Guide to the contents of a Cochrane Diagnostic Test Accuracy Protocol

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4.1 Rationale for protocols for systematic reviews

Protocols for systematic reviews provide clear statements of the objectives of the research, providing a focus on the comparisons that will be made and the outcomes that will be measured. They communicate important background information to provide a clinical context and define key clinical issues. The protocol also justifies the rationale and need for the review in terms of its context within existing scientific literature. Crucially, the protocol defines the methods by which the review will be undertaken, stating study eligibility criteria, search, selection and quality assessment methods, and a statistical analysis plan.

Why is it important to have a protocol for a systematic review? Good scientific practice involves pre-specifying objectives and methods. This is important in prospective studies, such as clinical trials, as it provides documentation to make sure that the hypothesis, the methodology, the data collected, and the analysis plan were decided before any data were available and not determined following review of findings and results. Pre-specification of methods provides protection against some aspects of bias and demonstrates scientific rigour.

Similar arguments exist for systematic reviews, but they are less strong because systematic reviews are retrospective rather than prospective pieces of research. The findings of the individual studies that are included in a review are based on available information, typically already published when the review protocol is written. Thus, the ability of a protocol to protect against bias is less than is the case for a truly prospective research study. It would be possible for unscrupulous reviewers, with knowledge of the results and the design of individual studies, to select eligibility criteria to bias a review to obtain a finding of their choosing.

The possibility of bias is reduced because protocols for Cochrane Systematic Reviews undergo a process of peer review and publication to ensure that the methods and selection criteria are transparent and are unlikely to be selected to obtain a particular outcome. The peer review process also facilitates expert methodological input at an early stage to ensure correct methods and optimal processes are followed.

Publication of protocols also reduces the risk of duplication of effort as it shows that reviews on certain topics are already in development. A good protocol also provides a project management plan, outlining the steps that the review will proceed through and the tasks allocated to individual members of the research team.

In summary, protocols are important documents because the methods for a systematic review should be planned before the review is done. Also, Cochrane protocols are in a standard format which facilitates their peer review and publication in the Cochrane Library. Production of a protocol involves a substantial amount of work but it is an effort worth making as it may avoid wasted time later.

Before you can produce a protocol you need to be clear about the clinical scenario and the diagnostic dilemma. You also need to have an understanding of the diagnostic test accuracy (DTA) review methodology to appropriately tailor and select the methods for use. Review authors should familiarise themselves with the content of this Handbook. It is necessary to understand the methods described in all subsequent chapters in order to write a satisfactory protocol which follows Cochrane DTA methodology. However, once a good protocol is written the review team is halfway to producing a good final review report.

4.2   Format of protocols of diagnostic test accuracy

All systematic reviews of diagnostic test accuracy published in the *Cochrane Database of Systematic Reviews* have the same format. This helps readers find the results of research quickly and assess the validity, applicability, and implications of those results. The structure guides review authors to report their work explicitly and concisely, and minimises the effort required to do this. The set format is also suited to electronic publication and updating, and facilitates the production of statistical summary figures and tables that are informative and readable when viewed on a computer monitor or printed.

In this chapter we discuss the format and reporting requirements for a protocol. In a subsequent Chapter (XX) we discuss the work needed to convert the protocol into a review.

The Review Manager software (RevMan) is designed to help review authors construct protocols and reviews in the appropriate format and to facilitate electronic publication. Protocols must be prepared in RevMan, although it is possible to cut-and-paste text from other software. The standard headings and tables embedded in RevMan guide review authors when preparing their report and are used by the publisher to structure the publication and link readers to the sections which are of particular interest to them. Table XX details the headings relevant to protocols and reviews. Where headings are common to both protocol and review it is likely that only minor changes in content will be required between stages, such as a change in writing tense (from future to past). The exception will be where there are declared differences between a published protocol and a review. The content that should follow each heading is described in this chapter.

For a protocol the main sections cover title (see Chapter 3), key information about the protocol including authorship (see Chapter 2), dates of publication and expected dates for completion, a main text section including the background, the objectives and the methods, statements of acknowledgements, and declarations of interest (see Chapter 2). Protocols can also include tables and figures, which are useful devices to display key information, they also have references to key studies cited in the background or methods. Sources of support should also be declared and protocols can include appendices, which are useful devices for displaying technical information.

