Cochrane Infectious Diseases Group

Guide to preparing and using the 'Methods of the review'

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1. Introduction

> Cochrane Infectious Diseases Group reviews should include randomized controlled trials. If you wish to include other study designs, such as quasi-randomized controlled trials and non-randomized studies, contact the editorial base before starting your review.

This guide is intended to help authors prepare (and use) methods for a Cochrane review supported by the Cochrane Infectious Diseases Group. It does not take the place of the Cochrane Reviewers' Handbook, which provides a comprehensive guide to analysis. You should be familiar with Chapter 8, 'Analysing and presenting results', before using this guide.

The methods section must describe in detail the methods you intend to use (if preparing the protocol) or have used (in your review). They should allow another person to follow your methods and reproduce the results.

If you are preparing these methods as part of your protocol, then write them in the future tense and consider all the possible methods you may need to use in the review stage. This is because you will need to follow the decisions that you take at the protocol stage when writing the main review.

If you are preparing it as part of your review, then you must change the tense to the past tense and clearly describe the methods that you used and the reasons why you were unable to use some methods (such as too few included trials).

There are three steps to preparing and using the methods.
(1) Preparing the methods as part of your protocol.
(2) Using the methods to locate relevant trials, assess methodological quality, and extract and analyse data.
(3) Presenting the results.

This section of your protocol must stand alone, that is, **do not reference this guide as it is often updated**. Ensure that your methods are sufficiently detailed to permit someone else to repeat your review.

2. The methods

You can help the reader by using subheadings to divide the methods text into the following four distinct sections: trial selection; assessment of methodological quality; data extraction; and data analysis.

2.1 Trial selection

Introduction

Selecting studies for inclusion in a review is a filtering process. It begins with the assessment of titles and abstracts of articles identified by the literature search to determine whether each article – or ‘potentially relevant trial’ – might meet the inclusion criteria.

This section of your protocol should explain the process you will use to determine which studies to include in the review. Imagine that you have just received the results of your search strategy, what will be your next step? Use the following questions to help you describe the process you plan to follow.

Step 1. Guiding questions for the protocol

(1) Who will scan the results of the literature search for potentially relevant trials?
One author, or two or more independent authors, may do this.

(2) Will you retrieve the **full** report for trials thought to be potentially relevant?

(3) How will you assess the trials for inclusion?
We recommend that you design and use an eligibility form based on the inclusion criteria (listed under 'Criteria for considering studies for this review'). See the sample eligibility form below.

(4) Who will assess the potentially relevant trials for inclusion in the review? If two authors plan to do this, how will you resolve any disagreements?
We recommend that two authors do this independently, and they could resolve disagreements through discussion or by involving another person, such as a third author or a named person at the editorial base.

(5) Are the trials independent?
Because some trials may be reported in more than one publication, you should scrutinize each of the trial reports to ensure that you include each trial only once.

(7) What will you do with the potentially relevant trials that are not eligible for the review?
You should list these as excluded studies and give the reason for excluding them in the 'Characteristics of excluded studies'.

(8) What will you do if you are unclear if a potentially relevant trial is eligible for the review?
We suggest that you attempt to contact the trial authors for clarification.

Step 2. Preparing an eligibility form

Eligibility forms are important because they help standardize the process of formally assessing the eligibility of 'potentially relevant trials' for inclusion. It is essential to train each author on how the form should be completed, as this will reduce the potential for disagreements. If any of the information is 'unclear' you should attempt to contact the trial authors for clarification.

