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How to write a Cochrane systematic review

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SUMMARY AT A GLANCE

Summary of the methods underlying the successful Cochrane review process, including the key methods to minimize systematic bias and include all relevant trials.

ABSTRACT:

The Cochrane Collaboration is a global network whose aim is to improve health-care decision making through systematic reviews of the effects of health-care interventions. Cochrane systematic reviews are published in the Cochrane Database of Systematic Reviews within *The Cochrane Library* (http://www.thecochranelibrary.com), and regularly updated as new evidence arises. Cochrane Reviews are undertaken by teams of volunteer authors, who have access to free training resources, reference texts and software for preparing and maintaining their review. Here we aim to describe the steps involved to undertake a new or update an existing Cochrane Review.

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CLINICAL SCENARIO

You are looking after a 28-year-old woman with active proliferative lupus nephritis (classified WHO stage IV on recent renal biopsy). You want to ensure she receives the most effective treatment but have concerns about the toxicity of potential therapies such as cyclophosphamide. You perform a literature search to find the most recent published research and realize the last systematic review of therapy for proliferative lupus nephritis was published 5 years previously in The Cochrane Library.[1] Alternative treatment strategies have been suggested since then and you know of at least three recent randomized trials. Rather than assume that the most recent intervention to be trialled and published is the most promising treatment for your patient, you want to base your recommendation on the best current evidence on the benefits and harms of all the treatment options. You decide that you want to update the Cochrane systematic review but need to know how.

SYSTEMATIC REVIEWS AND THE COCHRANE COLLABORATION

A systematic review aims to find, appraise and synthesize all relevant, high-quality research evidence to answer a particular question. When appropriate, a formal quantified summary of all the trials that study a specific research question, or meta-analysis, is also performed.[2] The potential benefits of a systematic review are to reduce random error (insufficient data, also referred to as 'power'), and also to reduce systematic error (bias). In answering questions of clinical interventions, such as the effectiveness of drug therapies as in our example, a systematic review may increase power to show differences in effect, as many individual studies are too small to detect modest but potentially important treatment differences. Increased power may also magnify bias, which mandates careful evaluation of each contributing study to identify and estimate the effect (both magnitude and direction) of potential weaknesses of trial conduct and reporting. Systematic review also facilitates evaluation of the consistency of results across different trials and settings. Where similar treatment effects are observed across a wide variety of studies and settings, users of evidence can have more confidence in the robustness and transferability of results to other clinical settings. Where study results are less consistent, systematic review allows investigation of potential sources of variation by subgroup and meta-regression analysis.

The Cochrane Collaboration is an international not-for-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide. The Cochrane Collaboration was founded in 1993 and named after the British epidemiologist, Archie Cochrane. The Cochrane Collaboration produces and disseminates systematic reviews of health-care interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. The major product of the Collaboration is the Cochrane Database of Systematic Reviews, which is now published monthly (previously quarterly) as part of *The Cochrane Library* (http://www.thecochranelibrary.com). The Library is available free of charge in many countries because of the purchase of national licenses by governments, and through special provision to low-income countries. The activities of the Cochrane Collaboration are directed by an elected Steering Group and are supported by staff in Cochrane Groups (Centres, Review Groups, Methods Groups, Fields/Networks, Cochrane Editorial Unit) around the world. Review production is coordinated by Cochrane Review Groups located around the globe, and each is responsible for a specialty area of health care. The Cochrane Renal Group is based at the Children's Hospital at Westmead, in New South Wales, Australia. Those who prepare reviews are mostly health-care professionals who volunteer to work with one of the many Cochrane Review Groups whose editorial teams oversee the preparation and maintenance of the reviews. The Review Group editorial teams also ensure that the rigorous quality standards for which Cochrane Reviews have become recognized are consistently applied. The Editor in Chief of *The Cochrane Library* is responsible for overseeing the work of Review Groups and ensuring consistent and acceptable quality of editorial processes and output.

