random effects, and how they examined the effects of covariates.

**Main results:** Twenty-four out of 44 analyses focused on time-to-event outcomes, and most analyses (n=28) estimated treatment effects within each trial and then combined the results assuming a common treatment effect across trials. Three analyses failed to stratify by trial, analysing the data as if they came from a single mega-trial. Only nine analyses used random-effects methods. Covariate-treatment interactions were generally investigated by subgrouping patients. Seven of the meta-analyses included data from less than 80% of the randomized patients sought, but did not address the resulting potential biases.

**Conclusions:** Although IPD meta-analyses have many advantages in assessing the effects of health care, there are several aspects that could be further developed to make fuller use of the potential of these time-consuming projects. In particular, IPD could be used to investigate more fully the influence of covariates on heterogeneity of treatment effects, both within and between trials. The impact of heterogeneity, or use of random-effects, are seldom discussed. There is thus considerable scope for enhancing the methods of analysis and presentation of IPD meta-analysis.

#### COMMENTARY

*Prepared by Catrin Tudur Smith*

Simmonds et al present a review of methods used in practice for undertaking and reporting meta-analyses based on individual patient data (IPD). This is an important area to address as a number of alternative analysis options are available which have received much less attention in this setting despite an IPD approach being considered as the "gold standard". In fact, we have recently submitted a paper<sup>1</sup> that compares the stratified log-rank analysis, an inverse variance weighted average of Cox model estimates and the



stratified Cox regression model for IPD meta-analysis with time-to-event data. Our investigations suggest that the most common method for IPD meta-analysis of time-to-event outcomes, the stratified log-rank analysis, may not always be the most appropriate and alternative methods should be considered at the protocol development stage of the review.

Simmonds et al clearly describe some commonly used terminology behind different methods for analysis. In particular, the one-stage analysis that combines all IPD from all studies, either with or without appropriate recognition of study effects, is distinguished from the two-stage analysis which analyses each study independently and combines summary statistics using standard aggregate data meta-analysis methods.

Their search identified 98 IPD reviews published between 1990 to 2001 but a full investigation of methods was restricted to 44 reviews published during 1999 to 2001 and predominantly included the clinical areas of cancer, cardiovascular conditions and areas of mental health. Approximately 65% of meta-analyses included 10 trials or fewer and 44% included fewer than 2000 patients. Two thirds of the meta-analyses used some form of two-stage approach such as a stratified log-rank analysis whilst three meta-analyses inappropriately ignored randomization within trials and analysed the IPD as one large trial. A similar distribution of one- and two-stage approaches was seen for exploring covariate effects.

A large number of meta-analyses (15/44) failed to report the amount of IPD obtained from all eligible trials. This is an important quality aspect of an IPD review that could indicate the strength of possible bias introduced from meta-analysing a subset of the randomized evidence. A clear description and justification of statistical methods was noted to be rare. Although IPD give considerable scope to investigate whether patient and trial characteristics influence the overall treatment effect, Simmonds et al found such investigations to be limited. IPD reviewers should be encouraged to exploit the valuable resource that they have available.

The limitations of undertaking and reporting IPD meta-analyses highlighted by Simmonds et al should be addressed, particularly as their number is growing steadily. Developing an extension to the currently available QUORUM agreement<sup>2</sup> incorporating aspects specific to IPD meta-analysis would seem appropriate.

## References

1. Tudur Smith C, Williamson PR. Meta-analysis of individual patient data with time-to-event outcomes. (Forthcoming 2006).
2. 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 QUORUM statement. *Lancet* 1999; 354:1896-1900.

## Principles for international registration of protocol information from human trials of health related interventions

Krleza-Jeric K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C. *BMJ* 2005; 330:956-958.

### STRUCTURED ABSTRACT

*Prepared by the Cochrane Methodology Review Group*

**Background:** Registering of clinical trials is essential to make sure all results are publicly available and that ethical obligations to participants are met.

**Objective:** To develop consensus on the principles for international registration of protocol information and the results from human trials of health related interventions (the Ottawa statement).

**Design:** An open meeting was held in Ottawa, Canada, in October 2004 to foster international consensus on trial registration. The resulting Ottawa statement aims to establish internationally recognised principles for clinical trial registration.

**Main results:** The Ottawa statement defines that the mandatory registration of all clinical trials has three components: obtaining an internationally unique identification number (unique ID); registering the original protocol along with subsequent amendments; registering the trial results. Full details of the Ottawa statement are available at <http://ottawagroup.ohri.ca/>. This article focuses on three of the key principles in the statement which have been the subject of much debate.

Registering all types of trials: Protocol information and results from all trials related to health or health care, irrespective of topic, design, outcomes, or market status of interventions examined, should be registered and publicly available.

Timing of public release of protocol information: The public should have cost-free access to the Unique ID, minimum protocol items, and consent forms prior to participant enrolment. Registered amendments should be made publicly available as they occur.

Registering unpublished trials: At a minimum, results for outcomes and analyses specified in the protocol (as approved by the institutional review boards/independent ethics committees), as well as data on harms, should be registered irrespective of whether or not they are published.

**Conclusions:** The Ottawa Group (currently consisting of over 80 individuals and organizations from five continents) will continue to consult broadly about the most effective and practical ways to enact these principles in a co-ordinated fashion worldwide. Difficult decisions will have to be made



related to timely and feasible implementation of the principles.

## COMMENTARY

*Prepared by Gerd Antes*

The Ottawa statement on principles for the international registration of protocol information and results from human trials was initiated at a meeting in October 2004 in Ottawa. That meeting led into a subsequent, still ongoing discussion and development process. The version published in the *BMJ* (2005) presents the principles as they were developed to that point.

The principles are based on evidence from many international studies which show the serious deficiencies of the publication process and the biases and distortions resulting from them. Therefore, the path towards trial registration seems to be beyond doubt from an ethical and scientific point of view and has been receiving wide agreement and a lot of support from various stakeholders. Putting it into practice, however, also incurs considerable resistance from others. Enormous impact came from the decision of the International Committee of Medical Journal Editors (ICMJE; [www.icmje.org](http://www.icmje.org)) to publish only reports of those trials which have been registered with an approved register.

The US-based register ClinicalTrials.gov was opened to international trial registration to fulfil the ICMJE's request. Together with the international register Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com)) there are now two registers for global registration. These registers, however, do not fill a crucial gap by not informing the population in non-English language countries in their local language about ongoing trials. For that purpose these registers would have to provide information about local trials in the corresponding language. As this cannot be expected and because the registration process is considered a complex task which can only be met within national research systems, several countries have started their own registers or will start soon. This will lead to a patchwork of registers, with potentially large differences between them, duplicate registration and duplication of effort. To minimize these risks WHO has decided to offer a platform to harmonize and unify the international efforts and develop a single access point to existing registers, the International Controlled Trials Registry Platform (ICTRP; [www.who.org/ictcp](http://www.who.org/ictcp)).

The two disputed issues of the registration are whether early trials (called Phase I trials in drug development) should be registered and whether trial registration information should be fully disclosed at the time of registration. After a lengthy consultation process with advisory groups and a special hearing about late disclosure issues, ICTRP positioned itself in a statement that was presented and published in connection with the International Clinical Trials Day (May 19, 2006). The statement was built on transparency as the watchword, thus rejecting the request for exclusion of early

trials and for late disclosure of five of the 20 data fields of the minimal dataset which should be registered.<sup>1</sup>

The first part of the registration process requires the registration of 20 data fields with trial characteristics in a freely accessible register. That part seems to be settled in principle and is consistent with the Ottawa statement. However, a large number of practical problems (e.g. de-duplication of multiple records) has to be resolved to provide a single access point for an efficient global search.

The far bigger challenge is the registration of results. Again, from an ethical point of view it is clear that all results have to be published as soon as possible once a trial is finished. What this means in practice has hardly been discussed so far. In what form the results should be made accessible, how or whether peer review of reports could be achieved etc. are questions which will need far more time than the issue of registration at trial inception.

The Cochrane Collaboration is benefiting from this development by the improvement of the evidence that is needed for systematic reviews. It is also directly affected in its present activities to reorganize its literature-based trial register CENTRAL. Transferring it into a trial based register should be closely linked with the evolving global trial register and hopefully lead to a unique, transparent system of evidence from clinical trials which is of utmost relevance for Cochrane reviews.

## Reference

1. Sim I, Chan A-W, Gülmezoglu AM, Evans T, Pang T. Clinical trial registration: transparency is the watchword. *Lancet* 2006; 367:1631-1633.

## Challenges in systematic reviews that assess treatment harms

Chou R, Helfand M. *Annals of Internal Medicine* 2005; 142(12 Pt 2):1090-1099.

## STRUCTURED ABSTRACT

*Prepared by the Cochrane Methodology Review Group*

**Background:** An evidence-based synthesis of a healthcare intervention should assess the balance of benefits and harms. Investigators performing systematic reviews of harms face challenges in finding data, rating the quality of harms reporting, and synthesizing and displaying data from different sources.

**Objective:** To highlight examples of approaches to methodologic issues associated with performing systematic reviews of harms.

**Design:** Narrative review.



**Data collection and analysis:** Examples were taken from 96 Evidence-based Practice Center evidence reports.

**Results:** A number of challenges to performing systematic reviews of harms were identified:

Identifying and selecting information about harms: Most systematic reviews rely on searches of electronic databases of published trials and handsearches of relevant journals. Identifying important harms of treatment and quantifying the risk associated with them, however, often require a broader range of data sources.

Assessing the quality of harms reporting: Special considerations suggest the need for a distinct set of criteria for judging harms reporting. Widely used criteria for assessing the quality of observational studies and randomized trials are not designed specifically to assess the quality of assessments of harms.

Synthesizing and displaying data from different studies: Synthesizing harms data from different sources requires careful consideration of internal validity, applicability, and sources of heterogeneity.

**Conclusions:** Better data about harms are needed to conduct balanced systematic reviews. Systematic reviewers often focus on analysing data from published trials. Information from a broader range of sources may help fill in gaps or provide a more comprehensive assessment of harms.

#### COMMENTARY

*Prepared by Jeff Aronson*

The vertical structure of the evidence hierarchy gives a misleading view of the proper use of different types of evidence, emphasizing as it does the virtues of meta-analysis of randomized studies at the expense of observational studies and anecdotes. But different types of evidence have value in different circumstances. Chou and Helfand stress this in their review of the assessment of treatment harms. "All [types of studies]," they write, "have some potential for yielding useful information."

Assessing harms is much more difficult than assessing benefits. Benefits are usually single, harms multiple; benefits are usually identifiable in advance, harms generally not; eliciting harms needs much larger studies, and studies are often stopped when benefit becomes apparent. Systematic reviews of harms are uncommon, because harms are often not reported, inconsistently reported when they are, and hard to retrieve from published literature because of poor indexing. Only about 2% of the world literature on harms from medicines is in the form of systematic reviews. We need more.

Chou and Helfand provide a detailed narrative review of the different types of evidence that can be adduced about harms: randomized trials, observational studies, large

databases and practice-based networks, case reports, and pharmacokinetic and pharmacodynamic data.

Problems that arise from their survey include: how to improve and judge the quality of harms reporting; how to interpret the results when different types of studies produce different conclusions; how to incorporate anecdotal reports (which contribute about 30% of the world literature on harms from medicines) into systematic reviews; how to apply teleoanalysis effectively, using the whole range of available evidence.

The main message is that when dealing with harms, reviewers should extend their horizons beyond randomized trials. To do that it will be important to combine the expertise of different types of individuals, including statisticians, epidemiologists, and clinical pharmacologists.

### A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy

Dinnes J, Deeks J, Kirby J, Roderick P. *Health Technology Assessment* 2005; 9(12):1-113.

#### STRUCTURED ABSTRACT

*Prepared by the Cochrane Methodology Review Group*

**Background:** Dealing with heterogeneity is particularly challenging for diagnostic test accuracy reviews. The choice of meta-analytical method depends, in part, on the amount of heterogeneity observed in the study. However, there is no current empirical guidance to judge which methods are appropriate in which circumstances, and the degree to which different methods yield comparable results.