Sample eligibility form

Date:			
Extractor (initials):			
Trial authors:			
Year of publication:			
Journal:			
(1) Design			
Described as randomized? If 'no', exclude. If 'yes', go to question (2).	Yes	No	Unclear
(2) Participants			
(a) Did the participants have confirmed falciparum malaria? NB Confirmed by blood slide	Yes	No	Unclear
(b) Did the participants have uncomplicated malaria?	Yes	No	Unclear
If 'no', exclude. Otherwise go to question (3).			
(3) Interventions			

(a) Was one group given oral artemether-lumefantrine as treatment? (either 4 or 6 doses)	Yes	No	Unclear
(b) Did another group receive another antimalarial drug and the same care?	Yes	No	Unclear
If 'no' to (a) or (b), exclude.			
Final decision			
Include (if all 'yes') Exclude (if any 'no') Unclear			
Excluded or unclear because:			
If 'unclear', action taken:			

Step 3. Presenting trial selection results in the review

We recommend that you present this information in the 'Description of studies' section. It can be helpful to use a 'Trial selection' subheading. Under this you can describe how many potentially relevant trials you assessed, how many met the inclusion criteria, and how many you excluded.

2.2 Assessment of methodological quality

Introduction

Once you have determined which trials are eligible for your review, you will need to assess their 'internal validity' or 'internal quality'. Quality means different things to different people, but here we are concerned with specific aspects of the trial design and conduct that have been used to minimize bias.

There are numerous scales and checklists that may be used to assess the validity of a randomized controlled trial. These scales and checklists incorporate various numbers of items used to determine quality and may produce a single value or category to describe the overall quality of the trial often referred to as a summary score. We recommend that authors avoid the use of these scales, checklists, and summary scores. This is because the results depend on the choice of the scale, the use of a summary score means that an arbitrary decision has been made about the amount each quality component contributes to the score, and the interpretation of findings is difficult. Further to this we do not recommend that authors use summary scores to attempt to weight studies by methodological quality within a meta-analysis.

Instead, we recommend that you use the four key factors that are considered to influence the methodological quality of the trial: generation of allocation sequence, allocation concealment, blinding, and inclusion of all randomized participants. We also recommend that you use the following categories to help you assess each of these factors.

Generation of allocation sequence

This is the process used to generate the randomization list. It should ensure that each person randomized into the trial has the same chance of being entered in to the treatment or control group. The process of randomization ensures that the two groups are comparable at baseline.

Category	Description	Example
Adequate*	if the method used is described and the resulting sequences are unpredictable	computer-generated random numbers, table of random numbers, drawing of lots or

		envelopes, tossing a coin, shuffling cards, throwing dice, or other methods of allocation that appear to be unbiased and lead to an unpredictable sequence
Unclear	stated that the trial is randomized, but the method is not described	trial described as being 'randomized' but no further information provided
Inadequate*	if sequences could be related to prognosis	according to case record number, date of birth, or date of admission; or alternative allocation
Not described	--	--

*As described in Juni 2001

Allocation concealment

Allocation concealment is a process used to prevent foreknowledge of group assignment in a randomized controlled trial. This is distinct from blinding. (**Note:** Allocation concealment is considered of primary importance in assessing methodological quality.)

Category	Description	Example
Adequate*	participants and the investigators enrolling participants cannot foresee assignment	a priori numbered or coded drug containers of identical appearance prepared by an independent pharmacy; central randomization performed at a site remote from trial location; sequentially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment
Unclear	method not described	--
Inadequate*	participants and investigators enrolling participants can foresee upcoming assignment	all procedures based on inadequate generation of allocation sequences, an open allocation schedule, unsealed or non-opaque envelopes, or reported an approach that could not be considered adequate
Not described	--	--

*As described in Juni 2001

Blinding

Blinding refers to whether the participant or care provider or outcome assessor is blind to the group to which the participants have been assigned. Blinding of participants or carers is not always possible. Frequently the blinding of the outcome assessor is not reported.

Blinding is often classified as double (use a placebo or a double dummy technique such that neither the participant or care provider/assessor know which treatment is given), single (the participant or care provider/assessor is aware of the treatment given), and open (all parties are aware of treatment). Because people sometimes define these terms differently, we recommend that authors note who was blinded in the trial instead of the type of blinding used.

Inclusion of all randomized participants
All randomized participants should be included in the analysis and kept in their original groups regardless of their adherence to the study protocol; this is called an intention-to-treat analysis or an as-randomized analysis. Be aware that even if a trial states that it has used an intention-to-treat analysis, this may be based on an inaccurate assumption that all participants lost to follow up are treatment failures (Hollis 1999). Depending on the review topic, you may present this information for all the participants in the review, or you may need to extract and present this information for each outcome or each time point for the outcomes.