Although other individuals, groups and organizations also produce systematic reviews, there are many advantages in performing a systematic review with the Cochrane Collaboration. The Cochrane Collaboration concentrates on producing systematic reviews of interventions and also of diagnostic test accuracy, but does not currently produce reviews on questions of prognosis or aetiology. The Cochrane Collaboration's core principles include fostering good communication, open decision-making and teamwork, reducing barriers to contributing, and encouraging diversity. All review authors have access to support and training, both online and face-to-face in free workshops, run around the globe several times per year. In addition, it is also possible to organize 1–2 week intensive visits to Cochrane centres or groups. The Cochrane Collaboration provides a free online handbook of systematic review methodology, and also makes available meta-analytical software, called Review Manager or RevMan (http://www2.cochrane.org/software/revman.htm). The Cochrane framework also benefits the user of reviews; there is evidence that Cochrane Reviews are better quality than many other reviews[3,4] and the Cochrane Database of Systematic reviews has a journal impact factor, which is currently 5.653 (Journal Citation Reports). Cochrane Reviews reach a large international audience and have had a real and significant impact on practice, policy decisions and research around the world. Examples of Cochrane Renal Group systematic reviews impacting on the field of Nephrology are present in many clinical guidelines, most recently in the KDIGO guide-

lines on care of the transplant patient and on chronic kidney disease mineral and bone disorder (http://www.kdigo.org/clinical_practice_guidelines). Globally, a search of *The Cochrane Library* is performed every second, an abstract viewed every two seconds and the full text of a review viewed every three seconds.

In this paper we describe how to become a Cochrane author, by outlining the basic steps involved in updating an existing review or undertaking a new Cochrane systematic review of a drug intervention

Step 1: Formulate a clinical question, register your interest and assemble a review team

Cochrane Reviews seek to answer questions that cause clinicians and consumers dilemmas. A good review question addresses a clinical problem for which there is uncertainty about the effects about interventions, and which is commonly associated with variation in practice. In this way, a review might clarify the strengths and weaknesses of current literature of smaller studies to answer a particular question, or might summarize a large, confusing and diverse literature where the volume of studies is otherwise overwhelming. The first step in performing or updating a Cochrane systematic review is to get in contact with the relevant Cochrane Review Group editorial base. For reviews and updates on topics in Nephrology and kidney transplantation, the relevant review group is the Cochrane Renal Group. Corresponding with the editorial group will assist you in formulating your idea into a well-framed question and review title that doesn't overlap with any other existing authors' work. In our example, the original review was published some time ago, and needs to be updated to include all new evidence that has arisen since the original review was published. In this situation the job of the editorial base is to liaise with the original review authors, and coordinate communication and resources for the update. The original title would be retained 'treatment of lupus nephritis', along with its objective 'to assess the benefits and harms of different treatments available for biopsy-proven proliferative lupus nephritis'.

A systematic review requires a considerable investment of time and energy, and as with any other research project, requires a research team, with each member fulfilling one or more roles. Ideally, a review team should include expertise in the topic content area and expertise in systematic review methodology. The lead author will typically do the review 'leg work' and coordinate the team's efforts. Each review also needs a second author to duplicate and verify key systematic review steps independently and to minimize potential person-error. Steps that require duplication include study selection, data extraction and data analysis. First-time authors are encouraged to work with others more experienced in the process of systematic reviews. A common way for more inexperienced review enthusiasts to start out is to act as a 'second author' on a review or update, to gain understanding of the complexity and process of a systematic review, before undertaking a review as lead author. In our example, a good way to include expertise in both the topic and the methodology would be to invite some or all of the original review authors onto the update team. An outline of steps involved and an approximate time-line are given in (Fig. 1).