**Objective:** To review how heterogeneity has been examined in systematic reviews of diagnostic test accuracy studies.

**Design:** A systematic review.

**Data collection and analysis:** Systematic reviews that evaluated a diagnostic or screening test by including studies that compared a test with a reference test were identified from DARE (Database of Abstracts of Reviews of Effects). Reviews for which structured abstracts had been written up to December 2002 were screened for inclusion. Data extraction was undertaken using standardised data extraction forms.

**Results:** A total of 189 systematic reviews met the inclusion criteria. The median number of studies included was 18. Meta-analyses have a higher number with a median of 22 studies compared with 11 for narrative reviews. Graphical plots to demonstrate the spread in study results were provided in 56% of meta-analyses; in 79% these were plots of sensitivity and specificity in the receiver operating characteristic (ROC) space. Statistical tests to identify



heterogeneity were used in 32% of reviews: 41% of meta-analyses and 9% of reviews using narrative syntheses. The chi-squared test and Fisher's exact test to assess heterogeneity in individual aspects of test performance were the most common. In contrast, only 16% of meta-analyses used correlation coefficients to test for a threshold effect. A narrative synthesis was used in 30% of reviews. Of the meta-analyses, 52% carried out statistical pooling alone, 18% conducted only summary receiver operator characteristic (SROC) analyses and 30% used both methods of statistical synthesis. For those undertaking SROC analyses, the main differences between the models used were the weights chosen for the regression models, although in 42% of cases the use of, or choice of, weight was not provided. The proportion of reviews using statistical pooling alone declined from 67% in 1995 to 42% in 2001, with a corresponding increase in the use of SROC methods, from 33% to 58%. However, two-thirds of those using SROC methods also carried out statistical pooling rather than presenting only SROC models. Reviews using SROC analyses also tended to present their results as some combination of sensitivity and specificity rather than using alternative, perhaps less clinically meaningful presentations such as diagnostic odds ratios. Three-quarters of meta-analyses attempted to investigate statistically possible sources of variation, using subgroup analysis or regression analysis. The impact of clinical or socio-demographic variables was investigated in 74% of these reviews and test- or threshold-related variables in 79%. At least one quality-related variable was investigated in 63% of reviews. Within this subset, the most commonly considered variables were the use of blinding, sample size, the reference test used and the avoidance of verification bias.

**Conclusions:** The emphasis on pooling individual aspects of diagnostic test performance and the under-use of statistical tests and graphical approaches to identify heterogeneity perhaps reflect the uncertainty in the most appropriate methods to use and also greater familiarity with more traditional indices of test accuracy. This indicates the difficulty and complexity of carrying out such reviews. In these cases it is strongly suggested that meta-analyses are carried out with the involvement of a statistician familiar with the field. Further methodological work on the statistical methods available for combining diagnostic test accuracy studies is needed, as are sufficiently large, prospectively designed studies of diagnostic test accuracy comparing two or more tests for the same target disorder. Use of individual patient data meta-analysis in diagnostic test accuracy reviews should be explored to allow heterogeneity to be considered in more detail.

#### COMMENTARY

Prepared by Roger Harbord

Systematic reviews of diagnostic test accuracy provide a number of challenges to those of us more familiar with reviews of therapeutic interventions, not least how to analyse and present the quantitative results of such reviews. Considerable heterogeneity between the results of

diagnostic studies of the same topic is commonplace. In addition to their stated objective of reviewing methods for examining heterogeneity in such reviews, Dinnes et al. provide a comprehensive review of the wide variety of summary measures of diagnostic accuracy and methods used for meta-analysing them. The study is well conducted and the report is thorough (though potential readers should not be put off by its apparent length – the main body of the report runs to only 34 of its 128 pages, the remainder being mainly appendices of detailed data). Most of the reviews included in the study were published before 2002, so it is likely that there has since been some improvement in methods, as guidelines on diagnostic reviewing have been published and more sophisticated statistical methods have become available.

The authors make two recommendations for reviewers, which are generally in agreement with the *Cochrane Diagnostic Reviewers' Handbook* that is currently being prepared: First, that reviewers should be encouraged to follow recent guidelines and to use the QUADAS tool<sup>1</sup> to assess quality of diagnostic accuracy studies. Second, that diagnostic test meta-analyses should not be carried out without the involvement of a statistician familiar with the field.

Readers of the report may feel disappointed that it does not give clear guidance on the choice of statistical method. However, as the authors point out, this requires further methodological research. Several groups are currently conducting such work, some of which was presented at the Cochrane Colloquium in Melbourne in 2005. The authors also point out the difficulty of investigating sources of heterogeneity based on study-level summary data. Such data appear to have particular limitations for diagnostic accuracy studies, pointing to the need for large well-designed primary studies comparing tests and to the potential value of individual patient data meta-analysis.

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### Identifying studies for systematic reviews of diagnostic tests was difficult due to the poor sensitivity and precision

Doust JA, Pietrzak E, Sanders S, Glasziou PP. *Journal of Clinical Epidemiology* 2005; 58:444-449.

#### STRUCTURED ABSTRACT

Prepared by the Cochrane Methodology Review Group

**Background:** Methods to identify studies for systematic reviews of diagnostic accuracy are less well developed than for reviews of intervention studies.



**Objective:** To assess the sensitivity and precision of five published search strategies. To assess the reliability and accuracy of reviewers in screening abstracts of the results of the search strategy.

**Design:** A systematic review.

**Data collection and analysis:** The results of the search filters from the studies included in two systematic reviews of diagnostic test accuracy were compared. The inter-observer reliability of two reviewers screening the list of articles generated by the search strategies was also assessed.

**Results:** In the first review, the search strategy published by van der Weijden had the greatest sensitivity, and in the second review, four search strategies had 100% sensitivity. There was "substantial" agreement between two reviewers, but in the first review each reviewer working on their own would have missed one paper eligible for inclusion in the review. Ascertainment intersection techniques indicate that it is unlikely that further papers have been missed in the screening process.

**Conclusions:** Published search strategies may miss papers for reviews of diagnostic test accuracy. Papers are not easily identified as studies of diagnostic test accuracy, and the lack of information in the abstract makes it difficult to assess eligibility for inclusion in a systematic review.

#### COMMENTARY

*Prepared by Penny Whiting*

This study highlights some of the problems of searching for primary studies to include in diagnostic test accuracy reviews. Searching for such studies is more complex than searching for randomized trials, mainly due to the lack of appropriate indexing terms. With plans to expand *The Cochrane Library* to include diagnostic test accuracy reviews, this topic is of particular importance.

This was generally a very well conducted study that addressed an important topic. However, a potential limitation is that a diagnostic filter was used to identify studies for inclusion in the review rather than using a content filter alone, although this was combined with snowballing references. This means that the list of included studies on which the filters were evaluated may not have included all studies indexed in MEDLINE that met the review inclusion criteria.

The majority of research relating to diagnostic test accuracy research has focused on developing filters for diagnostic studies<sup>1-9</sup> or on evaluating these filters<sup>10,11</sup>, mainly for MEDLINE. A recent study<sup>10</sup> evaluated 12 search filters in a sample of 27 published reviews from a broad range of clinical fields. It concluded, in line with the results of the Doust *et al* study, that the use of methodological filters to identify diagnostic test accuracy studies can lead to the omission of a considerable number of relevant studies.

Future research in this area could be expanded to assess the performance of search strategies on other databases such as EMBASE, Science Citation Index, BIOSIS, LILACS, and Pascal. Another important question is the value of searching a number of different databases: is it sufficient to limit searches to one or two databases or does a broader range of databases need to be searched?

The Doust *et al* study, supported by other research in this area,<sup>10,11</sup> suggests that the use of methodological filters to identify primary diagnostic test accuracy studies should be avoided. Instead broader searches, limited only to index test, reference standard, population and/or target condition, should be carried out wherever possible.

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## Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding?

Fergusson D, Glass KC, Hutton B, Shapiro S. *Clinical Trials* 2005; 2:218-229; discussion 229-232.

### STRUCTURED ABSTRACT

Prepared by the Cochrane Methodology Review Group

**Background:** Aprotinin is a serine protease inhibitor used to limit perioperative bleeding and reduce the need for donated blood transfusions during cardiac surgery. Randomized controlled trials (RCTs) of aprotinin evaluating its effect on the outcome of perioperative transfusion have been published since 1987, and systematic reviews were conducted in 1992 and 1997.

**Objective:** To assess whether trialists systematically reviewed the existing literature before conducting new research.

**Design:** A cohort study.

**Data collection and analysis:** A systematic search was conducted for all RCTs of aprotinin that used placebo controls or were open-label with no active control treatment. Data collection included the primary outcome, objective of each study, whether a systematic review was cited or conducted as part of the background and/or rationale for the study and the number of previously published RCTs cited. Cumulative meta-analyses were performed.

**Results:** Sixty-four RCTs of aprotinin were found, conducted between 1987 and 2002, reporting an endpoint of perioperative transfusion. The median trial size was 64 patients, with a range of 20 to 1784. A cumulative meta-analysis indicated that aprotinin greatly decreased the need for perioperative transfusion, stabilizing at an odds ratio of 0.25 ( $p < 0.000001$ ) by the twelfth study, published in June of 1992. The upper limit of the confidence interval never exceeded 0.65 and results were similar in all subgroups. Citation of previous RCTs was extremely low, with a

median of 20% of prior trials cited. Only seven of 44 (15%) subsequent reports referenced the largest trial (n=1784), which was 28 times larger than the median trial size.

**Conclusions:** This study demonstrates that investigators evaluating aprotinin were not adequately citing previous research, resulting in a large number of RCTs being conducted to address efficacy questions that prior trials had already definitively answered. Institutional review boards and journals could reduce the number of redundant trials by requiring investigators to conduct adequate searches for existing evidence and conducting systematic reviews.

### COMMENTARY

Prepared by Chris Hyde

It is self-evident to many of us that new research should build on the findings of existing research. Systematic reviews have a critical role in ensuring that this linkage occurs. Evidence that problems occur when systematic reviews do not inform research development are consequently important and we should be careful to foster such evidence. However such evidence requires careful interpretation. I will consider whether such care has been exercised in the interpretation of Fergusson et al and extends a previous consideration of this issue in the *Lancet* correspondence pages.<sup>1</sup>

The study in question is a cumulative meta-analysis of randomized trials of aprotinin versus placebo in cardiac surgery. The outcome examined is whether a patient received transfusion in the peri-operative period. However it is recognised that information on other outcomes, particularly amount of blood actually lost, amount of blood transfused and safety are also required to make an overall assessment of effectiveness. The study makes two claims a) that they have demonstrated that many of the recent randomized trials are redundant b) that requiring randomized trial investigators to undertake systematic reviews as part of proposal development will reduce redundancy. I offer a few key observations on these claims.

Concerning demonstration of redundancy the key issue is that it should be the contribution to assessment of overall effectiveness that is the arbiter of whether a randomized trial has added to knowledge. Thus claims based on the assessment of one outcome in isolation, must inevitably be interpreted cautiously. Ideally we need to look at how the profile of information across all relevant outcomes develops over time, a mammoth task, but essential to explore fully whether randomized trials are truly uninformative.

Concerning the assertion that systematic reviews will reduce redundancy, there are uncertainties that suggest that this logical proposal may not be as successful as hoped. First, average time from inception to publication will be considerably longer than one year and publications appearing after the randomized trial protocol has been accepted, should not reasonably influence whether the study is completed and the result published. Thus it seems likely



that some 'redundant' publications might be unavoidable and quantifying this proportion would be helpful. Acknowledged difficulties in incorporating partially published material like conference abstracts and on-going studies into systematic reviews and accurately reflecting them in recommendations for research, further emphasises that there are real limits to how much redundancy an up-to-date systematic review can avoid. Second, it is easy to over estimate the ability of systematic reviews to deliver clear unambiguous findings concerning the need for further research. Consider Figure 1 in the paper by Fergusson et al. Even if one considers that we can make a valid decision on redundancy looking at one outcome alone, how many people would honestly have called a complete halt to further randomized trials in June 1992 after the study by Dietrich? Try it! To me there appears to be marked statistical heterogeneity among the 12 studies by then. This factor, not mentioned by Fergusson et al, along with other variations between included randomized trials may contribute considerably to uncertainty about decisions on whether further research is required, independently of the actual value of the summary measure and its 95% CI, however impressive.