Category	Description
Adequate	> 90%* of all participants randomized into the trial were included in the analysis
Unclear	unclear how many participants were originally randomized into the trial
Inadequate	< 90%* of all participants randomized into the trial were included in the analysis
Not described	--

*choice of 90% is arbitrary and is suggested only as a guideline and not a rule

Step 1. Guiding questions for the protocol

In describing your approach to assessing methodological quality you will need to consider the following questions.

(1) Who will assess the methodological quality of the trials eligible for inclusion in the review?
We recommend that two authors independently assess the methodological quality using a specially designed form. See an example form below.

(2) If two authors plan to do this, how will you resolve any disagreements?
This could be through discussion, for example, or by involving another person such as a third author or a Cochrane Infectious Diseases Group Editor.

(3) Which of the four key factors will you use to consider methodological quality?
You should decide which of these factors are appropriate to your review.

(4) How will you assess each of the quality components?
Provide details on each of these as described above. For example, we recommend that you assess generation of allocation sequence and allocation concealment as adequate, inadequate, and unclear according to Juni 2001. If you are assessing blinding, state that you will report which parties were blinded in each trial. For inclusion of all randomized participants, describe what you mean by adequate and inadequate.

(5) State how you will report your assessment of methodological quality?
We recommend displaying the assessment in an additional table. You will describe the actual methods in the 'Characteristics of included studies'. (See Step 3 below for an example.)

(6) After you assess the methodological quality, should you use the information to conduct a sensitivity analysis?
A sensitivity analysis is where you investigate the same review question, but you are more stringent on trial methodological quality as inclusion criteria, particularly allocation concealment. Mention that you will use the methodological quality assessment for a sensitivity analysis, should there be sufficient trials, as described in the 'Data analysis' section (see 'Data analysis' below).

Step 2. Preparing a methodological quality form

Sample methodological quality form

Date:	
Extractor (initials):	
Trial authors:	
Year of publication:	
Journal:	
(1) Generation of allocation sequence	
Method:	Adequate Inadequate Unclear
(2) Allocation concealment	
Method:	Adequate Inadequate Unclear
(3) Blinding	
Participants blinded?	Yes No Unclear
Provider blinded?	Yes No Unclear
Outcome assessor blinded?	Yes No Unclear
(4) Inclusion of all randomized participants	
Number assessed for eligibility:	

Number	**Treatment group 1**	**Treatment group 2**
Randomized		
Discontinued intervention		
Analysed		

Overall status:	Adequate (> 90%) Inadequate (< 90%) Unclear
Source:	
Notes:	

Step 3. Presenting the results of the methodological quality assessment in the review

You will describe these results in the 'Methodological quality of included studies' section of your review. This is a descriptive summary of the information in the associated ‘Additional table’ and the 'Characteristics of included studies'. It may be helpful to use subheadings in the text.

You will present your quality assessment (eg 'adequate' or 'open') in an ‘Additional table’ as shown below.

Trial	**Sequence***	**Concealment***	**Blinding**	**Inclusion***
Davis 2001	Unclear	Adequate	Assessor	Unclear
Smith 1999	Adequate	Unclear	Participants and assessor	Adequate
	* Generation of allocation sequence; Allocation concealment; Inclusion of			

	all randomized participants			

Note: Review Manager permits only short column headings. We suggest you use these shortened versions in your review.

You should also provide a short description of the method in the 'Characteristics of included studies'. (See the separate guide to preparing the 'Characteristics of included studies' table on the Infectious Diseases Group website.)

Trial	Methods
Davis 2001	Generation of allocation sequence: unclear Allocation concealment: sequentially numbered, opaque, sealed envelopes Blinding: assessor only Inclusion of all randomized participant: unclear
Smith 1999	Generation of allocation sequence: random-numbers table Allocation concealment: unclear Blinding: participants and assessor Inclusion of all randomized participant: 95%

2.3 Data extraction

Introduction

You should be familiar with the different types of data, such as dichotomous (also called binary) or continuous data, before you prepare this part or your protocol.

