

COCHRANE RENAL GROUP

A REVIEW GROUP OF THE COCHRANE COLLABORATION

How to Write a Protocol

This booklet has been produced to make the whole process of preparing a protocol as painless as possible. The editorial base has developed guidelines that detail each section of the protocol and what should be included. These guidelines are a distillation of the *Cochrane Handbook for Systematic Reviews of Interventions*, review group policies and recommendations from the Renal Group Editorial Team.

There are several sections of this booklet.

- Getting started
- Creating a protocol
- Renal Group guidelines
- Editorial process
- Checklist for protocol submission

Cochrane Renal Group Editorial Team



Based at:

the children's hospital at Westmead

Endorsements: Asia-Pacific Society of Nephrology, Australian and New Zealand Society of Nephrology, International Pediatric Nephrology Association, International Society of Nephrology, Kidney Health Australia, National Kidney Foundation

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Getting started

Now that your title has been registered there are several files you will need. All are available at www.cochrane.org and www.cc-ims.net. If you have problems downloading these files please contact the Review Group Coordinator. You should also have received an email notifying you that a user account has now been set up for you in Archie. Once you have activated this account you can check out your review.

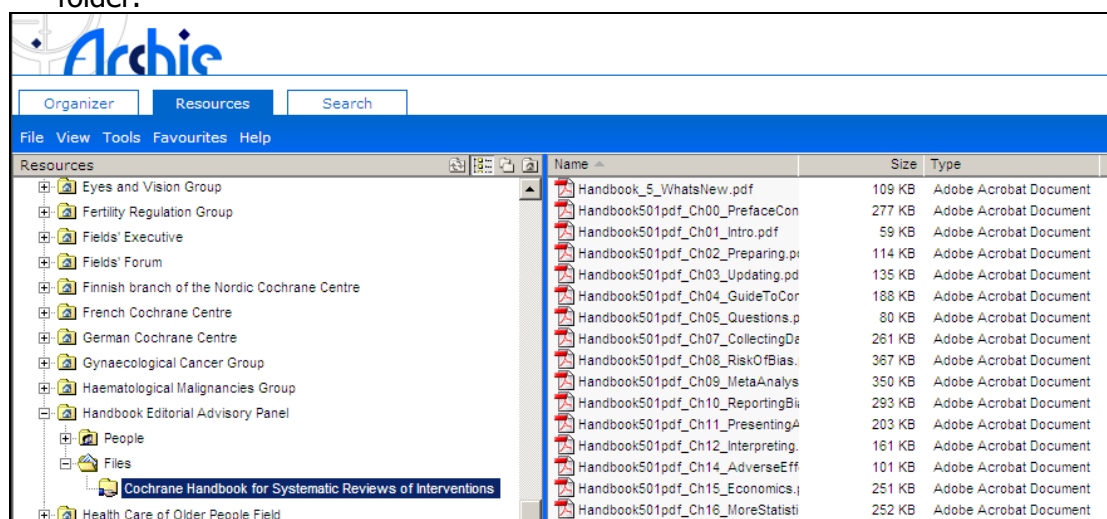
1) RevMan 5.0

This is the program which you must use to write your protocol and later your review. <http://ims.cochrane.org/revman>

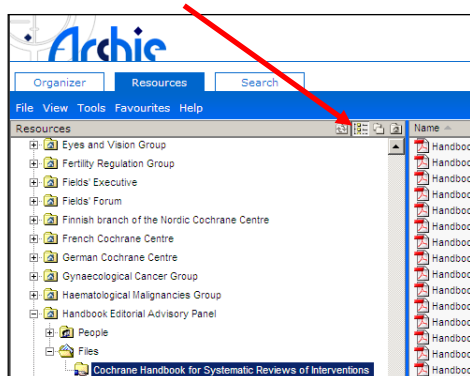
2) Cochrane Handbook for Systematic Reviews of Interventions

This explains the Review process (and parts have been summarised in this document). The handbook is incorporated in the RevMan 5 software and also available at <http://www.cochrane-handbook.org>. A PDF version is available in Archie. To access these files

- Log on to Archie (www.archie.cochrane.org)
- Under the resources tab locate the "Handbook Editorial Advisory Panel" Files folder.



- Right click on the Handbook chapter and select DOWNLOAD
- Select save and then save the file to you local computer.
- If you cannot see the Handbook Editorial Advisory Panel folder make sure you have selected "Show all entities" on the resources toolbar



3) RevMan 5 user guide

This guide explains how to use RevMan. It is a PDF within RevMan 5.

4) RevMan style guide

This guide explains the style conventions for a Cochrane review.

<http://www.cochrane.org/style/home.htm>

5) RevMan 5 tutorial

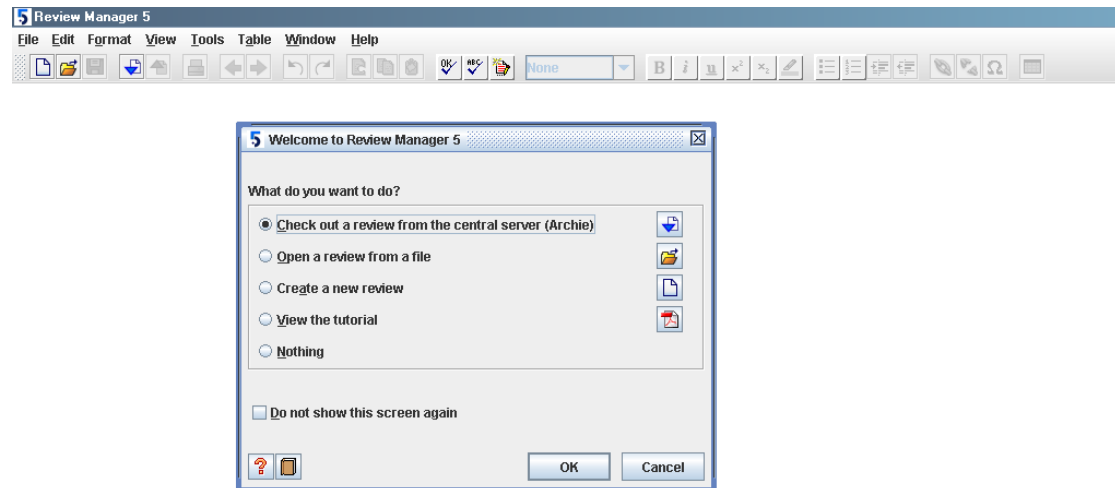
This tutorial is designed to give Cochrane review authors an introduction to the process of writing a Cochrane systematic review of a healthcare intervention using RevMan. It is available as a PDF within RevMan 5.

Checking out a review from Archie

Archie is the Cochrane Collaboration's Central server for managing documents and contact details.