In conclusion, the case for systematic reviews being an integral part of randomized trial design and reporting is well made. I agree that the example aprotinin in cardiac surgery provides support, but it is far from conclusive. Its results should not be over interpreted. The importance of this is that we must continue to seek further, clearer examples of where failure to conduct systematic reviews during the development of new randomized trial protocols has led to avoidable redundancy. More powerful would be examples where systematic reviews have led to a marked change in the nature and direction of research on a particular issue. One thing is clear, the aprotinin example reinforces that a well conducted systematic review in 1997<sup>2</sup> did not lead to the hoped for modification of trialist behaviour. More ammunition to convince doubters that systematic reviews *must* be an integral part of randomized trial development remains a priority.

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### High prevalence but low impact of data extraction and reporting errors were found in Cochrane systematic reviews

Jones AP, Remington T, Williamson PR, Ashby D, Smyth RL. *Journal of Clinical Epidemiology* 2005; 5:741-742.

#### STRUCTURED ABSTRACT

*Prepared by the Cochrane Methodology Review Group*

**Background:** Extracting data from articles is an essential component in conducting systematic reviews. Incorrect data extraction can lead to false conclusions.

**Objective:** Retrospectively to repeat the data extraction in all systematic reviews conducted by the Cochrane Cystic Fibrosis and Genetic Disorders Group and published in Issue 4, 2003 of *The Cochrane Library*.

**Design:** A cohort study.

**Data collection and analysis:** For each review data extraction was conducted by an experienced statistician for the same publications used by the reviewers. Results were compared with those obtained by the reviewers.

**Results:** Errors were found in 20 of 34 reviews, including incorrect calculations made when converting data in primary articles into data required for the review (two reviews) and misinterpretation of data that were reported in the primary article (seven reviews). All data-handling errors led to changes in the summary results, but none of these affected the review conclusions.

**Conclusions:** Important errors were identified in a high proportion of reviews. A variety of problems relating to the reporting of results within a review were identified, but these did not lead to substantial changes in any conclusion.

#### COMMENTARY

*Prepared by Harriet MacLehose*

This study highlights important stages in a review's development where two types of error may occur. It is one of a small group of studies looking at the quality of Cochrane reviews and one of the very few that focuses on modifying editorial practices as a means of improving review quality.

The statistician with the Cochrane Cystic Fibrosis and Genetic Disorders Group examined each of the Group's reviews against their component included studies for data handling errors (e.g. median entered instead of mean) and reporting errors (e.g. results reported in review text, but data not in RevMan). Of the 34 reviews that contained studies, errors were found in 20. None of the data handling errors were found to affect the reviews' conclusions even though they changed the summary results. It is not clear if the reporting errors had an effect on the integrity of the reviews.

The editorial team made two changes in response to these findings. The first was to request review authors to submit their data extraction forms with their reviews to allow the Group to check for data handling errors. This was in addition to the Group's existing recommendation that at least two review authors independently assess study



eligibility and methodological quality, and extract data. The second was to amend their peer referee checklists to capture reporting errors.

The authors do not mention having repeated their study since making these changes to see if they have had an effect. It would be interesting to know the Group's experience with collecting the data extraction forms and checking for data handling errors, particularly as the authors rightly note the difficulties editorial teams would have in checking all extracted data against the original reports. It would also be interesting to know if the editors, including copy and technical editors, have become more vigilant for the reporting errors.

The study recommends that other strategies for improving the quality of Cochrane reviews be considered. Although they do not outline specific strategies, their study highlights the need for editors and review authors alike to be vigilant and continue to improve their practices to minimize future errors.

### Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE

Wong SS, Wilczynski NL, Haynes RB. *Journal of the Medical Library Association* 2006; 94:41-47.

#### STRUCTURED ABSTRACT

*Prepared by the Cochrane Methodology Review Group*

**Background:** The ability to identify accurately articles about therapy in large bibliographic databases such as EMBASE is important for researchers and clinicians.

**Objective:** To develop optimal search strategies for detecting sound treatment studies in EMBASE in the year 2000.

**Design:** A cohort study.

**Data collection and analysis:** Handsearches of journals were compared with retrievals from EMBASE for candidate search strategies. Six trained research assistants reviewed 55 journals indexed in EMBASE and rated articles using purpose and quality indicators. Candidate search strategies were developed for identifying treatment articles and then tested, and the retrievals were compared with the handsearch data. The operating characteristics of the strategies were calculated.

**Results:** Three thousand eight hundred and fifty articles were original studies on treatment, of which 1,256 (32.6%) were deemed to be methodologically sound. Combining search terms revealed a top performing strategy (random:tw. OR clinical trial:mp. OR exp health care quality) with sensitivity of 99% and specificity of 72%. Maximizing specificity, a top performing strategy (double-

blind:mp. OR placebo:tw. OR blind:tw.) achieved a value over 96%, but with compromised sensitivity at 52%. A three-term strategy achieved the best optimization of sensitivity and specificity (random:tw. OR placebo:mp. OR double-blind:tw.), with both these values over 92%.

**Conclusions:** Search strategies can achieve high performance for retrieving sound treatment studies in EMBASE.

#### COMMENTARY

*Prepared by Anne Eisinga*

Methods of search strategy design have developed from subjectively derived strategies that were not performance tested<sup>1</sup>, to subjectively derived strategies performance tested on data sets of relevant reports,<sup>2,3</sup> (such as this report by Wong et al), and objectively derived strategies, performance tested on such data sets.<sup>4-6</sup>

Many methodological search strategies or "filters" have been developed to make it easier to find studies of various designs in MEDLINE but studies developing strategies for EMBASE are fewer. Wong et al's study is a welcome contribution to this research base.

They used subjectively derived search terms to identify "clinically sound" studies of treatment by compiling an initial list of index terms and text words and then seeking input from clinicians and librarians in the US and Canada. From a list of 5,385 terms, 3,524 returned results; 7164 search strategies were tested in the development of this treatment filter. It has been suggested that logistic regression analysis improves the accuracy of search term selection by taking into account the "best combination" of search terms<sup>7</sup>. Wong et al adopted a Boolean approach (using "OR" rather than "AND" to avoid reducing the number of citations retrieved and potentially compromising sensitivity) for developing their EMBASE strategies. This decision is based on their previous studies in MEDLINE, which compared logistic regression with a Boolean approach and found the former did not improve search strategy performance.<sup>3</sup>

The "gold standard" against which they compared the EMBASE search strategies came from the handsearching of 55 journals: a final set of 1256 articles. The extent to which the derived search strategies are generalizable depends upon the sample of journals in this "gold standard" and Boynton et al have warned that the journals used in such "gold standards" may not be representative of healthcare journals as a whole.<sup>4</sup> Furthermore, it has been suggested that higher impact journals may demand a higher standard of reporting which might bias the retrieval effectiveness of the filter when used for lower impact journals.<sup>5</sup> Wong et al chose journals through recommendations by clinicians and librarians, Science Citation Index impact factors and their ongoing yield of studies and reviews deemed to be of scientific merit. They have, therefore, not relied solely on journals with high impact factors and have also included



journals from mental health and nursing practice as well as internal medicine and general medical practice, but not journals in languages other than English. Although they had used larger journal sets (n=161) in their previous research in MEDLINE,<sup>3</sup> they found that the search strategies were robust in smaller journal sets.

Whether a filter developed and tested in one year will give the same results for other years is likely to be affected by additions and amendments to index terms over time. Wong et al acknowledge this, but their decision to confine the handsearch to the year 2000 was based on their study which established the robustness of search strategies across publication periods (1991 and 2000) in MEDLINE.<sup>8</sup>

The validation of a search filter is important in assessing the effectiveness of the filter outside the set used for deriving and testing it. If the same data set is used for both purposes it can introduce bias resulting in an overestimate of the effectiveness of the filter<sup>4</sup> because a strategy will tend to perform better on the set of records from which it was derived.<sup>5</sup> Wong et al chose not to divide their “gold standard” into a test set (used for deriving the search filter) and a validation set (used for testing it) for their EMBASE strategies but developed and tested the strategies using the whole data set, consisting of nearly 28,000 articles. This is because their MEDLINE study<sup>3</sup> found that strategies developed in 60% of the data set and validated in the remaining 40% showed no statistical differences in performance but it is unclear if this would also have been the case with their EMBASE strategies.

In recent years, the Centre for Reviews and Dissemination and the UK Cochrane Centre Search Filters Design Group have sought to improve the objectivity of the methods used to design search strategies. They have used word frequency analysis and discriminant analysis to derive objectively, through logistic regression, the most efficient search terms for particular study designs. The Group’s most recent study<sup>6</sup> presents a series of MEDLINE strategies with varying sensitivities and precision designed to accommodate the differing needs of busy clinicians and authors of systematic reviews in seeking randomized trials. One of these strategies (A) has become the revised version of the Cochrane Highly Sensitive Search Strategy. This Group intend to develop methodological search strategies for identifying randomized trials in EMBASE using this objective approach.

A useful collection of methodological search strategies has been compiled by the InterTASC Information Specialists’ Sub-Group (ISSG)

([www.york.ac.uk/inst/crd/intertasc/rct.htm](http://www.york.ac.uk/inst/crd/intertasc/rct.htm)).

Other studies assessing the performance of methodological search strategies can be found at [www.york.ac.uk/inst/crd/intertasc/surveys.htm](http://www.york.ac.uk/inst/crd/intertasc/surveys.htm)

There is also a useful checklist proposed by Jenkins<sup>7</sup> for appraising methodological search strategies, which I used as a basis for this commentary.

Finally, irrespective of which search strategies are used, Wong et al rightly remind us of the need to assess the quality of retrieved records before using them in decision-making or systematic reviews.

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## 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).

## How do conclusions change when Cochrane reviews are updated?

Simon French, Steve McDonald, Jo McKenzie and Sally Green

**Title:** Investing in updating: how do conclusions change when Cochrane systematic reviews are updated?

**Contact:** Simon French, Australasian Cochrane Centre, Institute of Health Services Research, Monash University, Monash Medical Centre, Locked Bag 29, Clayton, Victoria, 3168, Australia. Email: [simon.french@med.monash.edu.au](mailto:simon.french@med.monash.edu.au).

**Background:** Cochrane systematic reviews aim to provide readers with the most up-to-date evidence on the effects of healthcare interventions. The policy of updating Cochrane reviews every two years consumes valuable time and resources and may not be appropriate for all reviews.

**Objective:** To examine the effect of updating Cochrane systematic reviews over a four year period.

**Location:** Australasian Cochrane Centre, Australia.

**Methods:** This descriptive study examined all completed systematic reviews in the Cochrane Database of Systematic Reviews (CDSR) Issue 2, 1998. The latest version of each of these reviews was then identified in CDSR Issue 2, 2002 and changes in the reviews were described. For reviews that were updated within this time period and had additional studies, we determined whether their conclusions had changed and if there were factors that were predictive of this change.

**Summary of main results:** A total of 377 full reviews were published in CDSR Issue 2, 1998. In Issue 2, 2002, 14 of these reviews were withdrawn and one was split, leaving 362 reviews to examine for the purpose of this study. Of these reviews, 254 (70%) were updated. Of these updated reviews, 23 (9%) had a change in conclusion. Both an increase in precision and a change in statistical significance of the primary outcome were predictive of a change in conclusion of the review.

**Conclusions:** The concerns around a lack of updating for some reviews may not be justified considering the small proportion of updated reviews that resulted in a changed conclusion. A priority-setting approach to the updating of Cochrane reviews may be more appropriate than a time-based approach.