For Infectious Diseases Group reviews, two authors should extract data from the trials using a data extraction form. You should pilot this form before using for all the trials. The editorial team can provide advice on data extraction forms.

In trials where data are insufficient or missing, you should attempt to contact the authors for additional data or verification of methods, or both. It is not the editorial team's responsibility to negotiate permission for using unpublished data, but it can provide advice on appropriate approaches.

The following questions will help you decide how you will extract data from the trials included in your review.

Step 1. Guiding questions for the protocol

(1) Who will extract the data?
We recommend that two authors do this independently or one author extracts the data and a second author cross checks the data with the original paper for accuracy.

(2) Should you design a data extraction form for this process?
Use a data extraction form. You may need to pilot the form and amend it as necessary. If more than one author will use the form independently, you need to ensure the other authors understand how it is filled in correctly. See sample form below.

(3) If this is to be done by two authors, how will you resolve any disagreements?
The first approach should be by referring to the trial report, other options to consider are discussion, or involving another person such as a third author or a named person at the editorial base.

(4) Who will enter the data into Review Manager?
One or two authors may do this using double data entry.

(5) Under what circumstances will you contact the trial authors?
For those outcomes that are not reported in the trial articles or are reported in a format that is different to the format you require.

(6) What data will you extract?
The data you extract will depend on the types of outcomes you include in your review. The most common types are dichotomous and continuous; for other types of outcomes you may need to consult a statistician.

You will need to extract the number of participants in each group for all outcomes. The number of participants randomized in to each group may not be the same as the number analysed for a given outcome. Where this number is not the same, you should calculate the percentage lost to follow up.

Step 2. Preparing a data extraction form

Sample data extraction form

Date:		
Extractor (initials):		
Trial authors:		
Year of publication:		
Journal:		
(1) Participants		
Inclusion criteria:	Exclusion criteria:	
Median or mean age:		
Age range:		
Ethnicity:		
Gravidity:		
Early or late pregnancy:		
Preventive regimen received:		
Symptomatic or asymptomatic malaria:		
Anaemic:		
Local malaria endemicity/transmission:		
Local antimalarial drug resistance:		
Were all treatment groups comparable at baseline:	Yes No Unclear	
If no or unclear, describe any differences:		
Notes:		
(2) Interventions		
	Treatment group 1	**Treatment group 2**
Antimalarial used		

Formulation		
Route of administration		
Dose		
Duration of use		
Timing and frequency of dose		

Notes:

(3) Outcomes

Treatment failure (unadjusted)

Time point:

Definition:

	(n/N)
Treatment group 1	
Treatment group 2	

Fever clearance time

	N	Median	Range	95% CI	P value
Treatment group 1					
Treatment group 2					

Further information:

Trialists contacted for more information:	Yes No
Address:	
Telephone:	
E-mail:	
Data:	Available Requested Obtained
Comments:	

Step 3. Presenting these results in the review

Although you will use most of the extracted data for the data analysis, you will need to present some of this information in the 'Characteristics of included studies' table (see separate guide on Infectious Diseases Group website) and in the 'Description of studies' section of the text.

2.4 Data analysis

Introduction

The data analysis section should detail how you plan to manage the data you have extracted. You should be explicit about situations in which you *plan to* or *plan not to* conduct a meta-analysis and the effect measures you intend to use for each outcome. It should also contain the method you will

use to detect heterogeneity and the factors you will use to explain or investigate any heterogeneity. You should be familiar with the section 8 of the Cochrane Reviewers' Handbook before preparing this section; if you require additional statistical advice, you can contact the editorial base for help.

Check the trials details to see whether the participants were randomized to the intervention as individuals or as groups, such as households, villages, or health facilities. If they have been randomized as groups, this is a **cluster-randomized controlled trial**. If your review contains cluster-randomized controlled trials, read the relevant section of the Cochrane Reviewers' Handbook and contact the editorial base for assistance.