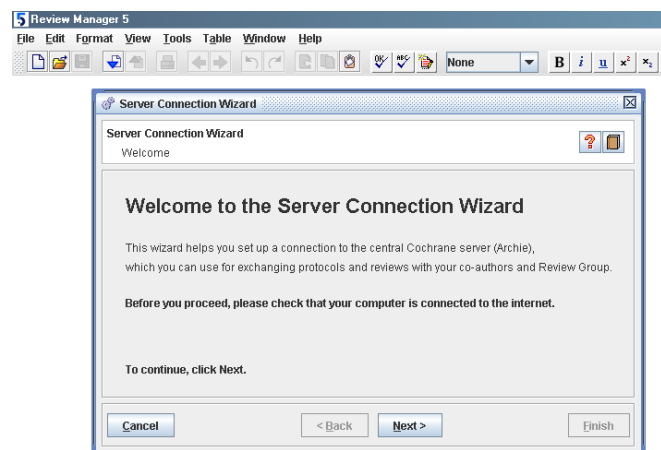
Don't forget, you must activate your user account before attempting to check out your review from Archie (see Appendix 6 for quick tips).

This is the opening screen in RevMan 5

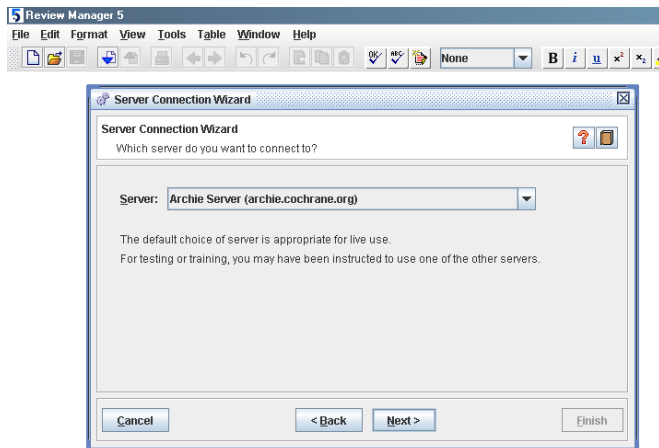


Check – *Check out review from the central server (Archie)*
Click - *OK*

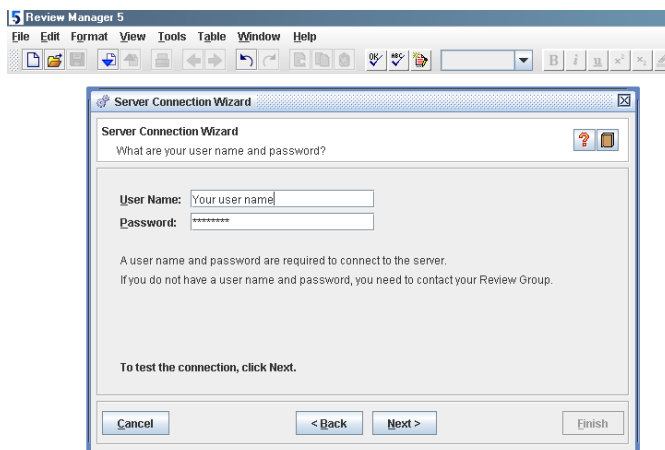
When you open for the first time the following Welcome screen will pop up.



Click - *Next*

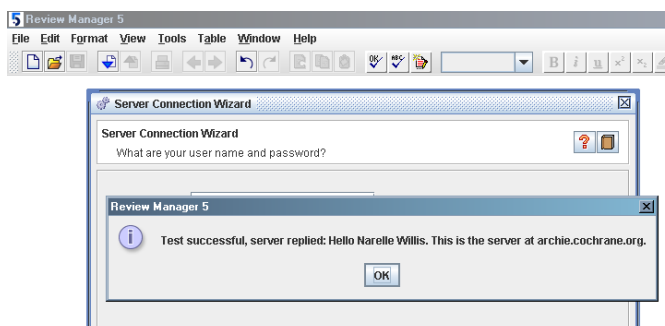


Select server – *Archie Server (archie.cochrane.org)*
Click - *OK*



Type – your User Name (should be your email address) and your password.
The program will now check your connection to the server.
Click – *Next*

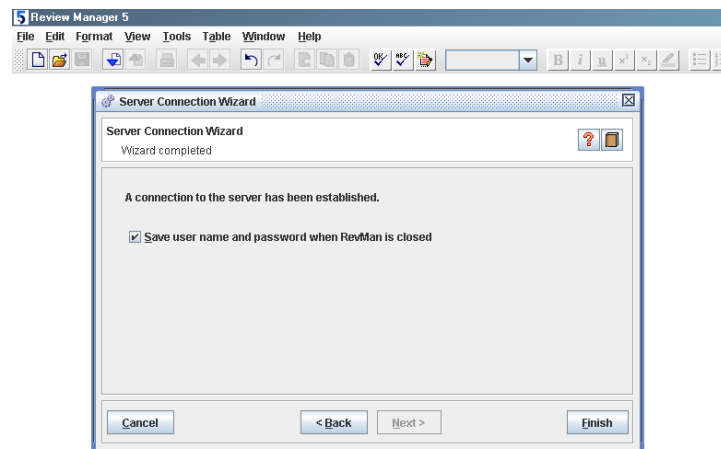
If RevMan 5 is able to access the server the following message will be seen



If not, please check

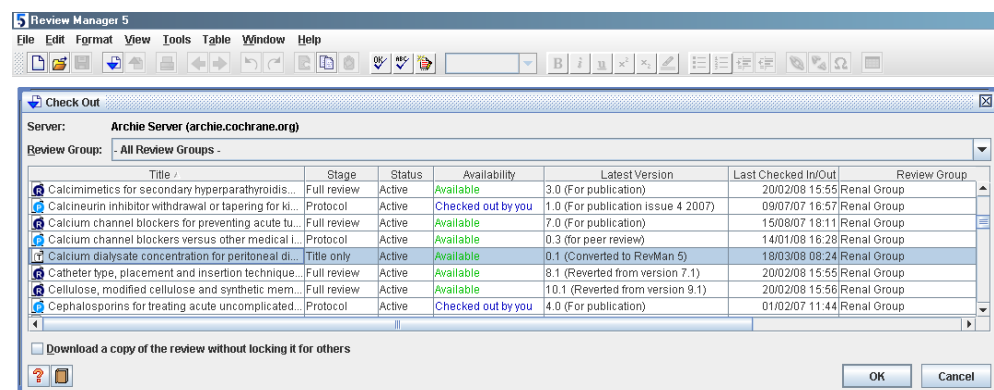
- you are connected to the internet,
- your user name and password has been entered correctly

If there is still a problem please check with your network administrator. The following technical guide for IT administrators may assist <http://www.ccs-ims.net/RevMan/RevMan5/RevMan5-installation-and-connection.pdf>.