**Recommendations:** Updating all reviews as frequently as every two years may not be necessary, however some reviews may need to be updated more often than every two years.

### Reference:

French SD, McDonald S, McKenzie JE, Green SE. Investing in updating: how do conclusions change when Cochrane systematic reviews are updated? *BMC Medical Research Methodology* 2005; 5:33.

## Reference bias in narrative review articles

Lasse Schmidt and Peter Gøtzsche

**Title:** Of mites and men: reference bias in narrative review articles: a systematic review.

**Contact:** Peter Gøtzsche, Nordic Cochrane Centre, Rigshospitalet, Dept. 7112, Blegdamsvej 9, Copenhagen Ø DK-2100, Denmark. Email: [pcg@cochrane.de](mailto:pcg@cochrane.de).

**Background:** Narrative review articles sometimes favour references supporting the views of the authors, giving credence to a particular treatment or hypothesis. This reference bias may lead to the conclusions of such articles being less reliable.

**Objective:** To assess whether there is reference bias in narrative review articles that discuss interventions against house dust mites for people with asthma.

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

**Methods:** Narrative review articles, that expressed an opinion about the clinical effects of physical or chemical intervention methods against house dust mites for people with asthma, were identified by searching MEDLINE (1966 to July 2002). Positive bias was judged to have occurred if the reference list contained a higher proportion of trial references with significant results than among all trials available to the authors (published two years or more prior to the review).

**Summary of main results:** Seventy reviews were included, of which 63 (90%) recommended physical interventions. Forty-six reviews had trial references, four of these were only to chemical interventions. In the remaining 42 reviews, reference bias was detected. The most quoted trial had only seven patients per group and did not report a clinical outcome. Intervention recommendations were often based on non-randomized evidence, and the most quoted non-randomized study included only 10 patients per group but claimed very positive results.

**Conclusions:** The narrative review articles were severely biased, and their positive intervention recommendations are at variance with the systematic Cochrane review on this topic and a recent very large trial of physical intervention, both of which failed to find an effect.



**Recommendations:** When assessing narrative review articles, it is important to consider carefully the possibility of reference bias.

#### References:

Schmidt LM, Gøtzsche PC. Of mites and men: reference bias in narrative review articles: a systematic review. *Journal of Family Practice* 2005; 54:334-338.

## Implications for research from Cochrane reviews

Lorcan Clarke, Tom Clarke and Mike Clarke

**Title:** Implications for research from Cochrane reviews.

**Contact:** Mike Clarke, UK Cochrane Centre, Summertown Pavilion, Middle Way, Oxford, OX2 7LG, UK. Email: [mclarke@cochrane.co.uk](mailto:mclarke@cochrane.co.uk).

**Objective:** To examine the “Implications for Research” section of all Cochrane reviews published in Issue 4, 2005 of *The Cochrane Library* in order to provide a comprehensive descriptive summary of their content.

**Location:** UK Cochrane Centre, England.

**Methods:** An electronic file containing the contents of the “Implications for Research” section of all 2535 Cochrane reviews in Issue 4, 2005 of *The Cochrane Library* was provided by the Information Management System team at the Nordic Cochrane Centre. The contents of this file were printed to allow the assessment to be done on paper. Each record was assessed to identify whether it mentions a specific ongoing or planned trial, and categorised on the basis of whether a recommendation is made about specific types of intervention, participant, or outcome measures that should be assessed or included in future research that would be eligible for the review; whether it recommends that no more research is needed or feasible; and whether the need for a new, expanded or updated systematic review is discussed.

**Summary of main results:** 82% of Cochrane reviews include, in the “Implications for Research” section, a suggestion about specific interventions, 30.2% suggest participants, and 51.9% suggest outcome measures for future research. The authors of 17.0% of the reviews include suggestions in all three domains, 11.7% of reviews do not include a specific suggestion about any of these domains, and 3.2% of reviews conclude that no more research is necessary or likely to be feasible. An ongoing or planned trial that would be eligible for the review is mentioned in the “Implications for Research” section of 3.9% of reviews. 6.0% of reviews mention explicitly the need to update or expand the current review, or to conduct reviews of related topics.

**Conclusions:** Cochrane reviews identify residual uncertainty for many of the interventions assessed in these reviews. The reviews are a rich source of suggestions for future healthcare research.

**Recommendations:** Cochrane authors and Cochrane Review Groups should follow the guidance in the Cochrane Handbook for Systematic Reviews of Interventions, which was revised in 2005<sup>1</sup>, when preparing the content of the “Implications for Research” section of Cochrane reviews.

**Dissemination of findings:** A fuller report was submitted to The Cochrane Collaboration Steering Group in January 2006 and a report has been submitted for publication in a journal.

#### Reference

1. Higgins JPT, Green S, editors. Guide to the contents of a protocol and review: Text of a review. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]; Section 3.4. [www.cochrane.org/resources/handbook/hbook](http://www.cochrane.org/resources/handbook/hbook). [Accessed 26 April 2006].

## A rapid review of economic evaluation methods in Cochrane reviews

Ian Shemilt, Miranda Mugford, Mike Drummond, Eric Eisenstein, Martin Knapp, Jacque Mallender, David McDaid, Luke Vale and Damian Walker.

**Title:** A rapid review of economic evaluation methods in Cochrane reviews relevant to health promotion and public health

**Contact:** Ian Shemilt, Research Co-ordinator, Campbell and Cochrane Economics Methods Group, Health Economics Group, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ. Email: [i.shemilt@uea.ac.uk](mailto:i.shemilt@uea.ac.uk).

**Background:** It is increasingly accepted that provision of evidence on cost-effectiveness can significantly enhance the usefulness and relevance of systematic reviews of effectiveness as a component of the basis for health care decision-making<sup>1</sup>. However, patterns of use of economic evaluation alongside systematic review methods remain unclear.

**Objective:** This rapid review aims to establish the current state of the art in economic evaluation methods alongside Cochrane reviews relevant to public health and health promotion, in order to inform the development of evidence-based guidance for reviewers on methods for making reviews more useful to economic decisions.

**Location:** Campbell and Cochrane Economics Methods Group, England.



**Methods:** *The Cochrane Database of Systematic Reviews* (Issue 3, 2005) was searched using a search strategy for potential economic evaluation studies<sup>2</sup>. We included current Cochrane reviews and protocols retrieved using the search that are also identified as relevant to health promotion or public health.<sup>3</sup> A researcher extracted and tabulated data which describe the economics component of included reviews. The data extraction form and a descriptive summary of the main results were developed in consultation with the co-authors.

**Summary of main results:** Twenty-one full Cochrane reviews and seven protocols met our inclusion criteria. None incorporates formal economic evaluation methods. Several reviews highlight a lack of economics studies and data amongst included primary studies. However, some reviews are likely to exclude economic studies and data because they do not incorporate use of key databases or searches tailored to the retrieval of such data and because stringent inclusion criteria relating to study design are applied to all encountered studies.

**Conclusions:** There is a need for increased dialogue between reviewers and economists to develop the capacity and scope for economic analyses alongside systematic reviews. In the context of complex interventions that may be organised across more than one economic sector (e.g. health, education, social welfare, criminal justice) - such as many public health or health promotion programmes - this will require a more integrated, interdisciplinary approach. This study will inform development of further guidance on the use of relevant, appropriate and unbiased economics methods. It has also acted as a pilot for a wider systematic review of methods at the interface of economic evaluation and a systematic review across several applied sectors, encompassing reviews of complex and multi-sector interventions.

#### References:

1. Lavis J, Davies H, Oxman A, Denis JL, Golden-Biddle K, Ferlie E: Towards systematic reviews that inform health care management and policy-making. *Journal of Health Services Research and Policy* 2005; 10 (Suppl 1):35-48.
2. Centre for Reviews and Dissemination. *Improving access to cost-effectiveness information for health care decision making: the NHS Economic Evaluation Database*. CRD Report Number 6, 2nd edition. York: Centre for Reviews and Dissemination, 2001.
3. Cochrane Public Health Field: *Cochrane reviews identified as relevant to health promotion and public health*. [\[www.vichealth.vic.gov.au/cochrane/activities/reviews.htm\]](http://www.vichealth.vic.gov.au/cochrane/activities/reviews.htm)

## Effect of different risk reduction communication formats for promoting healthcare choices

Cheryl Carling, Doris Kristoffersen, Andy Oxman, Signe Flottorp and Holger Schünemann

**Title:** HIPPO: A series of four Internet-based randomized trials comparing the effect of different risk reduction communication formats for promoting healthcare choices consistent with patients' values.

**Contact:** Cheryl Carling, Norwegian Knowledge Centre for Health Services, Box 7004 St. Olavs plass, N-0130 Oslo, Norway. Email: [Cheryl.carling@kunnskapssenteret.no](mailto:Cheryl.carling@kunnskapssenteret.no).

**Background:** Research has shown that the format used to present treatment effects influences decisions of both consumers and health professionals. However, little is known about how research-based estimates of treatment effects, and the uncertainty associated with them, should be presented in order to facilitate patient decisions that are most consistent with patients' own values.

**Objective:** To evaluate which ways of presenting information about the effects of healthcare best help people to make choices consistent with their own values.

**Location:** Norwegian Knowledge Centre for Health Services, Norway.

**Methods.** A series of four internet based randomized trials were conducted of the same information about the benefits of treatments presented in different ways. Participants were recruited for Study One (2978 people over 18 years old) via flyers and Internet links and news groups, and for Studies Two (1760 people), Three (1528 people) and Four (1262 people) through a weekly Norwegian-TV health programme. We compared a) six different summary statistics presenting the effect of cholesterol-lowering drugs b) four different graphical presentations for effects of penicillin on sore throat, and c) three ways of framing the effects of anti-hypertensives; d) a fourth study compared a table, a bar graph and words using qualitative expressions for presenting effects of anti-depressants (SSRIs). Participants entered data via the project's Internet site. Values for the states associated with each illness and its treatment were elicited using Visual Analogue Scales (VAS). Participants chose hypothetically to take or not take the proposed treatment. The data were analysed using binary logistic regression.

**Summary of main results:** Study One: Relative risk reduction gave the worst congruence between values and decisions about whether to use cholesterol-lowering drugs. Congruence between values and decisions was nearly identical for the other five presentations. Study Two: A graph showing the duration of sore throat led to decisions about taking penicillin that were most consistent with expressed values. Study Three: Negative framing over 10 years resulted in the best congruence between values and decisions for taking anti-hypertensives while positive framing over 10 years resulted in the least. Study Four: No



difference between presentations was found. (for more details please see [www.cochrane.no/Newsletter2006](http://www.cochrane.no/Newsletter2006)).

**Conclusions:** In three studies we found strong associations between preferences and decisions and important differences among the evaluated presentations. In the fourth study, we also found a strong association between preferences and decisions, but no differences between presentations, most likely because participants had strong opinions before participating in the study. The cholesterol and anti-hypertensive scenarios addressed primary prevention and reducing long-term risk, whereas the penicillin scenario addressed an acute, usually self-resolving problem. It is not clear to what extent the results of these studies can be applied to other conditions, to face-to-face communication, or to real versus hypothetical decisions.



### Thomas C Chalmers M.D. Award - 2005

The Thomas C Chalmers M.D. prize is awarded annually for the best oral or poster presentation at the Cochrane Colloquium. In 2005, in Melbourne, it was awarded to Georgia Salanti, Julian Higgins and Valeria Marinho for their study entitled "How to determine the best treatment: a mixed-treatment-comparisons meta-analysis (MTM) of trials of topical fluoride therapies for the prevention of dental caries" and to Jesper Brok, Kristian Thorlund, Jørn Wetterslev and Christian Gluud for their study entitled "Trial sequential analyses of six Cochrane neonatal group meta-analyses considering adequacy of allocation concealment".

#### How to determine the best treatment: a mixed-treatment-comparisons meta-analysis

Georgia Salanti, Julian Higgins and Valeria Marinho

**Title:** How to determine the best treatment: a mixed-treatment-comparisons meta-analysis (MTM) of trials of topical fluoride therapies for the prevention of dental caries.