Table: Format of Text for Protocols and Reviews of Diagnostic Test Accuracy

HEADINGS			
Title			P
Authors details			P
Contact person			P
Important dates	Assessed as up to date		P
	Date of search		P
	Next stage expected		P
	Protocol first published		P
	Review first published		
	Last citation issue		
What's new			
History			
Abstract	Background		
	Objectives		
	Search methods		
	Selection criteria		
	Data collection and analysis		
	Results		
	Authors' conclusions		
Plain language summary			
Background	Target condition being diagnosed*		P
	Index test(s)*		P
	Clinical pathway	Prior test(s)*	P
		Role of index test(s)*	P
		Alternative test(s) *	P
	Rationale*		P
Objectives	Secondary objectives*		P
Methods	Criteria for considering studies for this review	Types of studies	P
		Participants	P
		Index tests	P
		Target conditions	P
		Reference standards	P
	Search methods for identification of studies	Electronic searches	P
		Searching other resources *	P
	Data collection and analysis	Selection of studies	P
		Data extraction and management	P
		Assessment of methodological quality	P
		Statistical analysis and data synthesis	P
		Investigations of heterogeneity *	P
		Sensitivity analyses *	P
		Assessment of reporting bias *	P
Results	Results of search		
	Methodological quality of included studies		
	Findings		
Discussion	Summary of main results		
	Strengths and weaknesses of review		
	Applicability of findings to review question		
Authors conclusions	Implications for practice		
	Implications for research		
Acknowledgements			P
Contribution of authors			P
Declarations of interest			P
Differences between protocol and review			
Published notes			
Sources of support	Internal sources		
	External sources		
Feedback			
Appendices	Search strategy		P
	Review-specific tailoring of QUADAS/ QUADAS2		P
Tables	Characteristics of studies	Characteristics of included studies	
		Characteristics of excluded studies	
		Characteristics of studies awaiting classification	
		Characteristics of ongoing studies	

Summary of findings table	
Additional tables	
References to studies	Included studies
	Excluded studies
	Studies awaiting classification
	Ongoing studies
Other references	Background
	Other versions of this review published
	Classification pending references
Data and analysis	
Figures	

Notes to Table: **P**: required in protocol

4.3   Audience and writing style

As with all medical writing, it is important to consider the readers when deciding on the writing style, language, detail, and level of assumed knowledge. Cochrane protocols and reviews are read by informed patients as well as by clinicians, other health-care professionals, and policy makers. They are widely read by people who do not have English as their first language. It is thus important that the content and writing style, as far as possible, ensures these documents are accessible to this wide audience. Writing experts suggest the text has a readability level similar to that used in broadsheet newspapers, in common with international general medical journals. Writing clear, simple language is surprisingly difficult for most people. While DTA reviews will need to contain some technical language, take care to avoid jargon. Long words, unfamiliar words, and long sentences make text hard to read. Avoid sentences with more than 20 words, except when listing items. While some abbreviations can be helpful (e.g. if they condense long terms, or are familiar to readers) avoid over-use. Always spell out abbreviations the first time you use them and in any sections that may be read by themselves. Although there is no formal word limit on Cochrane protocols and reviews, brevity improves accessibility and the likely impact of a review.

The audience for Cochrane DTA Reviews may be different to that for reviews of interventions. The audience may be more technically able, as decisions about the provision and use of tests within healthcare systems are often made by groups of experts rather than individual doctors. Cochrane DTA Reviews will be only one of several pieces of evidence that inform policies about test use, or form the basis for guidelines.

Many aspects of diagnosis and testing, and the probabilistic relationships that are evaluated, are difficult to understand. Whilst reviews should aim for simplicity of language and presentation, essential detail, both clinical and methodological, must not be omitted.

4.4   Contents of a diagnostic test accuracy protocol

In this section we consider each item in a Cochrane DTA protocol and provide direction on how it should be completed.