Step 2: Write or update the protocol for your systematic review

As with any other research undertaking, once the research team is assembled, the second step is to draft a clear and transparent protocol detailing your research plan. The publication of protocols for Cochrane Reviews in the Cochrane Database of Systematic Reviews (CDSR) before publication of the full Cochrane review aims to reduce the impact of authors' biases, promote transparency of methods and processes, reduce the potential for duplication, and allow peer review of the planned methods. Many judgements are made by review authors during the review process, and a detailed protocol means these judgements are defined *a priori*, and not influenced by the findings of the studies included in the review, as decisions made when the impact on the results of a study are known, such as excluding selected studies from a systematic review, are likely to introduce bias.[5]

Cochrane review authors have access to a wide variety of additional training resources. First-time authors are encouraged to attend a face-to-face training workshop; these are run by Cochrane Review Groups and are free, and held over 2 days several times a year in Australia and New Zealand, as well as in other regions of the Asia pacific (see http://www.cochrane.org/events/w-shops/w-shops-asia). For those unable to attend in person, there are online training resources that can be accessed from the Collaboration website. Cochrane protocols for reviews, and the reviews themselves, are prepared in the Cochrane Collaboration's Review Manager (RevMan) software and have a uniform format. RevMan software can be downloaded and installed from the Cochrane renal group website (http://www.cochrane-renal.org), which incorporates the reviewer's handbook, RevMan user guide and Cochrane Collaboration 'style guide'. These guides explain the review process, how to use RevMan and style conventions for a Cochrane review, and include training exercises.

Once complete, the draft protocol for a new review is formally submitted to the editorial office, and sent for peer review. Once the protocol is amended in response to referees' comments, the protocol is copy-edited and published in the next monthly issue of Cochrane Database of Systematic Reviews in *The Cochrane Library.* For a review update, as in our example, an update to the original protocol may not be necessary, but there may be occasions when in addition to re-executing the search, an update to a review also involves