**Contact:** Georgia Salanti, MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Robinson Way, Cambridge CB2 2SR. Email: [Georgia.Salanti@mrc-bsu.cam.ac.uk](mailto:Georgia.Salanti@mrc-bsu.cam.ac.uk).

**Background:** A series of Cochrane reviews provides evidence on the effectiveness of topical fluoride therapies in various forms (toothpaste, gel, varnish and mouth-rinse) for the prevention of dental caries. Whereas evidence is based on a large number of trials for some forms of fluoride, there is more uncertainty about the effectiveness of other forms. Tailored placebo groups and among-study variation in trial

settings contribute to heterogeneity and complicate the analysis. Mixed-treatment-comparisons meta-analysis (MTM) offers a technique to synthesise the entirety of the evidence in a single analysis taking into account sources of heterogeneity. Moreover, MTM can be used to rank treatments in effectiveness despite a lack of trials that compare them directly.

**Objective:** To determine the most effective treatment among fluoride toothpastes, gels, varnishes and rinses using evidence from all relevant randomized trials, to increase precision in the estimates of the least studied interventions, and to evaluate heterogeneity and inconsistency across trials and across comparisons.

**Location:** MRC Biostatistics Unit, England.

**Methods:** Meta-analyses of placebo-controlled trials and head-to-head comparisons of the aforementioned fluoride interventions, previously published in *The Cochrane Library*, were assessed. A random-effects MTM synthesis within a Bayesian framework and meta-regression was used to account for variable study-level characteristics. The consistency of information from different sources was explored, and several assumptions regarding the compatibility of the various placebo implementations were compared.

**Summary of main results:** The meta-analysis includes 150 trials corresponding to 13 different comparisons. The precision increases, compared with simple pair-wise comparisons, for the less studied treatments when MTM is applied. Fluoride varnish appears as the most effective treatment, and the other fluoride forms seem similarly effective. Accounting for the different forms of placebo does not change the core conclusions of the meta-analysis and we did not identify important disagreements among the direct and indirect sources of information. However, examples are given where information is inconsistent, yielding misleading results.

**Conclusions:** The analysis of treatment networks is undertaken with greater precision and offers more clinically relevant conclusions when MTM is applied. However, the use of such models should be accompanied with justification of their plausibility, and applied after evaluation of the underlying assumptions.

#### Reference:

Salanti G, Higgins J, Marinho V. How to determine the best treatment: a mixed-treatment-comparisons meta-analysis (MTM) of trials of topical fluoride therapies for the prevention of dental caries [abstract] *XIII Cochrane Colloquium*; 2005 Oct 22-26; Melbourne, Australia:58.

#### Trial sequential analyses in meta-analyses considering adequacy of allocation concealment



Jesper Brok, Kristian Thorlund, Jørn Wetterslev and Christian Gluud

*XIII Cochrane Colloquium*; 2005 Oct 22-26; Melbourne, Australia:142-143.

**Title:** Trial sequential analyses of six Cochrane Neonatal Group meta-analyses considering adequacy of allocation concealment.

**Contact:** Jesper Brok, Copenhagen Trial Unit, Centre for Clinical Intervention Research, H:S Rigshospitalet, Dept. 7102, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. Email: [jbrok@ctu.rh.dk](mailto:jbrok@ctu.rh.dk)

**Background:** Meta-analyses are rarely analyzed with trial sequential boundaries (TSB). TSB require calculation of optimal information size (OIS) in order to determine when strong evidence is reached (Pogue and Yusuf *Controlled Clinical Trials* 1997;18(6):580-593; discussion 661-666). Allocation concealment of randomized controlled trials (RCTs) are categorized as adequate or inadequate by The Cochrane Neonatal Review Group (CNRG). RCTs with inadequate allocation concealment may overestimate intervention effects.

**Objective:** To examine meta-analyses for spurious  $p < 0.05$  values with Lan-DeMets discrete sequential boundaries based on OIS, calculated from empirical intervention effects of trials with adequate allocation concealment.

**Location:** Copenhagen Trial Unit, Denmark.

**Methods:** Six meta-analyses with at least five trials reporting a binary primary outcome were selected from the 171 systematic CNRG reviews in *The Cochrane Library* (Issue 2, 2004). Relations between the cumulated z-curve, each cumulative z-value determined by fixed or random-effects models, the traditional criterion  $z = 1.96$ , and the TSB were analyzed using OIS. OIS was calculated based on intervention effects from trials with adequate allocation concealment.

**Summary of main results:** Three meta-analyses presented firm evidence for a beneficial intervention effect as the cumulated z-curve crossed both the  $z = 1.96$  and the TSB during the first trials. Two z-curves crossed the  $z = 1.96$  temporarily but returned to non-significant values. These z-curves never crossed the TSB. One z-curve never crossed the  $z = 1.96$  or the TSB.

**Conclusions:** Three meta-analyses with  $p < 0.05$  were supported by z-curves crossing the TSB. However, two meta-analyses showing temporary  $p < 0.05$  never crossed the TSB. Accordingly, trial sequential analyses based on trials with adequate allocation concealment may reduce the risk of Type I errors without increasing the risk of Type II errors.

#### Reference:

Brok J, Thorlund K, Wetterslev J, Gluud C. Trial sequential analyses of six Cochrane neonatal group meta-analyses considering adequacy of allocation concealment [abstract]



## Cochrane Methodology Review Group

Elizabeth Paulsen

Mike Clarke and Andy Oxman continue as Co-ordinating Editors for the Cochrane Methodology Review Group (CMRG). The other editors are Peter Gøtzsche, Philippa Middleton, Karen Robinson, Paul Glasziou, Peter Jüni and Gordon Guyatt (Criticisms Editor). Marit Johansen is the Trials Search Co-ordinator. The CMRG welcomes a new Statistics Advisor to the Group: Jan Odgaard-Jensen. The Group thanks Doris Tove Kristoffersen for her previous work in the position and wishes her luck as she pursues her PhD.

In Issue 2, 2006 of *The Cochrane Library* there were 11 reviews and 11 protocols in the *Cochrane Database of Methodology Reviews*. Two reviews were updates: (1) Grey literature in meta-analyses of randomized trials of healthcare interventions by Sally Hopewell *et al.* and (2) Time to publication for results of clinical trials by Sally Hopewell *et al.* Two protocols were new: (1) When and how to update systematic reviews by David Moher *et al.* and (2) Search strategies to filter diagnostic accuracy studies in MEDLINE by Mariska Leeflang *et al.* Information on the current status of all Cochrane methodology reviews and protocols, completed and ongoing, is available on pages 33-34.

It has been proposed that the *Cochrane Database of Methodology Reviews* be incorporated into the *Cochrane Database of Systematic Reviews*. The proposal has been approved by the Publication Policy Group and Wiley are now developing a detailed requirements document regarding production and publication issues.

The CMRG currently has 70 members registered on the Group's electronic discussion list. For information about the list and to subscribe, go to <http://cochrane.de/mailman/listinfo/ems-mg>.

The next meeting of the CMRG editorial team will be in October 2006 at the Cochrane Colloquium in Dublin.





## INFORMATION FROM THE METHODS GROUPS

There are 11 registered Methods Groups. Reports from most of these Groups are given below.

### Registered groups

Applicability and Recommendations  
 Health Economics  
 Individual Patient Data Meta-analysis  
 Information Retrieval  
 Non-Randomised Studies  
 Patient-Reported Outcomes  
 Prospective Meta-Analysis  
 Qualitative  
 Reporting Bias  
 Screening and Diagnostic Tests  
 Statistical

## REGISTERED GROUPS

### Campbell-Cochrane Health Economics Methods Group

Ian Shemilt, Miranda Mugford and Luke Vale

The Campbell and Cochrane Economics Methods Group (CCEMG) is entering a new phase of development, as improving the relevance and usefulness of reviews has been the focus of ongoing discussion right across The Cochrane Collaboration.

It is in this context that recent research and successive Colloquium plenary speakers have continued to highlight a need for reviewers to consider inclusion of evidence on the cost-effectiveness of interventions alongside evidence on their effectiveness. Renewed interest in the use of economics methods amongst Cochrane authors and Cochrane Review Groups probably reflects this thinking. Methods Groups have a central role to play in guiding this debate and working with review authors to develop appropriate methodological solutions. Together we have an opportunity to make real progress in this area over the next few years.

CCEMG is responding to a growing number of requests for support from individual review authors and Cochrane Review Groups. Most requests have sought advice on best-practice methods of searching for economics studies, quality assessment and extracting economic data from included studies. CCEMG Co-convenors are currently finalising a chapter on incorporating economic evaluation into the systematic review process for the next edition of the *Cochrane Handbook for Systematic Reviews of*

*Interventions* that will include introductory guidance on these methods.

A recent online survey of members conducted by the Group indicates that its active members are collectively willing to provide advice and peer review for the economics components of reviews for at least half of all Cochrane Review Groups. The survey results show that many Cochrane Review Groups already have 'in principle' access to a network of economics support via our Methods Group. However, the Cochrane Review Groups and review authors do not necessarily know that this resource is available. As well as building capacity amongst our membership to cover all Cochrane Review Groups, we need to become more proactive about linking economists into review production.

CCEMG is co-ordinating a portfolio of research which aims to review, develop and test methods at the interface of economic evaluation and systematic reviews. In March 2006, the Group submitted a proposal for collaborative research involving the Musculoskeletal Group and the Developmental, Psychosocial and Learning Problems Group. The proposed project will use a decision analytic framework alongside two new Cochrane reviews to develop and test methods for modelling the costs and effects of interventions implemented in and across different policy and practice domains, which affect and are affected by public health.

Other planned research includes a seminar series on best-practice methods in economic evaluation alongside systematic reviews of health care, education, criminal justice and social welfare interventions, followed by a revised edition of the book 'Evidence-based health economics: from effectiveness to efficiency in systematic review' (London: BMJ Books, 2002). A series of methodology reviews and a database of methodological papers are also planned. Full details of the current research agenda will be available on the CCEMG website ([www.c-cemg.org](http://www.c-cemg.org)) from June 2006.

Contact Ian Shemilt, CCEMG Research Co-ordinator, by e-mail at [i.shemilt@uea.ac.uk](mailto:i.shemilt@uea.ac.uk) or telephone +44 1603 591086 to access the network of convenors and members. Join the Methods Group, as either an active or associate member, at [www.c-cemg.org](http://www.c-cemg.org).

### Cochrane Applicability and Recommendations Methods Group

Holger Schunemann and Gordon Guyatt

The Applicability and Recommendations Methods Group has new Co-convenors: Holger Schünemann, Associate Professor of Medicine, Preventive Medicine, Clinical Epidemiology and Biostatistics, Italian National Cancer Institute, Rome, Italy and Gordon Guyatt, Professor of Clinical Epidemiology, Biostatistics and Medicine at McMaster University. The Methods Group will be based in



Rome, Italy, and the Italian Cochrane Centre will serve as the reference Cochrane Centre.

## Cochrane Individual Patient Data Meta-analysis Methods Group

Jayne Tierney, Lesley Stewart, Lara Rydzewska and Mike Clarke

The Individual Patient Data (IPD) Meta-analysis Methods Group currently has 52 members from 13 countries. With the increased use of IPD in systematic reviews, we are seeking to recruit new members who are carrying out IPD reviews, or associated methodological projects. We hope this expansion will help capture the breadth of existing IPD projects, increase the range of methodological output and promote collaboration. Realising that some of our current members' interests have changed since they first joined the Group and that many are now too busy to be active members, we also plan to survey everyone on our membership list to establish those who would like to continue as active members, those who would just like to receive information on Group activities and those who no longer want to be part of the Group. If you are interested in becoming a member of the Group or finding out more please contact Lara Rydzewska ([lh@ctu.mrc.ac.uk](mailto:lh@ctu.mrc.ac.uk)). You can also find out more by visiting our website ([www.ctu.mrc.ac.uk/ukcccr/ipd/home.asp](http://www.ctu.mrc.ac.uk/ukcccr/ipd/home.asp)), where you can access databases of IPD meta-analyses and methodological projects carried out by the Group, as well as general information on IPD reviews.

