1

Starting a review

Toby J Lasserson, James Thomas, Julian PT Higgins

KEY POINTS

- Systematic reviews address a need for health decision makers to be able to access high quality, relevant, accessible and up-to-date information.
- Systematic reviews aim to minimize bias through the use of pre-specified research questions and methods that are documented in protocols, and by basing their findings on reliable research.
- Systematic reviews should be conducted by a team that includes domain expertise and methodological expertise, who are free of potential conflicts of interest.
- People who might make – or be affected by – decisions around the use of interventions should be involved in important decisions about the review.
- Good data management, project management and quality assurance mechanisms are essential for the completion of a successful systematic review.

1.1 Why do a systematic review?

Systematic reviews were developed out of a need to ensure that decisions affecting people’s lives can be informed by an up-to-date and complete understanding of the relevant research evidence. With the volume of research literature growing at an ever-increasing rate, it is impossible for individual decision makers to assess this vast quantity of primary research to enable them to make the most appropriate healthcare decisions that do more good than harm. By systematically assessing this primary research, systematic reviews aim to provide an up-to-date summary of the state of research knowledge on an intervention, diagnostic test, prognostic factor or other health or healthcare topic. Systematic reviews address the main problem with ad hoc searching and selection of research, namely that of bias. Just as primary research studies use methods to avoid bias, so should summaries and syntheses of that research.


© 2019 The Cochrane Collaboration. Published 2019 by John Wiley & Sons Ltd.
A systematic review attempts to collate all the empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made (Antman et al 1992, Oxman and Guyatt 1993). Systematic review methodology, pioneered and developed by Cochrane, sets out a highly structured, transparent and reproducible methodology (Chandler and Hopewell 2013). This involves: the a priori specification of a research question; clarity on the scope of the review and which studies are eligible for inclusion; making every effort to find all relevant research and to ensure that issues of bias in included studies are accounted for; and analysing the included studies in order to draw conclusions based on all the identified research in an impartial and objective way.

This Handbook is about systematic reviews on the effects of interventions, and specifically about methods used by Cochrane to undertake them. Cochrane Reviews use primary research to generate new knowledge about the effects of an intervention (or interventions) used in clinical, public health or policy settings. They aim to provide users with a balanced summary of the potential benefits and harms of interventions and give an indication of how certain they can be of the findings. They can also compare the effectiveness of different interventions with one another and so help users to choose the most appropriate intervention in particular situations. The primary purpose of Cochrane Reviews is therefore to inform people making decisions about health or health care.

Systematic reviews are important for other reasons. New research should be designed or commissioned only if it does not unnecessarily duplicate existing research (Chalmers et al 2014). Therefore, a systematic review should typically be undertaken before embarking on new primary research. Such a review will identify current and ongoing studies, as well as indicate where specific gaps in knowledge exist, or evidence is lacking; for example, where existing studies have not used outcomes that are important to users of research (Macleod et al 2014). A systematic review may also reveal limitations in the conduct of previous studies that might be addressed in the new study or studies.

Systematic reviews are important, often rewarding and, at times, exciting research projects. They offer the opportunity for authors to make authoritative statements about the extent of human knowledge in important areas and to identify priorities for further research. They sometimes cover issues high on the political agenda and receive attention from the media. Conducting research with these impacts is not without its challenges, however, and completing a high-quality systematic review is often demanding and time-consuming. In this chapter we introduce some of the key considerations for review authors who are about to start a systematic review.

1.2 What is the review question?

Getting the research question right is critical for the success of a systematic review. Review authors should ensure that the review addresses an important question to those who are expected to use and act upon its conclusions.
We discuss the formulation of questions in detail in Chapter 2. For a question about
the effects of an intervention, the PICO approach is usually used, which is an acronym
for Population, Intervention, Comparison(s) and Outcome. Reviews may have
additional questions, for example about how interventions were implemented,
economic issues, equity issues or patient experience.

To ensure that the review addresses a relevant question in a way that benefits users,
it is important to ensure wide input. In most cases, question formulation should
therefore be informed by people with various relevant – but potentially different –
perspectives (see Chapter 2, Section 2.4).