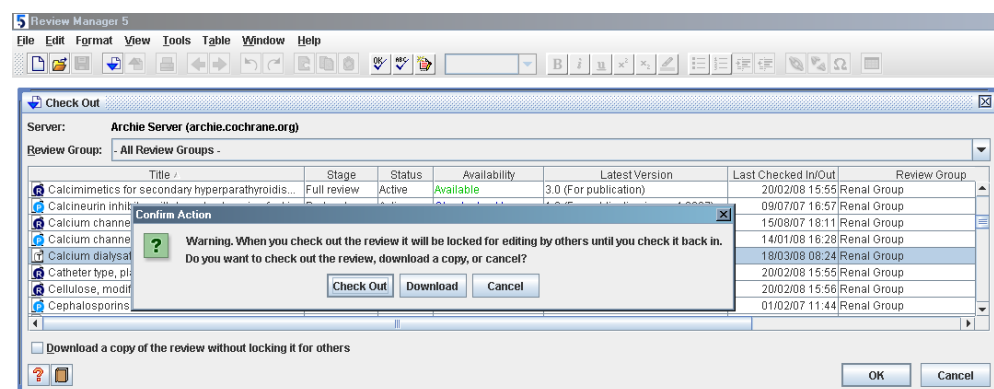


Check – *Save user name and password when RevMan is closed*
 Click – *Finish*

A modified version of this screen will appear (depending on how many reviews you are an author for).

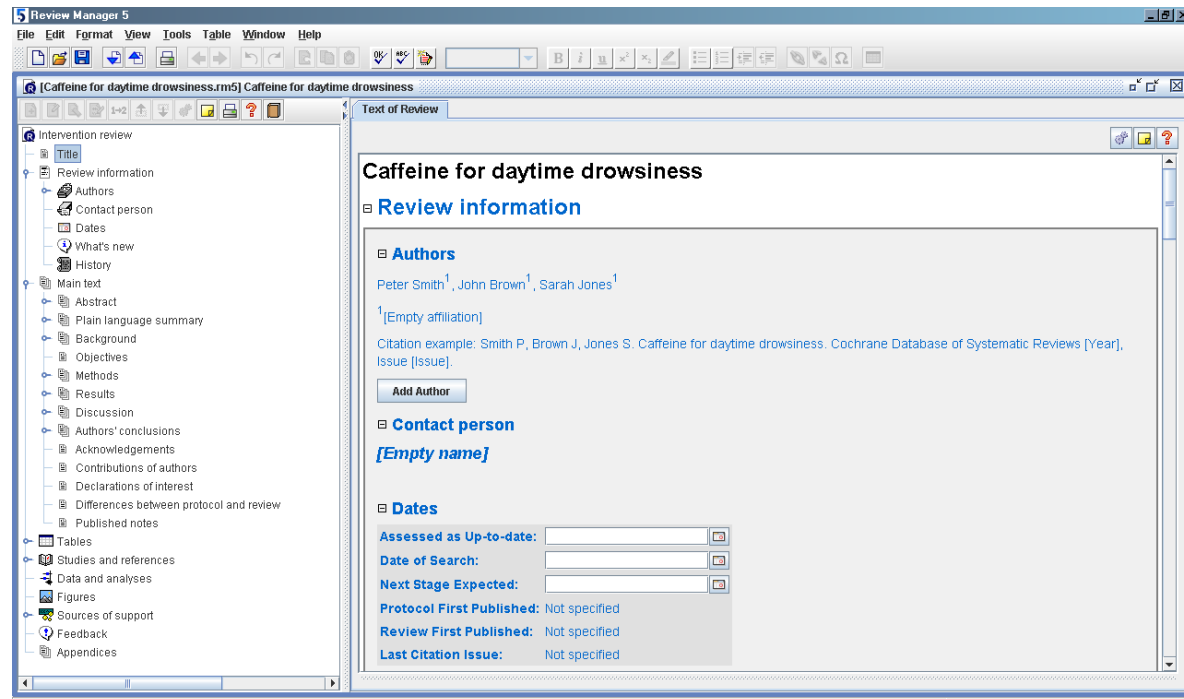


Click on the review title and Click – *OK*



Choose – *Check Out*

Below is the example from the RevMan 5 tutorial – WE STRONGLY RECOMMEND YOU WORK THROUGH THIS TUTORIAL BEFORE WORKING ON YOUR REVIEW.



Review information

The review information cover sheet includes the following information:

Title: Title as agreed upon by the Renal Group

Authors: Author by-line as it will appear in the published review.

Contact author: The person who is the contact person for this review.

Dates: Dates which will be published with the review. These dates include;

Assessed as Up-to-date:

Date of Search:

Next Stage Expected:

Protocol First Published:

Review First Published:

Last Citation Issue:

What's New: Describes the changes to the review or protocol since it was last published.

History: This is the audit trail for the review. "What's New" events that do not relate to the current version of the review should be listed in the History.

PLEASE NOTE

Only the sections required for a protocol are listed below.

Most of the sections have been completed for you, instructions can be found within the protocol.

Renal Group protocol guidelines

Background

The background should support the need for the systematic review by providing sufficient information on the frequency and severity of the clinical problem and the uncertainties in its management. RevMan 5 provides the following fixed headings:

- Description of the condition
- Description of the intervention
- How the intervention might work
- Why it is important to do this review

As a general rule the background should be kept to 1- 1.5 pages and should include 1-2 paragraphs for each heading.

Objectives

- A well formulated objective should be specified in terms of the interventions, the population with the clinical problem and the outcomes.
- In the renal group we have broad inclusion criteria but we separate studies at the analysis stage.
- The objective should be sufficiently broad to allow for variations in the interventions (different drugs, different doses of the same drug, different durations of the same drug) and populations (different age groups, different sexes) unless there are good reasons not to do so. Defining how broad or how narrow a review should be can be difficult. A narrow review is easier for the author but is less useful for the reader. Generally there should be only one clinical problem but in the renal group we try to be as broad as we can for populations, interventions and outcomes. This is mainly because we want to provide as much assistance to the decision making of health care providers and consumers as we can. Limiting a review to one intervention when there are many, possible means that many different places have to be searched to obtain all of the information, and study data becomes duplicated in many reviews. In renal medicine, there are usually only a small number of studies on any one intervention and so a "lumping" approach is usually feasible. Having a range of populations and interventions means that variations in treatment effects can also be explored which makes application of the review results to clinical practice easier.
- All clinically relevant outcomes both beneficial and harmful should be included.

Methods

To reduce errors, two authors should carry out each step of the review. Simple differences should be resolved in discussion but more substantial and unresolved differences should be resolved in discussion with a third author.

Criteria for considering studies for this review

Types of studies

- In the Renal group (as in most groups) we only include randomised controlled trials (RCTs) and quasi-RCTs, because they provide unconfounded comparisons of the effects of an intervention.
- A RCT uses a truly random sequence generation such as computer-generated or a random number table.
- In quasi- RCT (or pseudo RCT), the allocation process is known to all so that the physician or subject could influence the treatment group to which the subject is allocated. Examples of quasi-RCTs are where patients are allocated to groups according to odd and even medical record numbers, days of the week or month/year of birth.