In 2005, we ran two training workshops at the Colloquium in Melbourne, one on IPD methodology and the other on practical methods for incorporating time-to-event data into Cochrane reviews. Feedback on our workshops in previous years led us to develop a project that aims to improve the quality of Cochrane reviews that include time-to-event outcomes, for which we received some funding from The Cochrane Collaboration Steering Group. We are preparing user-friendly explanations of the methodology for these reviews and developing training materials tailored to the needs of different types of individual within the Collaboration. Thus far, we have submitted a manuscript setting out the step-by-step approach used in our workshops and completed a spreadsheet for performing the associated calculations. Both will be made freely available to Cochrane Review Groups (CRGs) and workshop attendees, when the manuscript is published. A recent survey of CRGs, has indicated that awareness and use of the methods is variable, even in those CRGs with an interest in time-to-event outcomes. Most respondents thought that further training and software could improve use of the methods. We are grateful to CRGs for taking the time to contribute to this survey, and will be using their responses to target further training and will send them a full report of the results of the survey.

Despite the greater availability of statistical software that performs or can be adapted for meta-analysis, the major

commercial packages and RevMan have been geared to the analysis of aggregate data. None specifically supports the direct manipulation, analysis and plotting of IPD. For example, to incorporate an IPD review in RevMan, summary statistics from the IPD have to be generated in other software and then entered into the IPD option in RevMan. As a result, most groups carrying out IPD reviews have developed their own software to facilitate their IPD analyses. Two of these Groups' Co-convenors (JT, LS), together with an SAS® consultant, have been responsible for the development of SCHARP, an SAS®-based application with a point-and-click interface. SCHARP has now been enhanced substantively so that it produces forest plots, Kaplan Meier curves (if appropriate) and corresponding summary statistics for time-to-event, dichotomous and continuous IPD. It also facilitates the interactive analysis of many trials and multiple outcomes either across all trials or by trial or patient subgroup, based on a single flat input data file. When the current version of SCHARP is finalised, we will make it freely available, under licence, to non-commercial groups. We will run a new workshop at the Colloquium in Dublin to demonstrate the features of SCHARP to those undertaking or planning IPD reviews. We also plan to hold a meeting of the Group during the Colloquium.

## Cochrane Information Retrieval Methods Group

Carol Lefebvre, Alison Weightman, Jesse McGowan and Bernadette Coles

Over the past year, the Group has continued to grow and we now have c. 140 members, many of whom are active in a number of the projects outlined below.

Steve Pritchard resigned as Co-convenor of the Group when he retired from Cardiff University and Alison Weightman, also from Cardiff and previously co-ordinator, joined Carol Lefebvre from the UK Cochrane Centre as co-convenor. We also appointed an additional co-convenor, Jessie McGowan from the Effective Practice and Organization of Care Group in Canada. Bernadette Coles, Cardiff University, took over as co-ordinator. We should like to thank Steve for his role in setting up the Group and organizing infrastructure funding for administrative support at Cardiff University.

The co-convenors of the Group have served on various Collaboration policy advisory groups relevant to information retrieval including the Search Testing Group, the Cochrane CENTRAL Advisory Group (now defunct) and the Handbook Advisory Group. Members of the Group have served on other advisory groups such as the Publishing Policy Group. Members of the Group are currently involved in updating Section 5 of the Cochrane Handbook for Systematic Reviews of Interventions for publication in 2007. Co-convenors and members of the Group conducted a number of workshops at the Colloquium in Melbourne in 2005.



Filters for importing records from *The Cochrane Library* into ProCite and Reference Manager are now available and updated on the Group's website ([www.cochrane.org/docs/import.htm](http://www.cochrane.org/docs/import.htm)).

A web resource of published methodological search filters has been developed by the information specialists associated with InterTASC (most of whom are members of the Group) ([www.york.ac.uk/inst/crd/intertasc/index.htm](http://www.york.ac.uk/inst/crd/intertasc/index.htm)).

Members of the Group have been involved in a number of methodological research projects:

Development of public health search filters. This includes a project within the UK National Institute for Health and Clinical Excellence (NICE) to map the National Public Health Language (NPHL) thesaurus to MeSH.

Redesigning the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE. This project by the Centre for Reviews and Dissemination at the University of York and the UK Cochrane Centre has now been published in the *Journal of the Medical Library Association* and the recommended search strategies will shortly be updated in the *Cochrane Handbook for Systematic Reviews of Interventions* ([www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1435857](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1435857)).

To address the issue of the description of search strategies in Cochrane reviews (Section 5 of the *Cochrane Handbook for Systematic Reviews of Interventions*) a joint programme of work is underway with the Health Technology Assessment international (HTAi) Special Interest Group on Information Retrieval and the information specialists associated with InterTASC, the body responsible for conducting technology appraisals for the National Institute for Health and Clinical Excellence in the UK. The first stage in this process was known as the EHTAS (Evaluating HTA Searches) Project, funded by the Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA), to develop a checklist for search strategies for systematic reviews. This project is now known as PRESS (Peer Review of Electronic Search Strategies) and CCOHTA is now known as The Canadian Agency for Drugs and Technologies in Health (CADTH).

The Information Retrieval Methods Group (IRMG) discussion list is used to notify members of activities such as the annual IRMG meeting at Colloquia, to circulate the minutes etc. It has been used to recruit participants to the EHTAS / PRESS Project (see above) and to find possible collaborators in other projects.

A meeting of the Group was held during the Colloquium in Melbourne in 2005 and a further meeting is planned for the Colloquium in Dublin in 2006.

Infrastructure support for the time of the Co-convenors is provided by the UK Cochrane Centre, the University of

Ottawa and Cardiff University. Support for the time of the Co-ordinator and administrative assistance is provided by Cardiff University.

## Cochrane Non-Randomised Studies Methods Group

Barney Reeves and George Wells

This year, the Non-Randomised Studies Methods Group (NRSMSG) has only been able to meet at the Colloquium in Melbourne in October 2005. The meeting discussed key issues that had arisen during the last year, the NRSMSG 'handbook' and prioritising the NRSMSG research agenda.

Key issues during the last year included:

Feedback from the NRSMSG to The Cochrane Collaboration Steering Group about a proposal to develop Cochrane Review Group specific registers of non-randomized studies. The NRSMSG did not support this proposal because of the difficulties of defining, and applying, eligibility criteria and the potential dangers of registers where completeness cannot be determined. On a related matter, members welcomed the registration of the Information Retrieval Methods Group and look forward to collaborating in the future on search strategies for non-randomized studies.

As described in last year's Methods Groups Newsletter, the Adverse Events Subgroup is now seeking registration as a separate Methods Group; this process is on-going.

Members also considered the issue of whether Methods Groups should be allowed to accept commercial funding to support their administrative activities and methodological research. On behalf of all Methods Groups, a recommendation was made to the Steering Group that this should be the case, subject to appropriate safeguards, and this was approved in April 2006.

The status of the NRSMSG 'handbook' (guidance to reviewers about including non-randomized studies in systematic reviews) was also discussed; this will now form an appendix to the Cochrane Handbook for Systematic Reviews of Interventions. The deadline for a full draft is June 2006.

Finally, two research priorities were set: (a) to identify systematic reviews in *The Cochrane Library* that include non-randomized studies and appraise the methods used and the susceptibility to bias of the conclusions of the reviews; (b) to develop and assess/evaluate search strategies for non-randomized studies (in collaboration with the Information Retrieval Methods Group).

The Ottawa workshop on extracting data from non-randomized studies for a systematic review was run again at the Colloquium in Melbourne last year. Participants reported that they found it very helpful to have some



practical experience of the difficulties, e.g. classifying non-randomized studies according to their features, assessing their quality, recording the methods used to control for confounding and the findings. There was some dissatisfaction about the technology evaluated in the paper used for group work (surgery). This will be changed for this year's Colloquium in Dublin, where the training workshop (see above) will again be offered – this time it will focus on including non-randomized studies in systematic reviews of public health interventions.

The NRSMG took part in a methodological training workshop in London in February 2006, run for Editors and Co-ordinating Editors by the UK Cochrane Centre. The workshop included sessions on assessing bias in primary studies, common methodological pitfalls, incorporating adverse effects and challenges of including NRS in systematic reviews. Feedback was very positive and the UK Cochrane Centre expects to put on similar events in the future.

### **Cochrane Qualitative Methods Group**

Jennie Popay, Jane Noyes, Alan Pearson and Karin Hannes

For the Qualitative Research Methods Group the last year has been characterised by the familiar tensions between the enormous agenda facing the Group and the limited time available to deliver it. However, looking back it has been a watershed year in many ways. The year 'began' with our first sponsored training workshop organised by Janet Harris in June 2005 in Oxford, UK. The workshop aimed to give people in the field an opportunity to learn by sharing experiences of qualitative systematic reviewing. Participants included both people currently completing reviews as well as those who have an interest in trying to do a review in the future. It was well appraised and raised many issues for the Group to pick up. We organised another training workshop at the Colloquium in Melbourne and it was at our annual meeting in Melbourne that we recruited two new Co-ordinators: Alan Pearson from the Joanna Briggs Institute in Adelaide Australia and Karin Hannes from the Belgian Centre for Evidence-Based Medicine which is a branch of the Dutch Cochrane Centre and hosts the Belgian Campbell Group. Alan and Karin have given the Group new energy and we are planning a step change in our activities in the next 12 months.

Our website has been revamped and the new site should be live this year. We are hoping to use it to support dialogue amongst Group members as well as maintaining and developing the embryonic databases we have had up there for some time: protocols for systematic reviews of qualitative research and registers of methodological literature and completed qualitative systematic reviews. We are planning a survey of our many members to identify those willing to be more actively involved in one of our three working groups: registers, training, and guidance development. Jennie Popay, with other colleagues in the

UK, has recently completed guidance on the conduct of narrative synthesis in the context of systematic reviews, funded by the UK Economic and Social Research Council, which will be available as a free download from the website. This guidance together with the considerable methodological resources and experience of other members of the Group will inform the development of guidance on qualitative research synthesis in the context of Cochrane reviews which we hope to complete in the next 12 months.

Our educational programme will also be developing in new and exciting ways this year. With the Joanna Briggs Institute, a training workshop is planned for 10-11 July 2006 in Adelaide and two courses will be organized in Belgium. A one-day programme on narrative synthesis is taking place on 6 July 2006 led by Nicky Britten from the Peninsula Medical School, Universities of Plymouth and Exeter and another two-day course programme on meta-analysis of qualitative research will take place 20-21 November 2006. This course will be given by an international team of experts on synthesizing qualitative research including Alan Pearson and Tiffany Conroy-Hiller from the Joanna Briggs Institute in Adelaide, Australia and Etienne Vermeire from the University of Antwerp, Belgium. All our courses are open to participants from any countries and the programmes will be in English. More information on the Adelaide meeting is available from Tim Schultz ([tim.schultz@adelaide.edu.au](mailto:tim.schultz@adelaide.edu.au)) and for the training in Belgium from Karin Hannes ([karin.hannes@med.kuleuven.be](mailto:karin.hannes@med.kuleuven.be)).

### **Cochrane Reporting Bias Methods Group**

David Moher, Jonathan Sterne, Matthias Egger and Jennifer Tetzlaff

The Reporting Bias Methods Group (RBMG) started the Cochrane year with another successful meeting at the Cochrane Colloquium in Melbourne. In December 2005 the Group received confirmation of infrastructure funding for five years (2005 to 2010) as part of the commitment by the Canadian Institutes of Health Research and the Canadian Agency for Drugs and Technologies in Health (formerly CCOHTA) to fund Canadian Cochrane entities. This funding has enabled the Group to recruit a Co-ordinator, Jennifer Tetzlaff, who is working at the Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute. The Group has initiated monthly conference calls between the Co-convenors, helping to facilitate the draft development plans for the next few years.