1.3 Who should do a systematic review?

Systematic reviews should be undertaken by a team. Indeed, Cochrane will not publish
a review that is proposed to be undertaken by a single person. Working as a team not
only spreads the effort, but ensures that tasks such as the selection of studies for
eligibility, data extraction and rating the certainty of the evidence will be performed
by at least two people independently, minimizing the likelihood of errors. First-time
review authors are encouraged to work with others who are experienced in the process
of systematic reviews and to attend relevant training.

Review teams must include expertise in the topic area under review. Topic expert-
tise should not be overly narrow, to ensure that all relevant perspectives are consid-
ered. Perspectives from different disciplines can help to avoid assumptions or
terminology stemming from an over-reliance on a single discipline. Review teams
should also include expertise in systematic review methodology, including statistical
expertise.

Arguments have been made that methodological expertise is sufficient to perform a
review, and that content expertise should be avoided because of the risk of preconcep-
tions about the effects of interventions (Gøtzsche and Ioannidis 2012). However, it is
important that both topic and methodological expertise is present to ensure a good
mix of skills, knowledge and objectivity, because topic expertise provides important
insight into the implementation of the intervention(s), the nature of the condition being
treated or prevented, the relationships between outcomes measured, and other factors
that may have an impact on decision making.

A Cochrane Review should represent an independent assessment of the evidence
and avoiding financial and non-financial conflicts of interest often requires careful
management. It will be important to consider if there are any relevant interests that
may constitute real or perceived conflicts. There are situations where employment,
holding of patents and other financial support should prevent people joining an author
team. Funding of Cochrane Reviews by commercial organizations with an interest in
the outcome of the review is not permitted. To ensure that any issues are identified
early in the process, authors planning Cochrane Reviews should consult the conflicts
of interest policy before starting the review. Authors should make complete
declarations of interest at the outset of the review, and refresh these throughout
the review life cycle (title, protocol, review, update) or at any point when their
circumstances change.
1.3.1 Involving consumers and other stakeholders

Because the priorities of decision makers and consumers may be different from those of researchers, it is important that review authors consider carefully what questions are important to these different stakeholders. Systematic reviews are more likely to be relevant to a broad range of end users if they are informed by the involvement of people with a range of experiences, in terms of both the topic and the methodology (Thomas et al 2004, Rees and Oliver 2017). Engaging consumers and other stakeholders, such as policy makers, research funders and healthcare professionals, increases relevance, promotes mutual learning, improved uptake and decreases research waste.

Mapping out all potential stakeholders specific to the review question is a helpful first step to considering who might be invited to be involved in a review. Stakeholders typically include: patients and consumers; consumer advocates; policy makers and other public officials; guideline developers; professional organizations; researchers; funders of health services and research; healthcare practitioners, and, on occasion, journalists and other media professionals. Balancing seniority, credibility within the given field, and diversity should be considered. Review authors should also take account of the needs of resource-poor countries and regions in the review process (see Chapter 16) and invite appropriate input on the scope of the review and the questions it will address.

It is established good practice to ensure that consumers are involved and engaged in health research, including systematic reviews. Cochrane uses the term ‘consumers’ to refer to a wide range of people, including patients or people with personal experience of a healthcare condition, carers and family members, representatives of patients and carers, service users and members of the public. In 2017, a Statement of Principles for consumer involvement in Cochrane was agreed. This seeks to change the culture of research practice to one where both consumers and other stakeholders are joint partners in research from planning, conduct, and reporting to dissemination. Systematic reviews that have had consumer involvement should be more directly applicable to decision makers than those that have not (see online Chapter II).

1.3.2 Working with consumers and other stakeholders

Methods for working with consumers and other stakeholders include surveys, workshops, focus groups and involvement in advisory groups. Decisions about what methods to use will typically be based on resource availability, but review teams should be aware of the merits and limitations of such methods. Authors will need to decide who to involve and how to provide adequate support for their involvement. This can include financial reimbursement, the provision of training, and stating clearly expectations of involvement, possibly in the form of terms of reference.

While a small number of consumers or other stakeholders may be part of the review team and become co-authors of the subsequent review, it is sometimes important to bring in a wider range of perspectives and to recognize that not everyone has the capacity or interest in becoming an author. Advisory groups offer a convenient approach to involving consumers and other relevant stakeholders, especially for topics in which opinions differ. Important points to ensure successful involvement include the following.
The review team should co-ordinate the input of the advisory group to inform key review decisions.