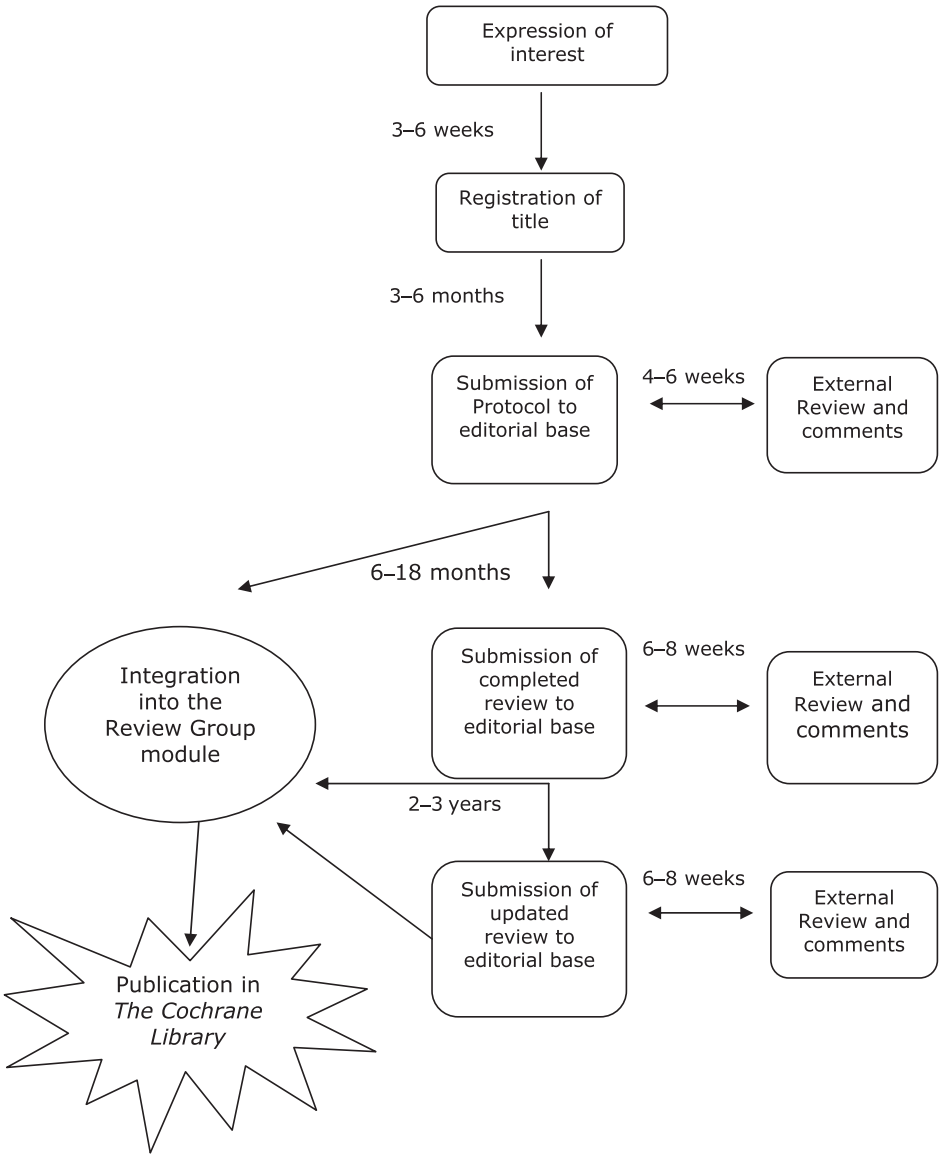


Fig. 1 Steps involved and approximate time-line in undertaking a new Cochrane systematic review of an intervention.

a change to the review question. This might entail an alteration to the literature search strategy, the study selection criteria, or other aspects such as addition of a new outcome or comparison, or adding a newly specified subgroup analysis following revised methods for categorizing or classifying the condition.

In our example of treatment for lupus nephritis, evolving technology has led to new drug therapies and so to new drug regimen comparisons not addressed in the original review. The original review looked at treatment comparisons involving steroids (intravenous and oral), cyclophosphamide, azathioprine, cyclosporine, mycophenolic acid, plasma exchange, misoprostol and intravenous gamma globulin. A review update will need to include all newer therapeutic options, such as regimens involving rituximab. As a consequence of this change in scope, best practice for update authors is to re-write the protocol to detail the specific questions to be answered in the update, namely: Do immunosuppressive agents other than cyclophosphamide provide similar or superior benefit to therapy in both paediatric and adult patients with biopsy proven lupus nephritis? If so, which agent, what dose, route of administration and duration of therapy is best and what toxicities occur with each therapy?

A review protocol also details explicit criteria for deciding which studies are included (*randomized controlled trials*) and excluded (*not randomized, or patients without biopsy proven lupus nephritis*), and the sources and search methods used to find the relevant studies. All Cochrane Reviews include critical appraisal of the methodological quality of the studies (see

Table 1 Risk of bias assessment is a key step in Cochrane Reviews, as critical appraisal of trial methods can establish possible sources of bias that need to be considered when interpreting trial results

	Risk of bias		
	YES (low risk of bias)	NO (high risk of bias)	UNCLEAR
Adequate sequence generation?	A random component in the sequence generation phase is described *e.g.* computer random number generator, shuffling cards	A non-random component in sequence generation is described *e.g.* sequence generated by date of birth or clinic record number	Insufficient information
Adequate allocation concealment?	Participants and investigators cannot foresee assignment *e.g.* central allocation (telephone, web-based, sequentially numbered drug containers of similar appearance, opaque, sealed envelopes)	Can possibly foresee assignment *e.g.* allocation using envelopes that are not sealed or opaque, DOB, case record no.	Insufficient information
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Measures are described to blind study participants (subjective outcomes) and personnel (objective outcomes) from knowledge of which intervention a participant received ***or*** no blinding but authors deem that outcomes measured unlikely to be influenced.	No or incomplete blinding and outcomes measured likely to be influenced by lack of blinding.	Insufficient information/ study did not address this outcome
Incomplete data outcome addressed?	The participants included in the analysis are exactly those randomised into the trial.	The numbers randomised into each intervention group are not clearly reported	Insufficient information
Free of selective reporting?	Study protocol available and all of the study's pre-specified outcomes reported in a pre-specified way	Not all of the study's pre-specified primary outcomes have been reported adequately	Insufficient information
Free of other bias?	*e.g.* trial not received funding from Pharmaceutical industry.	Trial stopped early due to some independent process	Insufficient information