Step 1. Guiding questions for the protocol

(1) Which effect measure do you plan to use for each of your outcomes?
If you have outcomes with dichotomous you may use relative risk (risk ratio), odds ratio, or risk difference. You may need help deciding which is the most appropriate to use for each of your dichotomous outcomes. If you have continuous data, you should use the weighted mean difference unless the trials report the outcome on different scales that cannot be converted to a common scale. In this situation you should use the standard mean difference.

(2) Will you use the fixed-effect model or random-effects model?

(3) Will you present your results with 90%, 95%, or 99% confidence intervals?

(4) Are there any situations in which you would not consider a meta-analysis?
For example, it may not be appropriate to combine trials with different control groups.

(5) How do you intend to check for the existence of heterogeneity?
We recommend that you visually examine the forest plot and use the chi-squared test for homogeneity. You should state in advance if you will use a 5% or 10% level of statistical significance.

(6) What will you do if you detect heterogeneity?
If you detect heterogeneity, the options that are available to you are described in section 8.7 of the Cochrane Reviewers' Handbook, 'Heterogeneity'. We recommend that you explore the heterogeneity using subgroup analyses (when you investigate a particular subset of the results by some characteristic), and that you use a random-effects model if you decide it is appropriate to combine trials.

(7) If you use subgroup analyses, which factors will you use to investigate heterogeneity?
Avoid producing an exhaustive list; instead state four or five factors that you feel are most likely to influence the strength of the observed treatment effect such as age, dosage, and trial setting. (Make sure that the reason for these factors potentially causing heterogeneity is clear in the 'Background' section.)

(6) After you assess the methodological quality, will you conduct a sensitivity analysis based on your assessment of methodological quality?
A sensitivity analysis is where you investigate the same review question, but you are more stringent on trial methodological quality, particularly allocation concealment. If there are enough trials in your review, we recommend that you repeat the analyses by separating the trials with adequate allocation concealment from those with inadequate or unclear allocation concealment

(7) Will you produce a funnel plot?
An asymmetrical funnel plot may suggest the existence of publication bias, heterogeneity of results, or differences in the methodological quality.

Step 2. Analysing your data

Analyse your data using Review Manager (RevMan), which is the official Cochrane Collaboration software. (You can download this from http://www.cc-ims.net/RevMan; the RevMan Users Guide may also be helpful.) Sometimes you will be unable to pool the results, but you may be able to still present the results in the graphs with the meta-analysis option switched off. In other cases it may be more appropriate to present the results in an additional table or to provide a narrative summary.

If your review does not have any included trials, see the Infectious Diseases guide on 'Methods sections with no included studies', which is on the website.

Step 3. Presenting the results in the review

Once you have completed your data analysis, you will need to consider how to present the results for the reader. The text needs to be clear and concise, and any graphs or tables need to be clearly labelled and referred to in the text.

Text

- Use subheadings (bold and italic) when you present the results for a new outcome.
- The order of the outcomes must match the order in the 'Types of outcomes' section.
- Reference each graph and table that presents results, for example, (RR 1.14, 0.82 to 1.56; Graph 04-03) or "The primary outcome for Smith 1999 was safety and accordingly provided more adverse event data than the other trials (*see* Table 04)."

Graphs

- The order of the graphs needs to match the order of the results presented in the text.
- Change the 'Group labels' and 'Meta-analysis graph labels' to match the type of intervention and control used in your review.
- Adjust the 'Default graph scale' to make each data point clearly visible on the graph.
- Make sure you have selected the correct 'Default statistical method'.

3. References and further information

Alderson 2004
Alderson P, Green S, Higgins J, editors. *Cochrane Reviewers' Handbook.* www.cochrane.org/resources/handbook/index.htm (accessed 28 January 2004).

Hollis 1999
Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999;319(7211):670-4.

Juni 2001
Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ 2001;323(7303):42-6.

Review Manager and RevMan User Guide (http://www.cc-ims.net/RevMan)
Review Manager (RevMan) [Computer program]. Version 4.2 for Windows. Oxford, England: The Cochrane Collaboration.