The advisory group’s input should continue throughout the systematic review process to ensure relevance of the review to end users is maintained.

Advisory group membership should reflect the breadth of the review question, and consideration should be given to involving vulnerable and marginalized people (Steel 2004) to ensure that conclusions on the value of the interventions are well-informed and applicable to all groups in society (see Chapter 16).

Templates such as terms of reference, job descriptions, or person specifications for an advisory group help to ensure clarity about the task(s) required and are available from INVOLVE. The website also gives further information on setting and organizing advisory groups. See also the Cochrane training website for further resources to support consumer involvement.

1.4 The importance of reliability

Systematic reviews aim to be an accurate representation of the current state of knowledge about a given issue. As understanding improves, the review can be updated. Nevertheless, it is important that the review itself is accurate at the time of publication. There are two main reasons for this imperative for accuracy. First, health decisions that affect people’s lives are increasingly taken based on systematic review findings. Current knowledge may be imperfect, but decisions will be better informed when taken in the light of the best of current knowledge. Second, systematic reviews form a critical component of legal and regulatory frameworks; for example, drug licensing or insurance coverage. Here, systematic reviews also need to hold up as auditable processes for legal examination. As systematic reviews need to be both correct, and be seen to be correct, detailed evidence-based methods have been developed to guide review authors as to the most appropriate procedures to follow, and what information to include in their reports to aid auditability.

1.4.1 Expectations for the conduct and reporting of Cochrane Reviews

Cochrane has developed methodological expectations for the conduct, reporting and updating of systematic reviews of interventions (MECIR) and their plain language summaries (Plain Language Expectations for Authors of Cochrane Summaries; PLEACS). Developed collaboratively by methodologists and Cochrane editors, they are intended to describe the desirable attributes of a Cochrane Review. The expectations are not all relevant at the same stage of review conduct, so care should be taken to identify those that are relevant at specific points during the review. Different methods should be used at different stages of the review in terms of the planning, conduct, reporting and updating of the review.

Each expectation has a title, a rationale and an elaboration. For the purposes of publication of a review with Cochrane, each has the status of either ‘mandatory’ or ‘highly desirable’. Items described as mandatory are expected to be applied, and if they are not then an appropriate justification should be provided; failure to implement such items
may be used as a basis for deciding not to publish a review in the Cochrane Database of Systematic Reviews (CDSR). Items described as highly desirable should generally be implemented, but there are reasonable exceptions and justifications are not required.

All MECIR expectations for the conduct of a review are presented in the relevant chapters of this Handbook. Expectations for reporting of completed reviews (including PLEACS) are described in online Chapter III. The recommendations provided in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement have been incorporated into the Cochrane reporting expectations, ensuring compliance with the PRISMA recommendations and summarizing attributes of reporting that should allow a full assessment of the methods and findings of the review (Moher et al 2009).

1.5 Protocol development

Preparing a systematic review is complex and involves many judgements. To minimize the potential for bias in the review process, these judgements should be made as far as possible in ways that do not depend on the findings of the studies included in the review. Review authors’ prior knowledge of the evidence may, for example, influence the definition of a systematic review question, the choice of criteria for study eligibility, or the pre-specification of intervention comparisons and outcomes to analyse. It is important that the methods to be used should be established and documented in advance (see MECIR Box 1.5.a, MECIR Box 1.5.b and below MECIR Box 1.5.c).

MECIR Box 1.5.a Relevant expectations for conduct of intervention reviews

<table>
<thead>
<tr>
<th>C19: Planning the search (Mandatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan in advance the methods to be used for identifying studies. Design searches to capture as many studies as possible that meet the eligibility criteria, ensuring that relevant time periods and sources are covered and not restricted by language or publication status.</td>
</tr>
<tr>
<td>Searches should be motivated directly by the eligibility criteria for the review, and it is important that all types of eligible studies are considered when planning the search. If searches are restricted by publication status or by language of publication, there is a possibility of publication bias, or language bias (whereby the language of publication is selected in a way that depends on the findings of the study), or both. Removing language restrictions in English language databases is not a good substitute for searching non-English language journals and databases.</td>
</tr>
</tbody>
</table>
MECIR Box 1.5.b Relevant expectations for the conduct of intervention reviews

C20: Planning the assessment of risk of bias in included studies (Mandatory)

Plan in advance the methods to be used for assessing risk of bias in included studies, including the tool(s) to be used, how the tool(s) will be implemented, and the criteria used to assign studies, for example, to judgements of low risk, high risk and unclear risk of bias.