Types of participants

- The disease or condition of interest should be described here, including any restrictions such as diagnoses, age groups and settings.

Types of interventions

- In general a systematic review is of more value to a user if all interventions for the clinical problem are included. In general all possible interventions available for the clinical problem should be included unless this is not feasible.
- Just because all interventions are included in a review does not mean that they will be pooled to achieve a (potentially) meaningless summary effect measure.

Types of outcome measures

- The outcomes to be considered should be those that are of clinical relevance and of relevance to the patient. Surrogate outcomes, which measure a change in a laboratory measurement (e.g. protein excretion), are less valuable than a clinical outcome (e.g. requiring dialysis for end stage renal failure) even if the surrogate is believed to be a marker for the clinical outcome. Clinical outcomes such as survival tend to be those considered most important by investigators. They may however not capture all the outcomes considered important by the patient. For example interventions that improve patient survival, may result in adverse reactions that the patient may consider so detrimental to their quality of life that they may prefer not to have the intervention. One way to construct this list of benefits and harms is to consider yourself as the patient and think of all of the outcomes that would matter to you. You can then add the biochemical markers if you like. Remember that timing of outcomes also needs

to be considered. Long term outcomes are generally going to be more important for patients even though they are more difficult for trialists to obtain.

- The outcomes included should include all effects of the intervention - both the benefits and harms.

Search methods for identification of studies

- The aim of the search strategy is to locate all relevant studies. The strategy used by the Cochrane Renal Group for searching MEDLINE and EMBASE can be seen in Appendix 1 and 2. However neither database provides a complete list of published studies and, of course, they do not include studies that were never published.
- We have a clean and comprehensive register of nephrology studies. Once your title has been registered, our Trials Search Coordinators (ruthm4@chw.edu.au or gailh2@chw.edu.au) will work with you to develop your search strategy.

The biases that result from an incomplete literature search are publication bias, duplication bias, location bias and language bias.

- Publication bias: A study in which the experimental intervention proves to be no more effective than the control intervention is less likely to be published. Failure to locate such studies and include them in a systematic review could result in the summary estimate of effect overestimating the true effect of an intervention due to publication bias. Hand-searching conference proceedings and reference lists of textbooks and previous studies and contacting experts in the field may help to identify unpublished studies. A graphical test that can be used to detect publication bias if large numbers of studies are available is described later in the "Methods of the Review" section.
- Duplication bias: Many studies are published more than once under the same or different authors and may include different amounts of data, especially if initial reports do not cover the entire period of follow-up. Where there are multiple reports of the same trial, with different data sets included in each publication, you may need to extract data from several different publications to obtain all the outcomes. It is important to specify in the protocol how duplicate publication will be dealt with.
- Location bias: New or exciting results with large treatment effects are more likely to be published in major journals. Results deemed to be less interesting may be published in second line or local journals that may not be indexed in the major databases.
- Language bias: Failure to search for and include studies published in a language other than English can result in language bias.

Data collection and analysis

Selection of studies

At least two authors should screen the potential titles and abstracts. This is one of the most critical steps particularly when there are large numbers of potential

studies. Documentation is important and there are several reference management software packages available which will assist you with this. The Trials Search Coordinator can send you a file that can be imported directly into the reference management software. Software can be discussed directly with the Trials Search Coordinator.

Data extraction and management

The method used to extract or obtain data from published reports or from the original researchers should be stated (e.g. using a data collection form). Each author should extract data on to a standard data collection form. A specimen data extraction form is shown in Appendix 4.

Assessment of risk of bias in included studies

Often we assume that all studies are equally valid (accurate), but this is not the case. Some studies are better than others. Assessing the risk of bias is necessary because bias can affect the results of a study. Because we want our systematic reviews to limit bias we need to carefully analyze the individual studies included in each review. Studies with high risks of bias tend to overestimate the benefits of interventions (Moher 1998). Important domains are allocation concealment, blinding (of investigators, subjects and those assessing outcomes), intention-to-treat analysis and completeness of follow-up.

Studies with inadequate allocation concealment tend to overestimate the effectiveness of the intervention by 30% to 40% while studies, that are not double-blinded, tend to overestimate effectiveness by 17% (Schulz 1995). Unblinded outcome assessment has been shown to overestimate efficacy by 35% (Juni 1999). Intention-to-treat analysis and loss to follow-up seem to be less important in contributing to bias.

Allocation concealment: It is important to determine if the random allocation of a subject to an intervention group in a study could be influenced by the investigator (or subject) resulting in biased selection of subjects to one group or the other. This is prevented if there is no way of knowing what the next subject is going to get, and is called "adequate allocation concealment". If the investigator is aware or could be aware of the intervention group to which the subject could be assigned, it is possible for that knowledge to influence the intervention the subject receives. This is obviously the situation in quasi-RCTs. It may be less obvious in RCTs but may occur if allocation is simply using sealed but non-opaque envelopes. If the investigator preferred one intervention over another, they might decide not to enter their patient into the study at that time but wait until an envelope containing the preferred treatment group was opened. Alternatively the investigator could change the order of envelopes to achieve their preferred sequence. The randomisation method needs to be described in detail (e.g. central computerised randomisation system) for an author to determine whether allocation was concealed or not. In many studies, the method of randomisation is not described and allocation concealment has to be considered "not stated" unless more information can be obtained from the investigators.

Blinding: Ideally studies should be quadruple blind – the treatment assignment should be unknown to the investigators, the subjects, those evaluating outcomes and those analysing the data. Double-blinded studies generally mean neither the investigator nor the patient are aware of treatment assignment, but they do not refer to blinded outcome assessment, which is probably the most important. Blinding prevents performance or co-intervention bias (differences in care provided apart from the intervention being evaluated) and detection bias (differences in outcome assessment). Blinding becomes particularly important with subjective outcomes such as pain. It may not be possible to implement completely. For example it is not possible to blind the investigator and subject if a surgical intervention (ureteric reimplantation for ureteric reflux) is compared with a medical intervention (antibiotic prophylaxis). In that situation, it is essential that those evaluating the outcomes (new cortical renal scars on intravenous pyelogram) are blinded to the intervention. In some studies, the investigators and subjects may be blinded but the investigators may be able to determine the intervention group from the adverse effects experienced by the patients.

Adequate allocation concealment will generally ensure that the intervention groups are similar at entry to a study (if the study is large enough). Publications of most studies will include a table demonstrating the similarity of treatment groups at the beginning of the trial. It is important that the groups be similar at the completion of the evaluation to avoid attrition bias. This requires that the results should be analysed with the patients in the intervention groups to which they were allocated even if they did not receive the intervention, if they deviated from protocol or if they withdrew from the study but follow-up continued. Frequently a publication report will only include data on those patients who actually received the interventions and completed the study.

Completeness of follow-up: Losses of participants to follow-up will also lead to differences between treatment groups at the end of the study. In assessing a study, it is important to account for all the participants in the study.