Table 1 for more details) and appropriate methods (qualitative or quantitative, as in meta-analysis) for combining the review findings. Review updates need to incorporate any changes or improvements to systematic review methodology that have arisen since the publication of the original review. When updating an existing review, in general the amended protocol is not re-published, but minor changes and additions to the protocol are marked explicitly in the 'Differences between protocol and review' section and the 'What's new' table of the updated version of the review, so the changes are transparent and clear.

Step 3: Search for evidence, critically appraise and extract data from included studies

Once the review or update protocol is established, the hard work begins for the lead and second authors in particular. The next step involves searching for and identifying all relevant studies in the published and unpublished biomedical literature that might answer the review question. Liaison with the Cochrane Renal Group's Trials Search Coordinators will help to develop appropriate new search terms and execute appropriate search strategies for the review update, which typically involves searching multiple databases. Cochrane Reviews do not limit searches by language, year or publication status, as limiting reviews to English language and excluding non-published studies are known to produce bias in review results.[5–9] The Cochrane Central Register of Controlled Trials (CENTRAL) was formed in the 90s, when the Cochrane Collaboration checked titles and abstracts of almost 300 000 MEDLINE and EMBASE records to look for clinical controlled trials. CENTRAL now includes over 500 000 records and is the best single source of randomized trial reports for inclusion in systematic reviews. The Cochrane Renal Group maintains a specialized register of reports of randomized trials in nephrology and kidney transplantation, which is periodically used to update the CENTRAL database (Fig. 2). In addition to MEDLINE, EMBASE and other database records, the specialized register includes the results of hand-searching through conference proceedings to identify reports of randomized trials presented at scientific meetings. This specialized register is organized by study, collecting all conference reports and journal articles arising from a single trial under one label, which can save review authors considerable time in reviewing and sorting search results. The Cochrane Renal Group's Trials Search Coordinators will automatically include this database in a search for a new review. For a review update, searching the specialized register may be all that is necessary, as the register is continually updated with records from MEDLINE and EMBASE. One of the benefits of performing a Cochrane systematic review is an easier, timely and more comprehensive literature search, as authors have direct access to these resources.

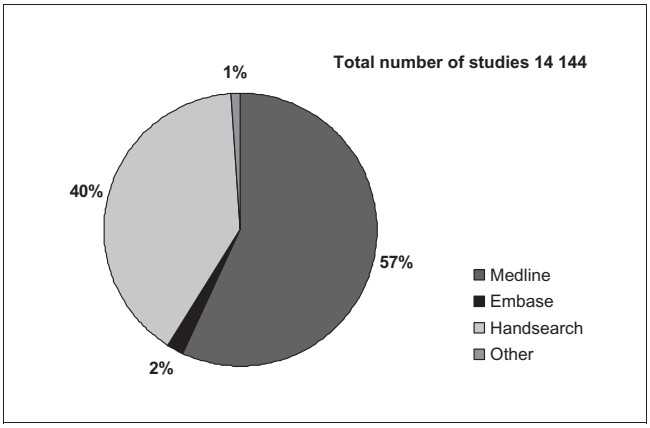


Fig. 2 Source of randomized trials in the Specialist Register of the Cochrane Renal Group (as at January 2010). In building the Specialised Register for the Cochrane Renal Group, databases are searched sequentially, starting with Medline. Hand-searching records are entered by creating an electronic record once relevant reports are identified from searching the pages of conference reports and abstract books. The Register is study based, so all conference and journal reports of a randomized trial are grouped and organized under one trial label.

Typically, a sensitive search will produce a large number of results, aiming to find all new evidence, but at the cost of also identifying some citations that are not relevant. In our example, the Cochrane Renal Group will provide an updated search covering the period from January 2003 (the date of the last search in the original review) until the present day. Update authors then work through search results to identify reports of trials relevant for inclusion in the systematic review, and discard those not relevant. To minimize human error, first and second authors work independently to finalize the citations they want to include, and then discuss and resolve any differences.