Predefining the methods and criteria for assessing risk of bias is important since analysis or interpretation of the review findings may be affected by the judgements made during this process. For randomized trials, use of the Cochrane risk-of-bias tool is Mandatory, so it is sufficient (and easiest) simply to refer to the definitions of low risk, unclear risk and high risk of bias provided in the Handbook.

MECIR Box 1.5.c Relevant expectations for conduct of intervention reviews

C21: Planning the synthesis of results (Mandatory)

Plan in advance the methods to be used to synthesize the results of the included studies, including whether a quantitative synthesis is planned, how heterogeneity will be assessed, choice of effect measure (e.g. odds ratio, risk ratio, risk difference or other for dichotomous outcomes), and methods for meta-analysis (e.g. inverse variance or Mantel Haenszel, fixed-effect or random-effects model).

Predefining the synthesis methods, particularly the statistical methods, is important, since analysis or interpretation of the review findings may be affected by the judgements made during this process.

C22: Planning sub-group analyses (Mandatory)

Predefine potential effect modifiers (e.g. for subgroup analyses) at the protocol stage; restrict these in number, and provide rationale for each.

Pre-specification reduces the risk that large numbers of undirected subgroup analyses will lead to spurious explanations of heterogeneity.

C23: Planning the GRADE assessment and ‘Summary of findings’ table (Mandatory)

Plan in advance the methods to be used for assessing the certainty of the body of evidence, and summarizing the findings of the review.

Methods for assessing the certainty of evidence for the most important outcomes in the review need to be pre-specified. In ‘Summary of findings’ tables the most important feature is to predefine the choice of outcomes in order to guard against selective presentation of results in the review. The table should include the essential outcomes for decision making (typically up to seven), which generally should not include surrogate or interim outcomes. The choice of outcomes should not be based on any anticipated or observed magnitude of effect, or because they are likely to have been addressed in the studies to be reviewed.
Publication of a protocol for a review that is written without knowledge of the available studies reduces the impact of review authors’ biases, promotes transparency of methods and processes, reduces the potential for duplication, allows peer review of the planned methods before they have been completed, and offers an opportunity for the review team to plan resources and logistics for undertaking the review itself. All chapters in the Handbook should be consulted when drafting the protocol. Since systematic reviews are by their nature retrospective, an element of knowledge of the evidence is often inevitable. This is one reason why non-content experts such as methodologists should be part of the review team (see Section 1.3). Two exceptions to the retrospective nature of a systematic review are a meta-analysis of a prospectively planned series of trials and some living systematic reviews, as described in Chapter 22.

The review question should determine the methods used in the review, and not vice versa. The question may concern a relatively straightforward comparison of one treatment with another; or it may necessitate plans to compare different treatments as part of a network meta-analysis, or assess differential effects of an intervention in different populations or delivered in different ways.

The protocol sets out the context in which the review is being conducted. It presents an opportunity to develop ideas that are foundational for the review. This concerns, most explicitly, definition of the eligibility criteria such as the study participants and the choice of comparators and outcomes. The eligibility criteria may also be defined following the development of a logic model (or an articulation of the aspects of an extent logic model that the review is addressing) to explain how the intervention might work (see Chapter 2, Section 2.5.1).

A key purpose of the protocol is to make plans to minimize bias in the eventual findings of the review. Reliable synthesis of available evidence requires a planned, systematic approach. Threats to the validity of systematic reviews can come from the studies they include or the process by which reviews are conducted. Biases within the studies can arise from the method by which participants are allocated to the intervention groups, awareness of intervention group assignment, and the collection, analysis and reporting of data. Methods for examining these issues should be specified in the protocol. Review processes can generate bias through a failure to identify an unbiased (and preferably complete) set of studies, and poor quality assurance throughout the review. The availability of research may be influenced by the nature of the results (i.e. reporting bias). To reduce the impact of this form of bias, searching may need to include unpublished sources of evidence (Dwan et al 2013) (MECIR Box 1.5.b).