Reporting on risk of bias

In the Cochrane Renal Group we assess each item separately rather than combine in a scoring system. This is because only individual items of quality have been found to be associated with observed treatment effects, and scoring systems give unpredictable and unreliable results (Juni 1999).

See Appendix 3 – Risk of bias assessment tool for the criteria used to assess bias.

Measures of treatment effect

By convention the outcome we chose is a bad one, which we aim to reduce with an intervention. This will mean that if beneficial, an intervention will reduce the number of adverse events and the point estimate will be to the left of the line of no effect.

Unit of analysis issues

Special issues in the analysis of studies with non-standard designs, such as cross-over trials and cluster-randomised trials, should be described.

Non-standard designs are discussed in detail in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions, including cluster-randomised trials (Section 16.3), cross-over trials (Section 16.4), and studies with multiple intervention groups (Section 16.5) (Cochrane Handbook 2008).

Dealing with missing data

Strategies for dealing with missing data should be described. This will principally include missing participants due to drop-out (and whether an intention-to-treat analysis will be conducted), and missing statistics (such as standard deviations or correlation coefficients).

Issues relevant to missing data are discussed in Chapter 16 (Sections 16.1) and intention-to-treat issues in Chapter 16 (Section 16.2) (Cochrane Handbook 2008).

Assessment of heterogeneity

RevMan automatically tests for significant between study differences (heterogeneity). Heterogeneity will also be evident by looking at the forest plot (the plot of the individual study results). It is important to distinguish between qualitative and quantitative differences. If all study results show benefit but there is heterogeneity in terms of how much benefit then the clinical implication is not likely to be as large as if some studies showed benefit and others showed harm. Heterogeneity should be welcomed and explored using subgroup analysis of the factors already stipulated in the protocol. If heterogeneity cannot be explained then it is probably better to disregard the pooled result and discuss the results of the study qualitatively. Cochran's Q is the test statistic for heterogeneity. In RevMan this is provided with its degrees of freedom. The corresponding p-value can be found in any statistical table. As a rough guide, heterogeneity is not significant if the degrees of freedom is greater than or equal to the Cochran Q statistic.

RevMan calculates the I^2 statistic (Higgins 2003). I^2 can be directly compared between meta-analyses with different numbers of studies and different types of outcome data. The lower the percentage the less likely any heterogeneity observed is due to chance or sampling error.

Assessment of reporting biases

If a large number of studies are available for review, it is useful to investigate for publication bias using a funnel plot. In a funnel plot, individual study weights are plotted on the y-axis against the study relative risks on the x-axis. Smaller studies have less precision than large studies so are more likely to have a result further from the "true" result than a large study. If no publication bias is present, the graph should have an inverted funnel shape with the largest study at the apex of

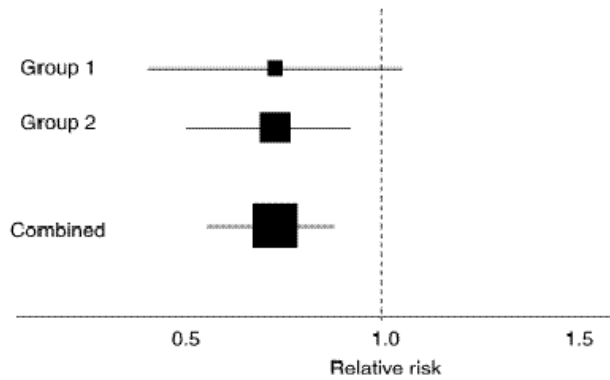
the funnel and smaller studies distributed equally on either side of the large study. If publication bias is present, the bottom right of the funnel (assuming that relative risks less than one indicate positive results) will be missing reflecting that small studies with a negative result are not included. Bias is also suggested if the summary effect estimate is situated to the left of the relative risk for the largest study.

Data synthesis

You don't have to be a statistician to do a systematic review, as RevMan does much of the work for you. You simply need to decide which option to choose. Our default position is to use the relative risk measure for individual study and summary results, with the random effects model used for the summary effect measure. The random effects model incorporates possible between study differences as well as within study differences and so is more conservative. The fixed effects model assumes that no between study differences exist. As expected both models give very similar results unless there is significant between study differences (heterogeneity). We have chosen relative risk (rather than odds ratios or risk difference) because we believe it provides the best trade-off in ease of understanding, consistency across studies, and mathematical properties (Berlin 1989; Sackett 1996).

Subgroup analysis and investigation of heterogeneity

Authors have the opportunity to explore whether there is a constant intervention effect or whether it varies across studies based upon plausible factors like risk of bias (see above), population (age, gender), clinical problem (severity of disease), intervention (dose, duration), and outcome (particularly timing). Authors need to decide which of these factors they would like to explain based upon biological plausibility, before they look at the study results. Sub-group analysis is used to see whether these potential factors actually do influence treatment effect, by comparing the treatment effect of studies with the factor of interest with those studies without the factor of interest. This is formally tested as for effect modification, but you will get a reasonable idea by seeing whether the 95% confidence intervals of the two groups of studies cross.



› **Hypothetical study showing combined and subgroup analysis: subgroups 1, 2 and the combined effect are all equivalent, but only group 2 and the combined groups are statistically significant**

The general approach to subgroup analysis should be to assume similarity unless a difference can be demonstrated. Thus individual subgroups should not be tested for significance of their main effects, but should be tested to see whether the subgroups differ significantly. In the figure, we have a hypothetical study which is clearer significant (the 95%CI do not cross 1). Now if subdivided into 2 groups, group 1 is no longer significant even though the intervention effect is clearly no different from group 2.

Sensitivity analysis

Sensitivity analyses are sometimes confused with subgroup analysis. Although some sensitivity analyses involve restricting the analysis to a subset of the totality of studies, the two methods differ in two ways. First, sensitivity analyses do not attempt to estimate the effect of the intervention in the group of studies removed from the analysis, whereas in subgroup analyses, estimates are produced for each subgroup. Second, in sensitivity analyses, informal comparisons are made between different ways of estimating the same thing, whereas in subgroup analyses, formal statistical comparisons are made across the subgroups.

Acknowledgements

This section should be used to acknowledge any individuals or organisations who may not have made a sufficient contribution to the review to be included in the Contributions section (e.g. secretarial support, protocol/review referees)

Contributions of authors

Examples of author contribution are:

- Draft the protocol
- Study selection
- Extract data from studies
- Enter data into RevMan
- Carry out the analysis

Interpret the analysis
Draft the final review
Disagreement resolution
Update the review

Potential conflict of interest

All Authors should report any present or past affiliations or other involvement in any organisation or entity with an interest in the review that might lead to a real or perceived conflict of interest. Situations that might be perceived by others as being capable of influencing a review author's judgements include personal, political, academic and other possible conflicts, as well as financial conflicts. Authors must state if they have been involved in a study included in the review.

If there are no known conflicts of interest, this should be stated explicitly, for example, by writing 'None known'.