Once citations for inclusion have been finalized, reviewers critically appraise each study and abstract relevant data using a standardized form. Data collection aims to gather key trial descriptors, methods and results, so review authors work independently to note the *research question, type of study, intervention and comparison (including dose and duration of therapy), methods and source of potential bias, participants, eligibility, interventions, types of outcome measured* and *results* and then meet to discuss discrepancies.[2] Where differences of opinion arise it is usual to involve a third author to arbitrate. Methodological quality appraisal is key to the review process, as it helps determine systematic error or deviation from the truth in results or inferences which may lead to under or overestimation of the true intervention effect. The extent to which a Cochrane Review can draw conclusions about the effects of an intervention depends on whether the data from the included studies are valid or biased. The Cochrane Handbook contains criteria and guidance for judging risk of bias which are simply presented and illustrated (see Table 1).

Step 4: Data synthesis and presentation: meta-analysis and forest plots

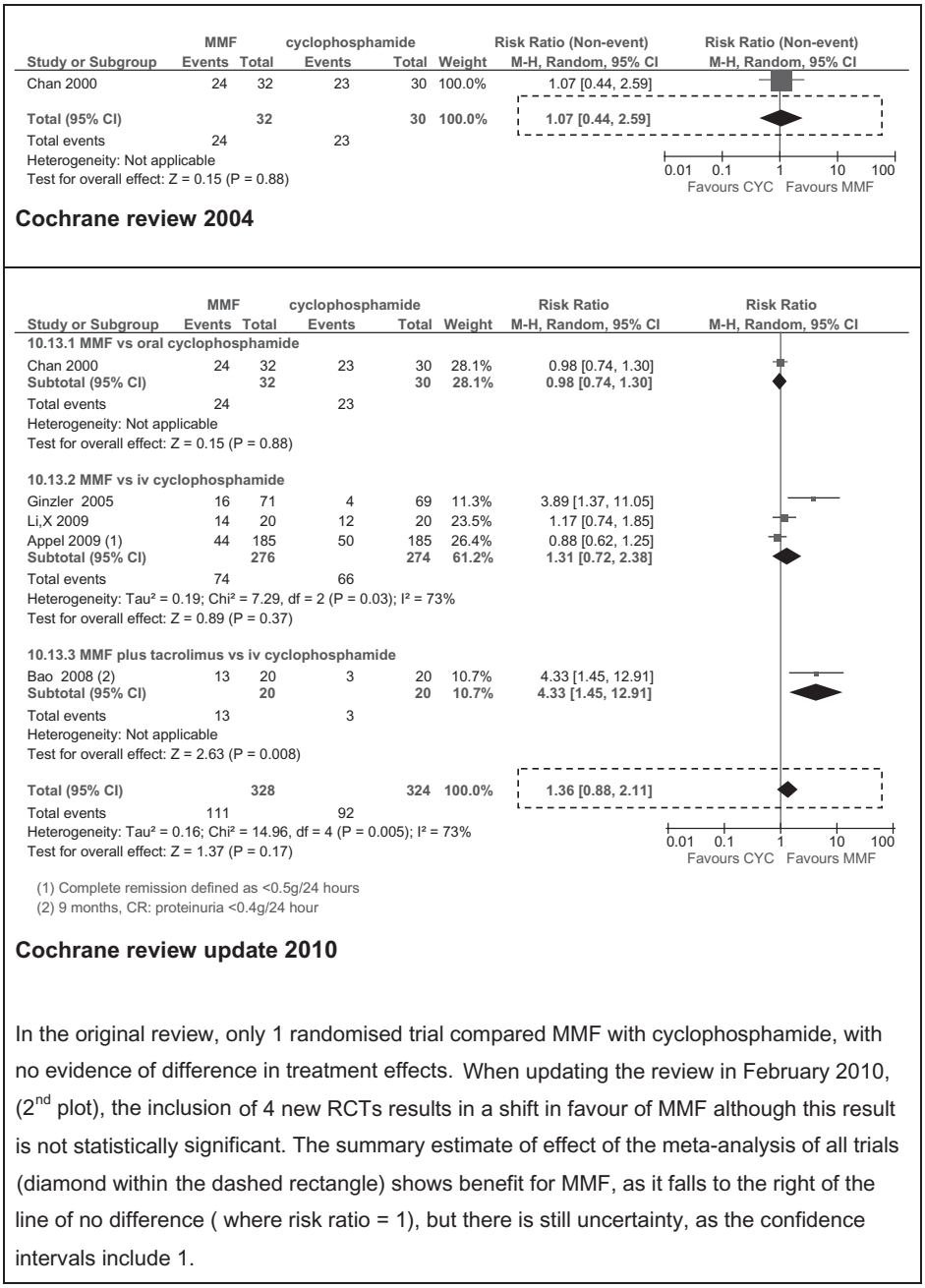
The data and analysis section of a Cochrane Review starts with a brief description of trials, with detail in tabular format. Where trials are sufficiently similar results may be pooled in meta-analysis. Meta-analysis quantifies treatment effects and their uncertainty and has a number of benefits, thus allowing assessment of the consistency of results and improving the precision of estimates. However meta-analysis is not always feasible if studies are clinically heterogeneous, and use different methods, study populations, interventions or outcomes.