RBMG members have been busy contributing to the *Cochrane Methodology Register*, *Cochrane Methodology Reviews* and paper-based journals. For example one study has recently been completed and a second is underway, that examine the reporting and methods of current systematic reviews in the literature. The completed review has targeted a number of areas of serious concern and will be used to inform topics where the RBMG can focus education and review training.



Several members of the RBMG are collaborating on a newly funded study (Bias in Randomised AND Observational studies: BRANDO), combining data from most existing meta-epidemiological studies to compare the results of randomized trials with observational studies. Peter Gøtzsche has recently completed a project “are relative risks and odds ratios in abstracts believable?”. RBMG members are working on the WHO International Clinical Trials Registry initiative.

Several RBMG members participated in a QUOROM meeting (to revise the QUOROM Statement) in June 2005. In addition, a number of initiatives are being considered for CONSORT extensions, through recent funding from the National Co-ordinating Centre for Research Methodology, NHS (UK) Research and Development Programme.

David Moher and colleagues have recently completed a Cochrane protocol for a systematic methodology review on when and how to update systematic reviews; this review should be completed in 2006. This Group also hosted an international task force meeting on the topic. In addition, we have recently completed a survey of systematic reviewers, methodologists and editors concerning the use of grey literature in systematic reviews.

Finally, the RBMG is currently developing a contribution for the update of the *Cochrane Handbook for Systematic Reviews of Interventions*, the update of a reference database, and is looking towards the development of review training workshops.

We are excited to be hosting a substantive meeting at the Cochrane Colloquium in Dublin in October 2006 to discuss these and other projects and we invite all those interested to join us.

For further information about group membership, the RBMG meeting in Dublin or other interests, please contact us at [jtetzlaff@cheo.on.ca](mailto:jtetzlaff@cheo.on.ca)

We look forward to seeing you in Dublin!

## Cochrane Screening and Diagnostic Tests Methods Group

Petra Macaskill and Constantine Gatsonis

The past year has again been a productive time for members of the Cochrane Screening and Diagnostic Tests Methods Group. Members of the Group are closely involved in the ongoing development of the *Handbook for the Systematic Reviews of Diagnostic Test Performance*. A full version of the Handbook is planned to be available in time for the Colloquium in Dublin. There are currently 13 teams piloting the materials and methods. Pilot reviewers, contributors to the Handbook and other interested parties met at the Colloquium in Melbourne to discuss progress. Most reviews

are now past the protocol stage and further feedback will be sought before final revisions are made to the first edition of the new Handbook. Software development is also currently underway to expand RevMan to implement the methods.

Group members made major contributions to five workshops on methods for the systematic review of diagnostic studies that were conducted during the Colloquium in Melbourne. The workshops were designed to complement each other and to cover all major areas including: formulating the research question, identifying studies, assessing study quality, meta-analytic methods, investigating heterogeneity, test comparisons and interpretation of results. Based on the high attendance and success of these, similar workshops will be offered at the Colloquium in Dublin.

Successful implementation of diagnostic test accuracy reviews across the Collaboration will naturally require infrastructure and resources. A proposal addressing these issues has been recently submitted to the Steering Group of the Collaboration.

A key aspect of the infrastructure is the establishment of a register of primary studies of diagnostic accuracy. Short-term funding has been obtained from outside the Collaboration to commence work on such a registry. Longer term funding will be sought to support this project.

We thank Group members for their many contributions in the past year, and look forward to the Colloquium in Dublin.



## CAMPBELL COLLABORATION METHODS GROUPS (C2)

Jeff Valentine

The Campbell Collaboration (C2) aims to utilize scientific standards in the conduct of systematic reviews of research on social and behavioural policies and programmes, and to make the findings easily available to policy makers, practitioners, and the public. Within this framework, the C2 Methods Group provides expertise to researchers conducting systematic reviews, improves systematic review methods, offers training on how to conduct reviews, and facilitates the use of systematic reviews in policy making and practice, particularly as this relates to the end-users' understanding of methodology and how to assess evaluations of policies and practices.

Several new developments occurred during the past year. First, C2 entered into an agreement with the American Institutes for Research (AIR), which provides C2 with



financial support for at least two years. C2 and AIR are currently interviewing candidates for the Executive Director position, which is being filled on a temporary basis by Dorothy DeMoya. This arrangement allowed each of the various substantive and Methods Groups to fund an editor, who help ensure that C2's products meet the highest scientific standards. Jeff Valentine (Duke University, USA) is serving as the editor for the Methods Group.

Julio Sanchez-Meca (University of Madrid, Spain) was appointed as the second Methods Group representative on C2's Steering Committee. Jeff Valentine agreed to co-chair the Methods Groups, joining Hannah Rothstein (Baruch College, USA) in that role.

The Methods Group worked with the Nordic Campbell Centre to conduct an advanced workshop in systematic review methods in Copenhagen in August 2005. This event was held in conjunction with the Nordic Social Science Conference

A meeting of the Methods Group was held in Los Angeles in conjunction with the annual C2 Colloquium in February 2006, and was attended by approximately 40 individuals. In addition to several methods sessions and workshops, 'expert office hours' were held at the Colloquium for individuals seeking methodological advice on an ongoing research synthesis.

Ties between the C2 Methods Group and The Cochrane Collaboration continue to strengthen in areas of mutual interest. The Economic Methods Group convened by Miranda Mugford (University of East Anglia, UK), is jointly registered, as is the Equity Group, which is co-chaired by Peter Tugwell (University of Ottawa) and Mark Petticrew (University of Glasgow). Finally, members of the Methods Groups will be participating in the North American Systematic Reviewers conference, which is sponsored by the US Cochrane Center in July 2006.



## FUTURE MEETINGS

### XIV Cochrane Colloquium

Dublin, Ireland  
October 23 - 26 2006

In October 2006, the XIV Cochrane Colloquium will take place in Dublin, the capital city of Ireland.

In 1992, the UK Cochrane Centre opened and, a year later, the first Cochrane Colloquium took place in the meeting room of the home of this Centre, an old, converted bakery in

Oxford. Seventy-seven people from 19 countries gathered together and The Cochrane Collaboration was established as an international organization. The growth in the Collaboration since then has been phenomenal. In 2006, more than 14,000 people from almost 100 countries are involved. *The Cochrane Database of Systematic Reviews*, with 36 reviews in 1995, has grown to more than 2600 full reviews and protocols for 1600 more. The reviews are serving to help people make evidence-informed decisions about health care. A great deal has clearly been achieved already but even more work remains ahead of us.

The XIV Cochrane Colloquium will be an opportunity to celebrate what has been achieved and also a chance to assess how the Collaboration can continue to grow and evolve to meet its aims. We look forward to welcoming The Cochrane Collaboration to this city of literature, history, excitement and fun.

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



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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:

The UK Cochrane Centre  
NHS R & D Programme  
Summertown Pavilion  
Middle Way  
Oxford OX2 7LG  
UK

The Newsletter is also available on The Cochrane Collaboration website at:

[www.cochrane.org/newslett/index.htm](http://www.cochrane.org/newslett/index.htm)



## CONTACT INFORMATION

### Methods Groups Newsletter Editors

Sally Hopewell, Co-scientific editor and technical editor  
The UK Cochrane Centre  
NHS R & D Programme  
Summertown Pavilion  
Middle Way  
Oxford OX2 7LG  
UK  
Tel: +44 1865 516300 Fax: +44 1865 516311  
[shopewell@cochrane.co.uk](mailto:shopewell@cochrane.co.uk)

Mike Clarke, Co-scientific editor  
The UK Cochrane Centre  
NHS R & D Programme  
Summertown Pavilion  
Middle Way  
Oxford OX2 7LG  
UK  
Tel: +44 1865 516300 Fax: +44 1865 516311  
[mclarke@cochrane.co.uk](mailto:mclarke@cochrane.co.uk)

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### Registered Methods Groups

#### Applicability and Recommendations

Holger Schünemann, Convenor  
Division of Clinical Research Development and Information Translation (INFORMA)  
Italian National Cancer Institute  
Istituto Regina Elena  
Via Elio Chianesi 53  
00144 Rome  
Italy  
Tel: +39 0652 665102 Fax: +1 443 3390565  
[hjs@buffalo.edu](mailto:hjs@buffalo.edu)

#### Health Economics

Miranda Mugford, Convenor  
School of Medicine, Health Policy and Practice  
University of East Anglia  
Norwich NR4 7TJ  
UK  
Tel: +44 1603 593583 Fax: +44 1603 593604  
[m.mugford@uea.ac.uk](mailto:m.mugford@uea.ac.uk)

[www.med.uea.ac.uk/research/research\\_econ/cochrane/cochrane\\_home.htm](http://www.med.uea.ac.uk/research/research_econ/cochrane/cochrane_home.htm)

#### Individual Patient Data Meta-analysis

Lesley Stewart, Convenor  
Cancer Division  
MRC Clinical Trials Unit  
222 Euston Road  
London NW1 2DA  
UK  
Tel: +44 20 76704724 Fax: +44 20 76704816  
[ls@ctu.mrc.ac.uk](mailto:ls@ctu.mrc.ac.uk)  
<http://212.219.75.236/ukcccr/ipd/home.asp>

#### Information Retrieval

Carol Lefebvre, Convenor  
The UK Cochrane Centre  
NHS R & D Programme  
Summertown Pavilion  
Middle Way  
Oxford OX2 7LG  
UK  
Tel: +44 1865 516300 Fax: +44 1865 516311  
[clefebvre@cochrane.co.uk](mailto:clefebvre@cochrane.co.uk)  
[www.cochrane.org/docs/irmg.htm](http://www.cochrane.org/docs/irmg.htm)

#### Non-Randomised Studies

Barney Reeves, Convenor  
Bristol Heart Institute  
University of Bristol  
Level 7, Bristol Royal Infirmary  
Marlborough Street  
Bristol BS2 8HW  
UK  
Tel: +44 117 9283143 Fax: +44 117 9299737  
[barney.reeves@bristol.ac.uk](mailto:barney.reeves@bristol.ac.uk)

#### Patient-Reported Outcomes

Catherine Acquadro, Convenor  
MAPI Research Institute  
27 Rue de la Villette  
Lyon 69003  
France  
Tel: +33 472 136575 Fax: +33 472 136682  
[cacquadro@mapi.fr](mailto:cacquadro@mapi.fr)  
[www.cochrane-pro-mg.org](http://www.cochrane-pro-mg.org)

#### Prospective Meta-analysis

Davina Ghersi, Convenor  
Cochrane Breast Cancer Group  
NHMRC Clinical Trials Centre  
The University of Sydney  
Locked Bag 77, Camperdown  
NSW 1450  
Australia  
Tel: +61 2 95625040 Fax: +61 2 95651863  
[davina@ctc.usyd.edu.au](mailto:davina@ctc.usyd.edu.au)  
[www.cochrane.org/docs/pma.htm](http://www.cochrane.org/docs/pma.htm)

**Qualitative Methods**

Jennie Popay, Convenor  
 Institute for Health Research  
 Alexandra Square  
 Lancaster University  
 Lancaster, LA1 4YT  
 UK  
 Tel: +44 1524 592493; Fax: +44 1524 592401  
[j.popay@lancaster.ac.uk](mailto:j.popay@lancaster.ac.uk)  
[http://mysite.wanadoomembers.co.uk/Cochrane\\_Qual\\_Method/index.htm](http://mysite.wanadoomembers.co.uk/Cochrane_Qual_Method/index.htm)

**Reporting Bias**

David Moher, Convenor  
 Chalmers Research Group  
 Children's Hospital of Eastern Ontario Research Institute  
 401 Smyth Road, Room R226  
 Ottawa Ontario K1H 8L1  
 Canada  
 Tel: +1-613 7383591 Fax: +1 613 7384800  
[dmoher@uottawa.ca](mailto:dmoher@uottawa.ca)  
[www.chalmersresearch.com/rbmg](http://www.chalmersresearch.com/rbmg)

