Supplementary material 1 to Chapter 1: Reporting template for Cochrane Protocols of diagnostic test accuracy

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The text of a Cochrane protocol contains a number of fixed headings and subheadings that are available in the Review Manager (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.

1.1 Title

1.2 Abstract

1.3 Background

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 clinical 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 four subheadings which can be used to help structure the text:

1.3.1 Target condition being diagnosed

The target condition needs to be defined together with any subcategories 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.

1.3.2 Index test(s)

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 for defining test positivity will be considered in 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.

1.3.3 Clinical pathway

This section should give details of 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. Three further optional subheadings can assist in this description. (See Chapter 5)

1.3.3.1 Prior tests

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 for the type and number of tests they might have received prior to receiving the index test.

1.3.3.2 Role of index test(s)

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

1.3.3.3 Alternative test(s)

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

1.3.4 Rationale

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 summarize why the questions are being asked and why they are important. If a suite of diagnostic test accuracy reviews is being planned (see Section 1.7) the place of the current review in the set of reviews should be explained.

1.4 Objectives

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 format: '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 of Diagnostic Test Accuracy usually compare one index test with another rather than simply evaluating the accuracy of a single index test. All comparisons between index tests should be listed as objectives.

1.4.1 Secondary objectives

If, for example, the primary objective is to compare the accuracy of two index tests, the secondary objectives may be to estimate the accuracy of 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 Section 1.5.3.5).

1.5 Methods

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), the methods used to identify and select relevant studies (see Chapter 6), the process used for collecting data (see Chapter 7), how the risk of bias and applicability will be assessed (see Chapter 8). A statistician is usually best placed to write the section describing the statistical analysis and data synthesis (see Chapter 9 and 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).

1.5.1 Criteria for considering studies for this review

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

1.5.1.1 Types of studies

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 test accuracy 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. Review 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 methodological 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 index tests, alternative study designs that make within-study comparisons of tests may be sought, notably comparative accuracy studies where all individuals receive all tests, and those where all individuals receive the reference standard but are randomized to receive different index tests. These latter studies should be described as randomized studies of test accuracy. Some reviews which compare tests may restrict study inclusion only to comparative studies of these designs that 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.

Randomized 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.

1.5.1.2 Participants

Review authors should specify the participants for whom the index test(s) 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.

1.5.1.3 Index tests

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 Protocols and Reviews of Diagnostic Test Accuracy to be published, tests

were separated into index (new) tests and comparator (existing) tests. However, it is often difficult to distinguish index from comparator tests and Cochrane Reviews of Diagnostic Test Accuracy no longer divide tests into these two categories. However, where it is clear that some tests are new experimental tests and others are existing standard comparator tests this should be noted.

1.5.1.4 Target conditions

The target condition is a particular disease or state 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.

1.5.1.5 Reference standards

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

1.5.2 Search methods for identification of studies

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

1.5.2.1 Electronic searches

The methods used to identify studies should be summarized. Recommendations about the content of these sections are given in Chapter 6. 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. The review protocol should at least include the verbatim search strategy for a single database as an example of the approach that will be used.

1.5.2.2 Searching other resources

Review authors should list grey literature sources, such as reports and conference proceedings. If journals will be handsearched for the review, this should also be noted. List people (e.g. researchers, experts) and/or organizations to be contacted. List any other sources, which may include, for example, reference lists, the internet or personal collections of articles.

This text may be organized 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 review authors. They can be used either in place of ‘Searching other resources’ or as subheadings to it.

1.5.3 Data collection and analysis

1.5.3.1 Selection of studies

The method used to apply the selection criteria should be described. Typically, this may start with a review of titles, proceed to a 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 and Chapter 7).

1.5.3.2 Data extraction and management

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 test(s) and the reference standard(s). 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 (e.g. using a data extraction/data collection form). Any planned reanalysis of individual patient data should be described. Review authors should state whether data will be extracted independently by more than one review author, and how disagreements will be resolved. If relevant, methods for processing data in preparation for analysis should be described (see Chapter 7).

1.5.3.3 Assessment of methodological quality

Review 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. In addition to using QUADAS-2, the QUADAS-C tool should be used for assessing comparative studies in reviews with a comparative objective. Review authors should describe any adaptations and additions to the standard QUADAS-2 and QUADAS-C tools 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). (See Chapter 8.)

Review authors should state whether the tool(s) will be applied independently by more than one review author and how disagreements will be resolved.

1.5.3.4 Statistical analysis and data synthesis

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, including for the comparisons between index tests.

Descriptive methods should be detailed here. These consist of tabulation, graphical displays of estimates of diagnostic accuracy (e.g. sensitivities and specificities), and plotting the study results in ROC space (see Chapter 9). authors can assume that readers will be familiar with key statistical summary measures. Therefore, it is not necessary to define sensitivity and specificity, likelihood ratios, etc.

Definitions of the reference standard (specifying any binary classifications required) and categorisations of positive and negative test results are required. Rules for handling known categories of inconclusive test results should be pre-stated where possible.

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 a summary 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. If one threshold per study is to be included in analyses, review authors should pre-specify (if possible) any common thresholds at which summary estimates of sensitivity and specificity will be obtained and also describe the strategy for choosing a threshold per study for the estimation of a SROC curve (see Section 9.3.1). 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 9. If non-standard methods are included, these should be described (with full details provided in an appendix) and their use justified.

If review authors expect to use more complex models, such as those for multiple thresholds or imperfect reference standards, they should outline the methods they intend to use. For example, they should outline the approach they intend to adopt for the simultaneous analysis of multiple thresholds per study (Section 9.4.5) and/or models for dealing with error in the reference standard (Section 9.5.1 and Chapter 10).

If the review aims to compare the accuracy of different index tests, then review authors should outline whether comparisons will be based on within-study comparisons only or on all studies, or whether both of these approaches will be presented. If both approaches are used, authors should indicate the primary analysis. Again, numbers of studies may affect the original intent (see Section 9.4.7).

1.5.3.5 Investigations of heterogeneity

Review authors should indicate how the sources of heterogeneity listed in the objectives will be investigated (see Chapter 9 and Chapter 10). This section should also describe the statistical methods that will be used to address the heterogeneity investigations outlined in the secondary objectives. State covariate codings if known, and the approaches used for building models (see Section 9.4.6).

1.5.3.6 Sensitivity analyses

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 high and unclear risk of bias due to participant selection (see Chapter 9). Also, where different choices may be made about operationalization of the reference standard or test positivity, the rationale for choosing between these should be described, along with plans for sensitivity analyses to investigate the robustness of the decisions made.

1.5.3.7 Assessment of reporting bias

If any tests or investigations will be used to detect reporting biases their methods should be explained here (see Chapter 9). Review authors often elect not to investigate reporting bias due to the lack of appropriate statistical methods.

1.6 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, labelling and captions is available in the RevMan 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 imported images as possible.

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1.7 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 methodological quality assessment tool, defining any tailored criteria that will be used in the review. Some review authors also include the data extraction forms 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.