A summary of the Collaboration's policy on conflicts of interest appears in Chapter 2 (Section 2.6) (Cochrane Handbook 2008).

References - Other references

Additional references

References cited in the text should be listed here. The style is First author surname year of publication (e.g. Smith 2001)

Other published versions of the review

If the review has been published in a journal or textbook it should be listed here.

References

Berlin JA, Laird NM, Sacks HS, Chalmers TC. A comparison of statistical methods of combining event rates from clinical trials. *Statistics in Medicine* 1989; **8(2)**: 141-151.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration. 2008. Available from www.cochrane-handbook.org.

Jüni P, Witschi A, Bloch, R, Egger M. The hazards of scoring the quality of clinical trials for Meta-analysis. *JAMA* 1999; **282**: 1054-1060.

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;**352**:609-613.

Sackett DL, Deeks JJ, Altman DG. Down with odds ratios! *Evidence-Based Medicine* 1996; **1**: 164.

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408-412.

Further reading

Dickersin K, Hewitt P. Look before you quote. *BMJ* 1986; 293:1000-2.

Eichorn P, Yankauer A. Do authors check their references? A survey of accuracy of references in three public health journals. *Am J Public Health* 1987; 77:1011-2.

Flanagin A, Carey LA, Fontarosa PB, Philips SG, Pace BP, Lundberg GD, Rennie D. Prevalence of articles with honorary articles and ghost authors in peer-reviewed medical journals. *JAMA* 1998; 280: 222-4.

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Canadian Medical Association Journal* 1997; 156: 270-85.

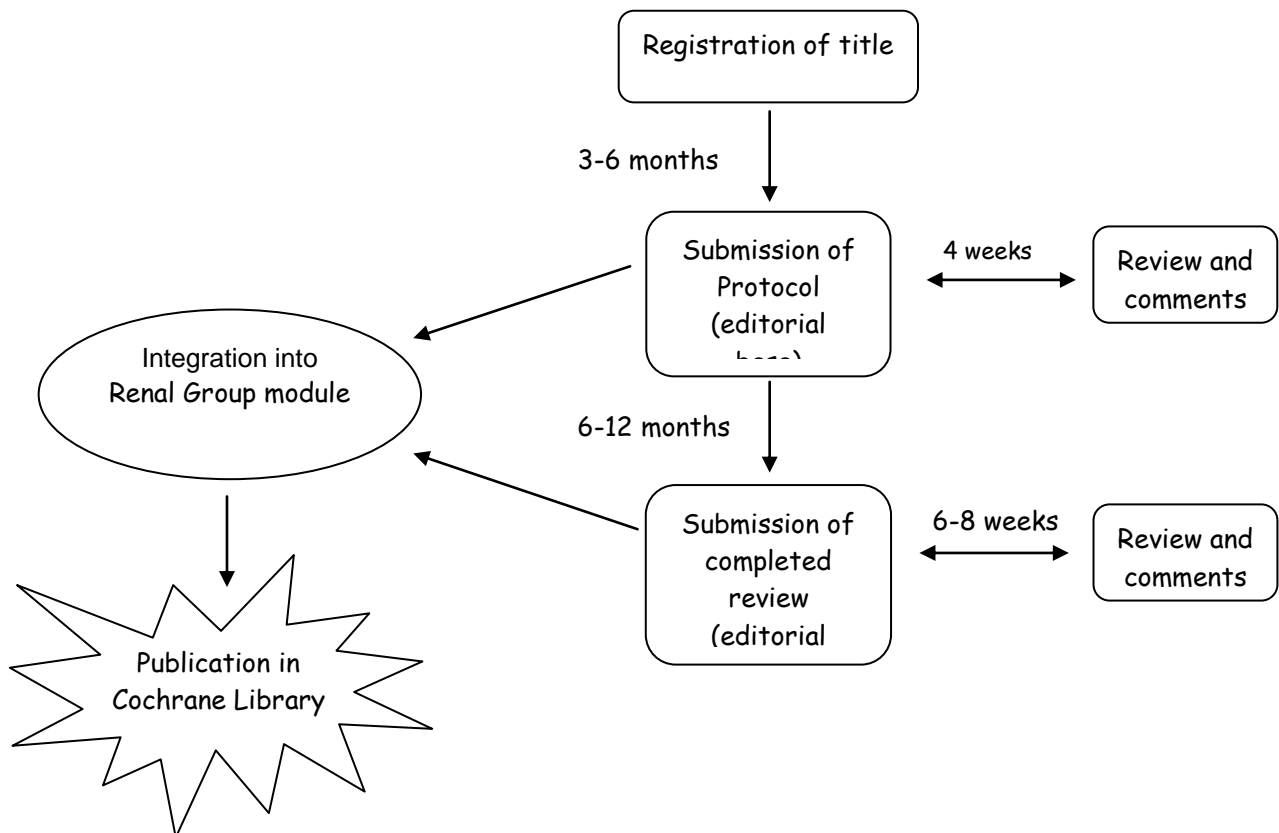
Rennie D, Emanuel L, Yank V. When authorship fails: a proposal to make contributors accountable. *JAMA* 1997;278:579-85.

Rennie D, Yank V. If authors become contributors, everyone would gain, especially the reader. *Amer J Public Health* 1998;88:828-30.

Yank V, Rennie D. Disclosure of researcher contributions: a study of original research articles in the *Lancet*. *Annals of Internal Medicine* 1999; 130: 661-70.

Renal Group editorial process

The overall process can be seen below



On completion of the draft protocol it should be submitted to the Coordinator who then organises four referees. They include; a Renal Group Editor, two content experts and a consumer. Once these referees have agreed to referee the protocol the relevant documents are sent and there is an understanding that the comments should be returned to the Coordinator within two weeks. In addition to the four referees, the Coordinating Editor also referees all protocols.

All the comments are compiled and sent to the author. Prompt reply and amendment will ensure quick inclusion into *The Cochrane Library*. On resubmission, the Coordinating Editor and the Coordinator will then review the changes. Once the changes have been approved, the Coordinator will copy edit the protocol (checking with the authors and obtaining a signed permission to publish form) and then submit the protocol for publication.

Appendix 1 – MEDLINE search strategy for RCTs

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic/
6. randomly.ab.
7. (crossover or cross-over).tw.
8. trial.ti.
9. or/1-8
10. humans/
11. and/9-10

Appendix 2 – EMBASE search strategy for RCTs

1. randomized controlled trial/
2. crossover procedure/
3. double-blind procedure/
4. single-blind procedure/
5. random\$.tw.
6. factorial\$.tw.
7. (crossover\$ or cross-over\$).tw.
8. placebo\$.tw.
9. (double\$ adj blind\$).tw.
10. (singl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. volunteer\$.tw.
14. or/1-13

Appendix 3 – Risk of bias assessment tool

See Table 8.5.c (Criteria for judging risk of bias in the 'Risk of bias' assessment tool) in *Cochrane Handbook for Systematic Reviews of Interventions*.