RevMan simplifies the process of data analysis by allowing authors to add study data and references and build tables showing characteristics and comparisons. Meta-analytical statistics are automatically calculated where data have been added in standardized format, and forest plots are generated, to give graphical representation of results. Analysis is supported by practical help files within Revman, and extended sections of the Cochrane Handbook, and the Cochrane Review Group can also give advice. Figure 3 shows an example of a forest plot from the lupus review update where the number of studies comparing mycophenolate mofetil (MMF) with cyclophophamide increased from one in 2004 to five in 2010. Although there is now more evidence that favours MMF over cyclophosphamide in achieving remission in proteinuria in the updated review (where there had been no difference between the two interventions in the earlier 2004 review), even with the update, the evidence is insufficient to show a statistically significant difference.

Where meta-analysis has shown heterogeneity among trial results, additional analyses are undertaken to try to explain the differences in findings. Sensitivity analyses examine the difference that trials with weaker methodology make to summary estimates of effect. Additionally, subgroup analyses can be helpful to show differences or similarities among results of trials that have common features, for example by stratifying trials by duration of therapy, or by patient subgroup. Revman software also has the ability to investigate possible bias with 'funnel plots'. A funnel plot is a graphical presentation that compares effect size and size of trial. A source of bias known to cause asymmetry in funnel plots is publication bias, which is the preferential publishing of trials showing beneficial effect of an intervention. An example of a funnel plot for the Lupus review update is shown in Figure 4.

Step 5: Interpret and present results and write the review

The final stage of systematic review is to summarize results, and draw conclusions that will assist and improve clinical decision-making. In a Cochrane Review, most of the information is collated automatically by Revman in a standard-



In the original review, only 1 randomised trial compared MMF with cyclophosphamide, with no evidence of difference in treatment effects. When updating the review in February 2010, (2nd plot), the inclusion of 4 new RCTs results in a shift in favour of MMF although this result is not statistically significant. The summary estimate of effect of the meta-analysis of all trials (diamond within the dashed rectangle) shows benefit for MMF, as it falls to the right of the line of no difference (where risk ratio = 1), but there is still uncertainty, as the confidence intervals include 1.