4.4.1   Dates

There are several dates associated with a Cochrane review and protocol. Some dates are automatically generated by RevMan, and some need to be entered by the review author. Dates are important both to inform readers of the review and to facilitate management of review publication. Review authors must apply the following definitions when entering dates into relevant fields during an update or amendment to a review.

4.4.1.1   Assessed as Up-to-date

This date is entered by review authors for full reviews only (not protocols).

4.4.1.2   Date of search

This date is entered by review authors for full reviews only (not protocols).

4.4.1.3   Next stage expected

This date is entered by protocol authors indicating the date on which the full review is expected (e.g. in 1 year).

4.4.1.4   Protocol first published

This date is automatically recorded in RevMan and generated when the protocol is published.

4.5   Main text

The text of a Cochrane protocol contains a number of fixed headings and subheadings that are available in the RevMan document structure. Additional optional subheadings are also included in the structure, but review authors should not be limited by these and should add their own subheadings where appropriate. Review authors are encouraged to use the optional subheadings included in the structure where possible, as headings help readers navigate around the review.

4.5.1   Background [fixed, level 1 heading]

What do readers need to learn from the background section of a protocol and review? First, they need to be clear what diagnostic clinical problem the review will address and why it is important. Second, they need to understand what disease or conditions are being identified, and third, what tests will be evaluated.

To put the evidence in context, review authors need to consider how diagnoses are currently made, describe diagnostic care pathways, and explain how new tests will change these pathways. Including information on how new tests might benefit patients, for example through more accurate, earlier, or safer diagnoses, will help put the value of test accuracy in context. Background sections should also specify how

the planned research relates to the existing body of scientific knowledge and what the review will add.

To ensure background sections of Cochrane reviews address these issues, the RevMan structure includes subheadings to help review authors provide the key information for these sections. Writing a good background involves balancing provision of detail against the brevity required to make a review accessible. Review authors should always consider placing technical material in appendices, particularly when it is only of interest to technical experts. The Background section should not be overly long. Whilst Cochrane reviews are not restricted by a word limit, the background sections should follow the guidance given for general medical journals, where the background rarely exceeds 1000 words.

The background section contains 4 subheadings which can be used to help structure the text:

Target condition being diagnosed [optional, level 2 heading]

The target condition needs to be defined together with any sub categories of the target condition, which will be considered as separate diagnostic classifications. It is important to describe the frequency, severity, prognosis, and possible treatments for the target condition. Note that this may be diagnosis of a condition, or it may be refining a group of patients with a condition into different treatment groups (e.g. differentiating between breast lumps that are benign and those that are malignant).   If there are Cochrane reviews of interventions for the target condition they should be cross-referenced here. It may also be helpful, in this section, to describe conditions that are similar to the target condition but will not be investigated directly in the review.

Index test(s) [optional, level 2 heading]

The index tests are those that will be evaluated in the review and the accuracy of which will be estimated and compared. Details of any variation in each test included should be given. For example whether there are different manufacturers of a test, who will be operating and interpreting the test, and whether more than one threshold will be considered by the review. Detailed specifications of included index tests which will be given as eligibility criteria later in the protocol need not be described in this section.

Clinical pathway [fixed, level 2 heading]

In this section, review authors should detail the existing clinical pathway of patients. It should outline how patients might present, the point in the pathway at which participants would be considered for testing with the index test (or tests), and the role of each index test. A diagram may be helpful, particularly if the pathway is complex. There are three further optional sub-headings to assist in this description.

Prior tests [optional, level 3 heading]

The population for the review may be selected as having had no previous testing, or on the basis of results of earlier tests, or of features identified at initial presentation. Details of prior testing should include clinical history and examination if relevant. The healthcare setting (community, primary, or secondary care) in which participants presented may be used as a surrogate measure of the type and number of tests they might have received prior to receiving the index test.

Role of index test(s) [optional, level 3 heading]

This describes how the index test is used in the diagnostic pathway, whether it is being used in addition to existing tests (add), replacing existing tests (replace), or to decide which patients should receive further testing (triage) (see Chapter 5) .

Alternative test(s) [optional, level 3 heading]

A description of other diagnostic tests and strategies that could be used in clinical practice, but that aren't evaluated in this review should be given. This helps readers place the review in the context of all available diagnostic options, and to link to other reviews that provide information on alternatives.