1) Was the allocation sequence adequately generated? (*Adequate sequence generation*)

- *Yes, low risk of bias*

Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization - Minimization may be implemented without a random element, and this is considered to be equivalent to being random

- *No, high risk of bias*

- Quasi-randomised approach: Sequence generated by odd or even date of birth; date (or day) of admission; Sequence generated by hospital or clinic record number.
- Non-random approaches: Allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.

- *Unclear*

Insufficient information about the sequence generation process to permit judgement

2) Was allocation adequately concealed? (*Allocation concealment*)

- *Yes, low risk of bias*

Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. Central allocation, including telephone, web-based, and pharmacy-controlled, randomization; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

- *No, high risk of bias*

Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

- *Unclear*

Randomisation stated but no information on method used is available.

3) Was knowledge of the allocated interventions adequately prevented during the study? (*Blinding*)

- *Yes, low risk of bias*

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding;
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;

- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
- *No, high risk of bias*
 - No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;
 - Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
 - Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
- *Unclear*

4) Were incomplete outcome data adequately addressed? (Incomplete outcome data)

- *Yes, low risk of bias*
 - No missing outcome data;
 - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
 - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
 - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
 - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
 - Missing data have been imputed using appropriate methods.
- *No, high risk of bias*
 - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
 - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
 - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
 - 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
 - Potentially inappropriate application of simple imputation.
- *Unclear*

5) Are reports of the study free of suggestion of selective outcome reporting? (Selective outcome reporting)

- *Yes, low risk of bias*
 - The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
 - The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
- *No, high risk of bias*
 - Not all of the study's pre-specified primary outcomes have been reported;
 - One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
 - One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
 - One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
 - The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- *Unclear*

6) Was the study apparently free of other problems that could put it at a risk of bias? (Free of other bias?)

- *Yes, low risk of bias*

The study appears to be free of other sources of bias
- *No, high risk of bias*
 - Had a potential source of bias related to the specific study design used;
 - Stopped early due to some data-dependent process (including a formal-stopping rule);
 - Had extreme baseline imbalance;
 - Has been claimed to have been fraudulent;
 - Had some other problem.
- *Unclear*

Appendix 4 - Data extraction form

Date.....

Author/s:

Review Title

Study details

First author	
Year of publication	
Country of publication	
Publication type	Journal / Abstract / other (specify)

Study Eligibility

	Inclusion criteria for review	Study inclusion criteria
Type of study	RCT or quasi-RCT	Yes no unclear
Participants	• • •	Other:
Types of intervention/s	• • •	Other:
Types of outcome/measures	• • •	Other:

Include Exclude

Reason for exclusion:

Methods: Study characteristics

	Study
Study inclusion criteria	
Study exclusion criteria	
Participants	<ul style="list-style-type: none"> • Sex (number): M.... F.... Both.... • age: Mean (SD):..... Median (range) • ethnicity:.... • Other:....
Setting	source e.g. multicentre, university teaching hospitals:
Study Intervention/s (incl. duration)	
Study control (incl. Duration)	
Duration of follow-up	
Compliance	
Matching of interventions	e.g. taste, smell, appearance, colour
Similarity between groups	e.g. numbers, dropouts age, sex
Notes	<ul style="list-style-type: none"> • Request for further information • Clarification of methods • Clarification of results • Funding source

Risk of bias assessment

Please refer to Chapter 8 - *Table 8.5.c: Criteria for judging risk of bias in the 'Risk of bias' assessment tool*

Study design	Parallel/crossover
Was the allocation sequence adequately generated?	Yes – low risk of bias No – high risk of bias Unclear – uncertain risk of bias <i>[Record description of sequence generation]</i>
Was allocation adequately concealed?	Yes – low risk of bias No – high risk of bias Unclear – uncertain risk of bias <i>[Record description of sequence generation]</i>
Was knowledge of the allocated interventions adequately prevented during the study? <i>Circle and record supporting statement for each assessment</i>	<ul style="list-style-type: none"> • Participants – yes, no, unclear <i>[record supporting statement from study].</i> • Investigators – yes, no, unclear <i>[record supporting statement from study].</i> • Outcomes assessors – yes, no, not stated <i>[record supporting statement from study].</i> • Data assessors – yes, no, unclear <i>[record supporting statement from study].</i>
Outcomes (assessment and measurement)	<ul style="list-style-type: none"> • Outcome methods • Outcome definitions
Intention-to-treat analysis <i>Circle and record supporting statement for each.</i>	<ul style="list-style-type: none"> • Participants: – yes, no, not stated <i>[supporting statement from study].</i> • Investigators – yes, no, not stated <i>[supporting statement from study].</i> • Outcome assessors – yes, no, not stated <i>[supporting statement from study].</i> • Data analysis – yes, no, not stated <i>[supporting statement from study].</i>

Results

Comparison: _____

Outcome: _____

Subcategory: _____

Treatment group:		Control group:	
Observed (n)	total (N)	observed (n)	total (N)

	Treatment group:	Control group:
Total randomised		
excluded*		
Observed		
lost to follow up*		

*Reasons for loss/exclusion:

Subcategory: _____

Treatment group:		Control group:	
Observed (n)	total (N)	observed (n)	total (N)

	Treatment group:	Control group:
Total randomised		
excluded*		
Observed		
lost to follow up*		

*Reasons for loss/exclusion

Appendix 5 – Checklist for submission

This checklist is sent with your protocol to the referees. Please ensure all sections have been addressed by your protocol. This will speed up the process and ensure your protocol is quickly included on the Cochrane Library. Please remove this section and use to check your protocol before submitting to the Coordinator.

Title

- Does the title follow the preferred format, i.e. *intervention for clinical problem in population*?
Corticosteroids for steroid responsive nephrotic syndrome in children

Background

- Does the background support the need for a systematic review by providing sufficient information on the frequency and severity of the clinical problem and the uncertainties in its management?

Objective/s

- Is the main objective of the review specified in terms of intervention(s), clinical problem, population and outcomes (both beneficial and harmful)?
To evaluate the benefits and harms of different agents, other than corticosteroids, that are used in children who pursue a relapsing course of steroid responsive nephrotic syndrome

Selection criteria

Types of studies

- Do you intend to include only randomised controlled trials (RCTs)?
 Do you intend to include quasi-RCTs?

Types of participants

- Are the characteristics of the clinical problem and the population with the clinical problem described?
Children aged 3 months to 18 years with steroid responsive nephrotic syndrome who have suffered one or more relapses.
- Has a clear case definition for establishing the presence of the clinical problem been included?
The child, who becomes free of oedema and whose urine protein is < 1+ on dipstick or <4mg/m²/hr for 3 consecutive days after receiving corticosteroid therapy.
- Have the population groups to be excluded been specified?
Children in their first episode of nephrotic syndrome, children with steroid resistant nephrotic syndrome, children with congenital nephrotic syndrome and children with other renal or systemic forms of nephrotic syndrome defined on renal biopsy, clinical features or serology
- Have the appropriate population groups been excluded?