Fig. 3 Forest plot, comparing mycophenolate mofetil *versus* cyclophosphamide for the treatment of Lupus nephritis, for the outcome of complete remission in proteinuria. The top plot is from the original 2004 Cochrane Review, and the lower plot shows results from the updated Cochrane Review in 2010. CYC, cyclophosphamide; MMF, mycophenolate mofetil (MMF); RCT, randomized controlled trial.

ized way. Authors draft text to summarize findings. In the discussion section, Cochrane Reviews use standard subheadings, to make review conclusions more accessible. In our example, under 'implications for practice' the review update might conclude that MMF is as effective in achieving complete remission of proteinuria in lupus nephritis and could be considered as an alternative (but not superior) treatment to cyclophosphamide (Fig. 3).

In some reviews the number of studies, their heterogeneity and quality may make firm treatment recommendations difficult, but the gaps in evidence much clearer. In this situation, when considering implications for research, review authors should suggest a future research agenda. In our lupus update example, although many new large studies were identified, there was considerable heterogeneity amongst interventions and comparators. In this situation

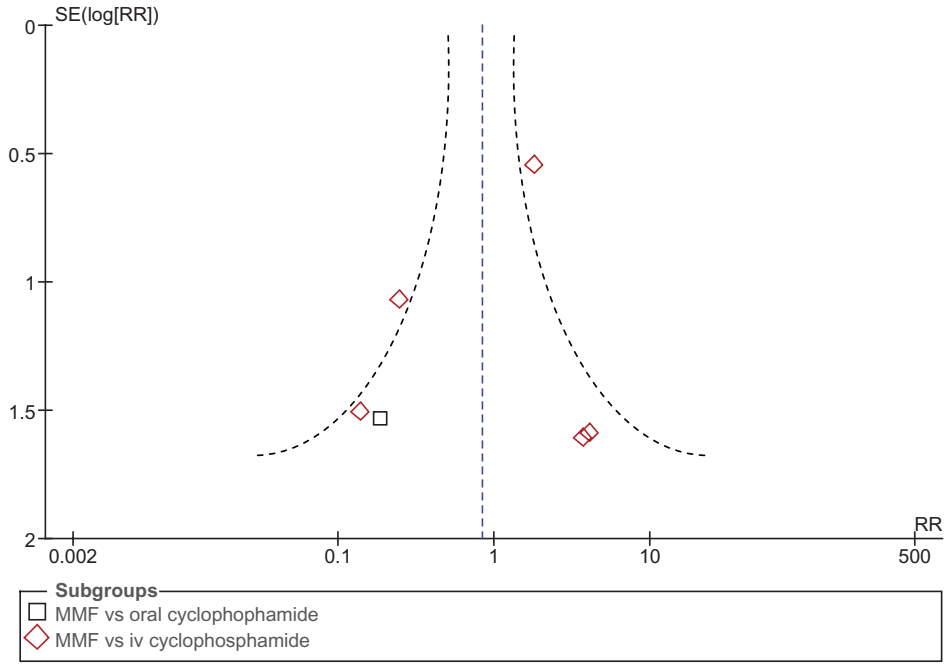


Fig. 4 Funnel plot from the updated treatment of lupus nephritis Cochrane Review. This plot shows trials comparing mycophenolate mofetil *versus* cyclophosphamide for the outcome of mortality.
The precision of an estimated intervention effect increases as the size of study increases. Effect estimates from small studies scatter more widely at the bottom of a graph, but the spread is narrower with larger studies. In the absence of bias, the plot should resemble a symmetrical 'inverted' funnel with points distributed evenly on either side of the summary estimate. Asymmetry suggests some trials may be missing, as a result of publication or other bias. MMF, mycophenolate mofetil.

authors might suggest a more strategic or collaborative approach to future trial designs to enable better comparison of treatment options.

The final stage of a Cochrane Review is to submit a draft to the Editorial base, where it will undergo a formal peer review process by external referees. Once referee comments have been addressed and satisfied, and the final approved by the Editorial Team, the review is copy-edited and published in the Cochrane Database of Systematic reviews, as part of the Cochrane Library.

Want to know more? *If you are interested in undertaking a review yourself, then to learn more, visit http://www.cochrane-renal.org, http://www.cochrane-handbook.org and http://www2.cochrane.org/docs/newcomersguide.htm*

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