Rationale [optional, level 2 heading]

Finally, the background section should give the rationale for the review questions and for undertaking the review. This section may also explain how the plans for the review will fit with existing evidence and indicate whether the review is needed because of changing practice or because previous reviews used poor methods. The rationale section should summarise why the questions are being asked and why they are important. If a suite of diagnostic test accuracy reviews is being planned (see 4.7) the place of the current review in the set of reviews should be explained.

4.5.2 Objectives [fixed, level 1 heading]

The review question should be clearly stated. The primary objective should relate to the accuracy of the index test(s) for the target condition as verified by the reference standard. Where possible, use the formula: 'To determine the diagnostic accuracy of [index test] for detecting [target condition] in [participant description]'. The objective should also communicate the proposed role of the index test(s) if this is known (see Chapter 5). Cochrane reviews usually compare one test with another rather than simply evaluating the accuracy of a single test. All comparisons between tests should be listed as objectives.

Secondary objectives [optional, level 2 heading]

If, for example, the primary objective is to compare the accuracy of two tests, the secondary objectives may be to estimate test accuracy for each test at pre-specified thresholds. Secondary objectives relating to the investigation of heterogeneity between study results should also be listed under this subheading but should be limited to describing the sources of heterogeneity to be investigated rather than

detailing the statistical methods for doing this. Methods for investigating heterogeneity should be detailed in the methods section (see XX).

4.5.3 Methods [fixed, level 1 heading]

Text cannot be placed immediately under the 'Methods' Level 1 subheading. Text for this section starts below the first subheading.

The Methods section in a protocol should fully describe the methods that will be used for the review. It is written in the future tense. When writing this section, remember that these details will be used again in the final review (albeit with the tense switched from the future to the past).

Review authors should clearly describe the selection criteria for considering studies for the review (see Chapter 5 and Chapter 6), the methods used to identify relevant studies (see Chapter 7), the process used for selecting studies and collecting data (see Chapter 8), and how the methodological quality of included studies will be assessed (see Chapter 9). A statistician is usually best placed to write the section describing the statistical analysis and data synthesis (see Chapter 10). In addition, information about how to investigate sources of heterogeneity and any pre-planned sensitivity analyses should be described clearly here (see Chapter 10).

Criteria for considering studies for this review [fixed, level 2 heading]

The eligibility criteria required for studies to be included in the review must be clearly stated. Five sets of criteria need to be described:

> **Types of studies [fixed, level 3 heading]**
>
> Identifiable design features of eligible studies must be stated. Review authors should describe the design as well as using a design name, as there is no universal terminology for diagnostic study designs. Key aspects include whether only prospective or both prospective and retrospective studies are to be included, to describe how and where participants were recruited (e.g. as a consecutive series of new presentations in primary care), and whether the study was cross-sectional or included longitudinal assessment for the reference standard. Authors should always state whether they included or excluded diagnostic case-control studies or the strategy used to make this decision.
>
> Any restrictions based on a minimal quality standard, minimal sample sizes, or numbers of diseased cases should be stated, but there is no clear guidance on how these limitations should be determined.
>
> In reviews that include comparisons between tests, alternative study designs which make within-study comparisons of tests may be sought, notably studies where all individuals receive all tests, and those where all individuals receive the reference standard but are randomised to receive different index tests. These latter studies should be described as randomised trials of test accuracy. Some reviews which compare tests may restrict study inclusion only to studies of these designs which make within-study comparisons, but others may include studies that evaluate one or other of the tests individually (particularly

where few such published studies exist). Any such restrictions should be stated.

Randomised trials of patient outcomes are rarely eligible for inclusion. They can only be included if individuals received both the index test and a reference standard – occasionally this information is available.

Participants [fixed, level 3 heading]

Review authors should specify the participants for whom the test would be applicable, including any restrictions on diagnoses, age groups and settings. Planned subgroup analyses related to participant characteristics should not be listed here – they should be listed under the sources of heterogeneity in the secondary objectives.