Types of interventions

- Have the study interventions been described?
- Have the control interventions been described?
- Have all relevant interventions for the clinical problem and question asked been identified?
 - Non corticosteroid agent versus placebo*
 - Non-corticosteroid agent versus prednisone used alone.*
 - Two different non-corticosteroid agents*
 - Different doses and durations of the same non-corticosteroid agent*
- Have the interventions to be excluded been described?
- Are the interventions to be excluded appropriate?

Types of outcome measures

- Are the outcome measures for benefits and harms of the intervention(s) clearly defined in nature and in timing?
- Are the outcome measures used important to the population with the clinical problem?
- Have all relevant outcomes (both beneficial and harmful) been included?
 - The prevention of relapse in steroid responsive nephrotic syndrome as measured by: The numbers of children with and without relapse at 6 months, 12 months and 2 years*
 - Mean relapse rates per patient per year*
 - Mean length of time to next relapse*
 - Serious adverse effects of therapy*
- If specific outcomes have not been included, does this conform with the question asked?

Search methods for identification of studies

- Has the search strategy been included?
- Are the dates that each source will be searched been indicated?

Will the following data sources be searched?

- The Cochrane Renal Group's specialised register
- Cochrane Central Register of Controlled Trials (CENTRAL) (most recent)
- MEDLINE (from 1950 -)
- EMBASE (from 1980 -)
- Reference lists of textbooks, reviews (including previous systematic reviews), and previous trials
- Conference proceedings
- Does the search strategy include contacting experts in the field?
- Have the appropriate subject headings, key words and text words for the clinical problem and population been used?

- Has the Cochrane Collaboration search strategy to identify RCTs been used?
- Has the Trials Search Coordinator been contacted?
- Are studies in languages other than English to be included?
- How will duplicate publications of the same study be identified and dealt with?

Assessment of risk of bias

- Have the criteria to be used to assess the individual studies risk of bias been reported?

Does the criteria to be used to assess study bias include:-

- Sequence generation
- Allocation concealment
- Blinding
 - Participants
 - Investigators
 - Outcome assessment
 - Data assessors
- Incomplete outcome data
- Selective outcome reporting
- Other potential biases

Methods of the Review

Will at least two authors of the review:-

- Perform the literature search?
- Determine study eligibility?
- Assess risk of bias of included studies?
- Extract data?
- Will authors work independently?

- Will consensus and/or liaison with a third author be used to resolve disagreement between the primary authors?
- Will authors of primary studies be contacted for clarification of unclear data or to obtain missing information?
- Will you attempt to analyse for possible publication bias using funnel plots or other methods?
- Will plausible explanations for variations in treatment effect be explored using subgroup analysis based on study quality, population and interventions?

Statistical analysis

- Will the results of primary studies be reported with 95% confidence intervals using relative risk (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes?
- Have the methods used to pool the results of the primary studies been reported?
- Are these methods relevant?
- Will RR and MD summary statistics be calculated using a random effects model?
Statistical analysis will be performed using RevMan. For dichotomous outcomes (relapse or no relapse) results will be expressed as relative risks with 95% confidence intervals. Data will be pooled using the random effects model. Where continuous scales of measurement are used to assess the effects of treatment (e.g. time to relapse), the weighted mean difference will be used, or the standardised mean difference if different scales have been used
- Have you stated how you will test for heterogeneity?
Heterogeneity will be analysed using the Cochran Q test on N-1 degrees of freedom, with an α of 0.1 used for statistical significance.
- Have you specified how you will determine the applicability of the results to individual patients?
Calculation of absolute risk reductions with therapy in relation to different baseline risk of the event with no treatment or a different therapy.

Statistical analysis

- Have you acknowledged all the relevant people and/or organizations?

Declarations of interest

- Have you and your coauthors declared any potential conflicts of interest?

References

- Have you checked your references?

Sources of support

- Have you listed your internal sources of support (e.g. hospital, university)?
- Have you listed your external sources of support (e.g. scholarship, bursaries)?

Appendix 6 – Tips for using Archie and RevMan

Here is a quick set of tips for manoeuvring through Archie and RevMan 5 (RM5) ('review' refers to all stages – title, protocol and review)

- Download RM5 from <http://www.cc-ims.net/RevMan/> . You will notice on the panel on the left side of the screen, a link for 'authors', which will take you here <http://www.cc-ims.net/authors> . This is an excellent resource page that gives you information on Archie, RM5, GRADEProfiler and how to start using them. Take the time to complete the tutorial on RM5, located under the 'help' button at the top of the screen. Although the basics are easy to learn, RM 5 has lots of new and time-saving features that will only be realized if you take the time to find out about them.
- Before you can start to work on your review in RM5, you need a user account. With this user account, you can update your own contact information and access reviews and files for which you have access permission.
All files must be started by the Editorial Office. This is done once the title is registered and the review team members are established.
Check the review out using RM5, not Archie (the Archie route is technically possible, but not as stable). Go to File > check out > click on the title you want > OK.

Tip: DO NOT chose the option 'download a copy of the review without locking it for others' – your co-authors will not know you are working on the file and may check it out to make some of their own edits -> RevMan does not merge files, so someone will end up copying/pasting their work!

- When you start working on the RM5 file, use the 'save as' function and save it to whatever drive/folder you ordinarily store your reviews – thereafter you can just 'save' and 'close' without losing it somewhere on your hard drive!
- The same person (i.e. same user account) must check the review out of Archie and back in (but you can do it from different computers if you have saved the file on your travel drive) Remember that while you have the file checked out, nobody else can access it

Tip: don't store the file for a long time on your own computer – check it back into Archie. The most recent version will always be available and you won't lose data when your home computer crashes!

Tip – sharing the file: depending on the size and proximity of your team, you can decide whether it is more expedient to share the file through email or have the members of your team check it out/into Archie (in which case everyone will need a user account). Depending on your co-authors' comfort with RM5, you may find it easier to share the html or word document via email. You can only export the review from RM5 as an html file – remember that some firewalls will block html files. In that case, you may be better off to export it and save it as a word document.

Checking the review back into Archie before it is finished:

- When you check in the file, you will be asked if you want to check it in as a 'draft' or for 'editorial approval'. If the team is still working on it, enter a description of the version (e.g. ROB tables finished, data entered) so that you and others will remember/know what you did. You will get a message saying it was successfully checked in.
If you want Narelle to review it prior to completion, check it in as a draft and send Narelle an email letting her know

Checking the review back into Archie for editorial consideration:

- Go to file > reports > validation report. Run the validation check and fix all the 'errors' and 'warnings' you can. You can check a file in to go through the editorial process with 'warnings' but not 'errors'.
Check it in for 'editorial approval' rather than as a draft – this will generate a message to Narelle – you can type a message in the text box, thus alleviating the need to send another email, unless you have an attachment you wish to send