Developing a protocol for a systematic review has benefits beyond reducing bias. Investing effort in designing a systematic review will make the process more manageable and help to inform key priorities for the review. Defining the question, referring to it throughout, and using appropriate methods to address the question focuses the analysis and reporting, ensuring the review is most likely to inform treatment decisions for funders, policy makers, healthcare professionals and consumers. Details of the planned analyses, including investigations of variability across studies, should be specified in the protocol, along with methods for interpreting the results through the systematic consideration of factors that affect confidence in estimates of intervention effect (MECIR Box 1.5.c).

While the intention should be that a review will adhere to the published protocol, changes in a review protocol are sometimes necessary. This is also the case for a
protocol for a randomized trial, which must sometimes be changed to adapt to unanticipated circumstances such as problems with participant recruitment, data collection or event rates. While every effort should be made to adhere to a predeter-
mind protocol, this is not always possible or appropriate. It is important, however,
that changes in the protocol should not be made based on how they affect the outcome
of the research study, whether it is a randomized trial or a systematic review. Post hoc
decisions made when the impact on the results of the research is known, such as
excluding selected studies from a systematic review, or changing the statistical analy-
sis, are highly susceptible to bias and should therefore be avoided unless there are rea-
sonable grounds for doing this.

Enabling access to a protocol through publication (all Cochrane Protocols are
published in the **CDSR** and registration on the PROSPERO register of systematic
reviews reduces duplication of effort, research waste, and promotes accountability.
Changes to the methods outlined in the protocol should be transparently declared.

This *Handbook* provides details of the systematic review methods developed or
selected by Cochrane. They are intended to address the need for rigour, comprehen-
siveness and transparency in preparing a Cochrane systematic review. All relevant
chapters – including those describing procedures to be followed in the later stages
of the review – should be consulted during the preparation of the protocol. A more spe-
cific description of the structure of Cochrane Protocols is provide in online Chapter II.

### 1.6 Data management and quality assurance

Systematic reviews should be replicable, and retaining a record of the inclusion deci-
sions, data collection, transformations or adjustment of data will help to establish a
secure and retrievable audit trail. They can be operationally complex projects, often
involving large research teams operating in different sites across the world. Good data
management processes are essential to ensure that data are not inadvertently lost,
facilitating the identification and correction of errors and supporting future efforts
to update and maintain the review. Transparent reporting of review decisions enables
readers to assess the reliability of the review for themselves.

Review management software, such as Covidence and EPPI-Reviewer, can be used to
assist data management and maintain consistent and standardized records of
decisions made throughout the review. These tools offer a central repository for review
data that can be accessed remotely throughout the world by members of the review
team. They record independent assessment of studies for inclusion, risk of bias and
extraction of data, enabling checks to be made later in the process if needed. Research
has shown that even experienced reviewers make mistakes and disagree with one
another on risk-of-bias assessments, so it is particularly important to maintain quality
assurance here, despite its cost in terms of author time. As more sophisticated
information technology tools begin to be deployed in reviews (see Chapter 4,
Section 4.6.6.2 and Chapter 22, Section 22.2.4), it is increasingly apparent that all review
data – including the initial decisions about study eligibility – have value beyond the
scope of the individual review. For example, review updates can be made more efficient
through (semi-) automation when data from the original review are available for
machine learning.
1 Starting a review

1.7 Chapter information

Authors: Toby J Lasserson, James Thomas, Julian PT Higgins

Acknowledgements: This chapter builds on earlier versions of the Handbook. We would like to thank Ruth Foxlee, Richard Morley, Soumyadeep Bhaumik, Mona Nasser, Dan Fox and Sally Crowe for their contributions to Section 1.3.

Funding: JT is supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care North Thames at Barts Health NHS Trust. JPTH is a member of the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. JPTH received funding from National Institute for Health Research Senior Investigator award NF-SI-0617-10145. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

1.8 References


Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gulmezoglu AM, Howells DW, Ioannidis JP, Oliver S. How to increase value and reduce waste when research priorities are set. Lancet 2014; 383: 156–165.


Gøtzsche PC, Ioannidis JPA. Content area experts as authors: helpful or harmful for systematic reviews and meta-analyses? BMJ 2012; 345.