**Screening and Diagnostic Tests**

Constantine Gatsonis, Convenor  
 Center for Statistical Studies  
 Brown University, Box G-H  
 Providence, RI 02912  
 USA  
 Tel: +1 401 8639183 Fax: +1 401 8639182  
[gatsonis@stat.brown.edu](mailto:gatsonis@stat.brown.edu)  
[www.cochrane.org/sadt/index.htm](http://www.cochrane.org/sadt/index.htm)

**Statistical Methods**

Doug Altman, Convenor  
 ICRF Medical Statistics Group  
 Centre for Statistics in Medicine  
 Wolfson College  
 University of Oxford  
 Linton Road  
 Oxford, OX2 6UD  
 UK  
 Tel: +44 1865 284401 Fax: +44 1865 284424  
[doug.altman@cancer.org.uk](mailto:doug.altman@cancer.org.uk)

**Newsletter contributors not listed above**

Gerd Antes  
 German Cochrane Centre  
 Universitätsklinikum  
 Stefan-Meier-Str. 26  
 79104 Freiburg  
 Germany  
 Tel: +49 761 2036715 Fax: +49 761 2036712  
[antes@cochrane.de](mailto:antes@cochrane.de)

Jeff Aronson  
 MRC Clinical Pharmacology Unit  
 Radcliffe Infirmary

Woodstock Road  
 Oxford, OX2 6HE  
 UK  
 Tel: +44 1865 224626  
[jeffrey.aronson@clinical-pharmacology.oxford.ac.uk](mailto:jeffrey.aronson@clinical-pharmacology.oxford.ac.uk)

Jesper Brok  
 Copenhagen Trial Unit  
 Centre for Clinical Intervention Research  
 H:S Rigshospitalet, Dept. 7102  
 Blegdamsvej 9,  
 DK-2100 Copenhagen Ø  
 Denmark  
[jbrok@ctu.rh.dk](mailto:jbrok@ctu.rh.dk)

Cheryl Carling  
 Norwegian Knowledge Centre for Health Services Research  
 P.O. Box 7004, St. Olavs plass  
 Oslo N-0130  
 Norway  
[Cheryl.carling@kunnskapssenteret.no](mailto:Cheryl.carling@kunnskapssenteret.no)

An-Wen Chan  
 Department of Medicine  
 University of Toronto  
 140 Simcoe St, Suite 718  
 Toronto, M5H 4E9  
 Canada  
 Tel: +1 416 3562881  
[anwen.chan@utoronto.ca](mailto:anwen.chan@utoronto.ca)

Anne Eisinga  
 The UK Cochrane Centre  
 NHS R & D Programme  
 Summertown Pavilion  
 Middle Way  
 Oxford OX2 7LG  
 UK  
 Tel: +44 1865 516300 Fax: +44 1865 516311  
[aeisinga@cochrane.co.uk](mailto:aeisinga@cochrane.co.uk)

Mark Fenton  
 James Lind Library  
 Summertown Pavilion  
 Middle Way  
 Oxford, OX2 7LG  
 UK  
 Tel: +44 1865 517622; Fax +44 1865 516311  
[mfenton@lindalliance.org](mailto:mfenton@lindalliance.org)

Simon French  
 Australasian Cochrane Centre  
 Institute of Health Services Research  
 Monash University  
 Monash Medical Centre  
 Locked Bag 29, Clayton  
 Victoria, 3168  
 Australia  
 Tel: +61 3 9594 7526 Fax: +61 3 9594 7554  
[simon.french@med.monash.edu.au](mailto:simon.french@med.monash.edu.au)



Peter Gøtzsche  
The Nordic Cochrane Centre  
Rigshospitalet  
Dept 7112  
Blegdamsvej 9  
DK-2100 Copenhagen Ø  
Denmark  
Tel: +45 35 457112; Fax: +45 35 457007  
[pcg@cochrane.dk](mailto:pcg@cochrane.dk)

Roger Harbord  
MRC Health Services Research Collaboration  
Department of Social Medicine  
University of Bristol  
Canyng Hall  
Whiteladies Road  
Bristol, BS8 2PR  
UK  
Tel: +44 117 9287289 Fax: +44 117 9287325  
[roger.harbord@bristol.ac.uk](mailto:roger.harbord@bristol.ac.uk)

Chris Hyde  
Systematic Review Initiative  
National Blood Service  
Level 2, John Radcliffe Hospital  
Headington  
Oxford, OX3 9BQ  
UK  
Tel: +44 1865 447942  
[chris.hyde@nbs.nhs.uk](mailto:chris.hyde@nbs.nhs.uk)

Harriet MacLehose  
International Health Research Group  
Liverpool School of Tropical Medicine  
Pembroke Place  
Liverpool, L3 5QA  
UK  
Tel: +44 151 708 9393 Fax: +44 151 705 3364  
[hgmacc@liv.ac.uk](mailto:hgmacc@liv.ac.uk)

Elizabeth Paulsen  
Methodology Review Group  
Norwegian Knowledge Centre for Health Services Research  
P.O. Box 7004, St. Olavs plass  
Oslo N-0130  
Norway  
Tel: +47 46 400415 Fax: +47 46 23255010  
[elizabeth.paulsen@nokc.no](mailto:elizabeth.paulsen@nokc.no)

Catrin Tudur Smith  
Centre for Medical Statistics and Health Evaluation School  
of Health Sciences University of Liverpool  
Shelley's Cottage  
Brownlow Street  
Liverpool, L69 3GS  
UK  
Tel: +44 151 794 4059  
[cat1@liverpool.ac.uk](mailto:cat1@liverpool.ac.uk)

Georgia Salanti  
MRC Biostatistics Unit  
Institute of Public Health  
University Forvie Site,  
Robinson Way,  
Cambridge, CB2 2SR  
UK  
[Georgia.Salanti@mrc-bsu.cam.ac.uk](mailto:Georgia.Salanti@mrc-bsu.cam.ac.uk)

Rob Scholten  
Dutch Cochrane Centre  
Academic Medical Centre  
Room J1B - 108  
P.O. Box 22700  
1100 DE Amsterdam  
Netherlands  
Tel: 31 20 566 7651 Fax: +31 20 691 2683  
[r.j.scholten@amc.uva.nl](mailto:r.j.scholten@amc.uva.nl)

Ian Shemilt  
Campbell and Cochrane Economics Methods Group  
Health Economics Group  
School of Medicine  
Health Policy and Practice  
University of East Anglia  
Norwich NR4 7TJ  
UK  
Tel: +44 1603 591086 Fax: +44 1603 593752  
[i.shemilt@uea.ac.uk](mailto:i.shemilt@uea.ac.uk)

Jeff Valentine  
Department of Psychology  
Center for Research Synthesis Methodology  
University of Missouri  
McAlester Hall  
Columbia, Missouri 65211  
USA  
Tel: +1 573 8825824 Fax +1 573 8844537  
[valentinejc@missouri.edu](mailto:valentinejc@missouri.edu)

Gunn Vist  
Norwegian Knowledge Centre for Health Services Research  
P.O. Box 7004, St. Olavs plass  
Oslo N-0130  
Norway  
Tel: +47 46 400420 Fax: +47 23 255010  
[gev@nokc.no](mailto:gev@nokc.no)



## MORE INFORMATION

*The Cochrane Library*



The *Cochrane Library* is available at [www.cochranelibrary.com](http://www.cochranelibrary.com). It contains five main databases: the *Cochrane Database of Systematic Reviews* (CDSR), the *Database of Abstracts of Reviews of Effects* (DARE), the *Cochrane Central Register of Controlled Trials* (CENTRAL), the *Cochrane Database of Methodology Reviews* (CDMR), and the *Cochrane Methodology Register* (CMR). In addition, *The Cochrane Library* contains information about the Collaboration, complete contact details for all Cochrane entities, and links to the *Cochrane Handbook for Systematic Reviews of Interventions* (formerly the *Cochrane Reviewers' Handbook*) and a glossary of Cochrane and methodological terminology. Information about how to subscribe is available from:

Sarah Stevens  
Cochrane Library Customer Services Advisor  
John Wiley & Sons Ltd  
1 Oldlands Way  
Bognor Regis  
West Sussex  
PO22 9SA  
UK  
Tel: +44 1243 843355; Fax: +44 1243 843232  
[sasteven@wiley.co.uk](mailto:sasteven@wiley.co.uk)

#### Cochrane Collaboration Internet Site

A wide range of Cochrane Collaboration information is available from [www.cochrane.org](http://www.cochrane.org) including the abstracts from all the Cochrane reviews in the current issue of *The Cochrane Library*, details of Cochrane email lists, opportunities to download Cochrane software, contact details for all Cochrane entities, copies of the Cochrane Methods Groups Newsletters and much more.

#### International Cochrane email list: CCINFO

This moderated list offers an excellent means of keeping informed about the activities and policies of The Cochrane Collaboration. The list is used for announcements and discussion of matters relevant to the Collaboration as a whole. To subscribe send an email to: [ccinfo@mcmaster.ca](mailto:ccinfo@mcmaster.ca) with the message:

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Do not fill in the subject or add a signature. You will receive confirmation that you have been added to the list.

#### Cochrane Centre Internet Sites

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**Canadian Cochrane Centre**  
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**Chinese Cochrane Center**  
[www.ebm.org.cn/](http://www.ebm.org.cn/)

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[www.cochrane.nl](http://www.cochrane.nl)

**German Cochrane Centre**  
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**Italian Cochrane Centre**  
[www.cochrane.it/](http://www.cochrane.it/)

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[www.cochrane.dk](http://www.cochrane.dk)

**South African Cochrane Centre**  
[www.mrc.ac.za/cochrane](http://www.mrc.ac.za/cochrane)

**UK Cochrane Centre**  
[www.cochrane.co.uk](http://www.cochrane.co.uk)

**United States Cochrane Center**  
[www.cochrane.us](http://www.cochrane.us)



## APPENDIX

### Previous structured abstracts and commentaries

**Methods Groups Newsletter Volume 9, June 2005**  
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## CURRENT STATUS OF COCHRANE METHODOLOGY REVIEWS

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### Published reviews recently updated

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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

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### Published reviews updated in 2005

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Edwards P, et al.	Methods to increase response rates to postal questionnaires
Scherer R, et al.	Full publication of results initially presented in abstracts

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### Published reviews

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Wager E, et al.	Technical editing of research reports in biomedical journals
Demicheli V, et al.	Peer review for improving the quality of grant applications
Hopewell S, et al.	Handsearching versus electronic searching to identify reports of randomized trials
Kunz R, et al.	Randomisation to protect against selection bias in healthcare trials
Mapstone J, et al.	Strategies to improve recruitment to research studies
Vist G, et al.	Outcomes of patients who participate in randomised controlled trials compared to similar patients receiving similar interventions who do not participate

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### Reviews in progress

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Edwards P, et al.	Methods to influence the completeness of response to self-administered questionnaires
Rendell J, et al.	Incentives and disincentives to participation by clinicians in randomised controlled trials

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### Published protocols

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Gherzi 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
Clarke M, et al.	Individual patient data meta-analyses compared with meta-analyses based on aggregate data
Villanueva E, et al.	N-of-1 trials for making therapy decisions
Olsen K, et al.	Publication bias in clinical trials
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
Song F, et al.	Adjusted indirect comparison for estimating relative effects of competing healthcare interventions
Leeflang M, et al..	Search strategies to identify diagnostic accuracy studies in Medline
Moher D, et al.	When and how to update systematic reviews

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### Protocols in progress

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Djulfbegovic B, et al.	How often are new better than established treatments?
Armour T, et al.	The contribution of checking reference lists to systematic reviews

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**Registered titles**

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Gates S, et al.      Double versus single data entry for reducing data transcription errors

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**Proposed titles**

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McKenzie J, et al.      Interventions for improving the conduct and reporting of randomized controlled trials

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Summertown Pavilion  
Middle Way  
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UK

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Fax: + 44 1865 516311  
Email: [smoore@cochrane.co.uk](mailto:smoore@cochrane.co.uk)

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