Index tests [fixed, level 3 heading]

Review authors should specify the test(s) to be evaluated in the review. If multiple tests are being reviewed and compared with each other details for each test should be given. In the first Cochrane DTA protocols and reviews tests were separated into new index tests or existing comparator tests. However it is often difficult to distinguish index from comparator tests and tests are no longer divided into these two categories. However, where it is clear that some tests are new experimental tests and others are existing standard comparative tests this should be noted.

Target conditions [fixed, level 3 heading]

The target condition is a particular disease or disease stage that the index test is intended to identify. Some reviews may evaluate the ability of tests to differentiate between several target conditions – if this is the case, the multiple target conditions should all be listed here.

Reference standards [fixed, level 3 heading]

Describe the clinical reference standards required to establish the presence or absence of the target condition in the tested population. If any reference standards are commonly used but considered inadequate this should be stated here as an exclusion criteria. If the review covers multiple target conditions, the reference standard for each should be stated.

Search methods for identification of studies [fixed, level 2 heading]

The search methods to be used in the review can be described under two headings:

Electronic searches [fixed, level 3 heading]

The methods used to identify studies should be summarised. Recommendations about the content of these sections are given in Chapter 7. The bibliographic databases searched, the dates and periods searched, and any constraints, such as language, should be stated. The full search strategies for each database should be listed in an appendix to the review. At protocol stage,

it is acceptable to include a search strategy for a single database as an example of the approach that will be used rather than listing specific strategies for each database to be searched.

Searching other resources [optional, level 3 heading]

List grey literature sources, such as reports and conference proceedings. If journals are specifically hand-searched for the review, this should also be noted. List people (for example, researchers, experts) and/or organisations to be contacted. List any other sources, which may include, for example, reference lists, the World Wide Web or personal collections of articles.

This text may be organised under the following four subheadings:

- Grey literature,
- Handsearching,
- References lists, and
- Correspondence.

These subheadings are not included in the RevMan structure, so if required, need to be created by the authors. They can be used either in place of 'Searching other resources' or as subheadings to it.

Data collection and analysis [fixed, level 2 heading]

Selection of studies [fixed, level 3 heading]

The method used to apply the selection criteria should be described. Typically, this may start with a review of titles, proceed to review of abstracts where titles indicated that a study might be of relevance, and finally the identification of eligible studies on the basis of their full text. This section should indicate the rigour of the selection and data extraction processes by describing any process of duplicate selection and extraction decisions, the method by which discrepancies will be resolved, and how key data will be checked (and double checked), and entered into RevMan (see Chapter 6).

Data extraction and management [fixed, level 3 heading]

It is important to indicate the characteristics of studies that will be recorded, such as the setting, the presentation at recruitment, and the use of tests, both for the index tests and the reference standard. In addition, authors should describe the method that will be used to extract or obtain data from published reports or from primary authors of included studies (for example, using a data extraction/data collection form). Any planned reanalysis of individual patient data should be described. Authors should state whether data will be extracted independently by more than one author, and how disagreements will be resolved. If relevant, methods for processing data in preparation for analysis should be described (see Chapter 8).

Assessment of methodological quality [fixed, level 3 heading]

Authors should describe both the tool used to assess methodological quality and the method by which it was applied. Quality assessment must be undertaken using the

QUADAS-2 tool as future versions of RevMan will not support reviews structured with the original QUADAS tool. Authors should describe any adaptations and additions to the standard tool and provide definitions of any items that need to be tailored according to the clinical context of the review. For example, assessing applicability often involves making judgements about whether patients are representative of those who experience the condition. This requires a definition of what a representative patient group would look like. Operational definitions used within the quality assessment tool should be stated (preferably using an additional table in an Appendix).

Authors should state whether the tool will be applied independently by more than one review author and how disagreements will be resolved.

Statistical analysis and data synthesis [fixed, level 3 heading]

The protocol must include key definitions and an analysis plan. For example, review authors should define how disease positive and test positive will be determined, and describe plans of the analyses that will be made, particularly for the comparisons between tests.

Descriptive methods should be detailed here. These consist of tabulation, graphical displays of estimates of diagnostic accuracy (for example sensitivities and specificities), and plotting the study results in ROC space (see Chapter 10).

Review authors should describe the type of statistical model(s) to be used or the methods that will be used to select them. This will largely depend on whether the review will provide an average estimate of sensitivity and specificity or will estimate an underlying summary ROC curve. This may be determined by the mix of thresholds that were used in the primary research studies. Review authors must describe their strategy for handling multiple thresholds, pre-stating any thresholds considered important for the analysis. The statistical software to be used for the analysis should be stated. Full details of the requirements for the statistical section of the protocol are given in Chapter 10.

Investigations of heterogeneity [optional, level 3 heading]

Indicate how the sources of heterogeneity listed in the objectives will be investigated (see Chapter 10). This section should also describe the statistical methods that will be used to address the heterogeneity investigations outlined in the secondary objectives.

Sensitivity analyses [optional, level 3 heading]

Pre-planned sensitivity analyses should be stated here. These could include restricting analyses to a particular subgroup of patients, or excluding studies with a particular methodological shortcoming, for example verification bias or review bias (see Chapter 10).

Assessment of reporting bias [optional, level 3 heading]

If any tests or investigations will be used to detect reporting biases their methods should be explained here (see Chapter 10). Review authors often elect not to

investigate reporting bias due to the lack of sensitive and appropriate statistical methods.

4.6   Figures

In addition to those generated by RevMan, review authors can import their own figures (e.g. to illustrate clinical pathways). Guidance on technical aspects of preparing additional figures, including appropriate file size, guidance on labelling and captions is available in the RevMan5.2 help files. Any images uploaded as additional figures will not be edited or otherwise improved by others, but will be published 'as is'. It is therefore important that images are fit for publication. Large images take up lots of disk space. A single large image can easily take up ten times the total space required for the text and tables of the review. This leads to very large export files. Scanned images can be especially space-consuming because the resolution may be much higher than needed. Always use images with a good balance between resolution and detail, and include as few images as possible.

Check the copyright position for any figures reproduced from other publications. In many cases, copyright is held by the publisher rather than the author, so review authors will need permission to reproduce their own work. However, permission may not be needed for figures published under a Creative Commons licence, but the source should, nevertheless be properly acknowledged. If permission to publish a copyrighted figure is granted, the final phrase of the figure caption must be: "Copyright © [Year] [Name of copyright holder, any wording required by the copyright holder]: reproduced with permission."

4.7   Appendices

Appendices are useful to give extra technical details of the index tests and the reference standards. They can also be used to detail the electronic search strategies and to give a full description of the quality assessment tool, defining any tailored criteria that will be used in the review. Some review authors also include the data extraction sheets in the appendix. If non-standard statistical methods will be used, full technical details and software code should be reported in an appendix.

Appendices should be considered as supplementary information as they may not appear in some reduced formats of the published review.

4.8   Suites of reviews and generic protocols

Reviews should be planned in such a way that they can be completed in a timely manner and will produce reports that are not overly complex or detailed, and thus inaccessible. If a review is large, it may be wise to consider splitting it into a series of reviews. This may be particularly useful where there are large numbers of tests to be assessed, or multiple target disorders that are closely related. Separate reviews may also be needed when tests are used for the same purpose but in different settings or on different clinical pathways, as these will include different studies.

Where there is a common core methodology, it may be efficient, both in terms of the research management and also for peer review, to produce a single generic protocol.

This protocol should include sufficient background to explain the plan and the rationale for separating the work into several reviews. Typically, the linked reviews will use a common single search strategy, but the methodology may need to permit differences that arise because of variation in reference standards for different target conditions, differences in the ways in which the QUADAS-2 quality assessment criteria are tailored, and different approaches to statistical analysis required by different tests. The protocol should also include the plan for producing an overview document to synthesize the results from the individual reviews to produce a summary useful for patients, doctors, and other decision makers.

4.9 Contributions to this chapter

Editors: Jonathan Deeks, Susanna Wisniewski, Clare Davenport.

This chapter drew on material published in Higgins JPT, Green S (editors). Chapter 4: Guide to the contents of a Cochrane protocol and review. In: 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 http://www.cochrane.org/resources/handbook.

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