

What is a 'complex systematic review'? Criteria, definition, and examples

Kamal R Mahtani, Tom Jefferson, Carl Heneghan, David Nunan, Jeffrey K Aronson

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Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Correspondence to: **Dr Kamal R Mahtani**, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX1 2JD, UK; kamal.mahtani@phc.ox.ac.uk

Systematic reviews involve systematically searching for all available evidence, appraising the quality of the included studies, and synthesising the evidence into a usable form. They contribute to the pool of best available evidence, translating research into practice, and are powerful tools for clinicians, policymakers, and patients.¹

To be useful for decision making, systematic reviews need to include high-quality evidence. However, there are systemic failings with the publishing, reporting, and interpretation of much of the evidence base, which undermine the findings of systematic reviews.^{2,3} In some cases, the evidence remains hidden from view or, when published, important outcomes are selectively reported, further hindering interpretation of reviews.⁴ Also, multiple interventions often have not been compared head to head, requiring more complex and indirect methods of evaluation. Finally, best practice guidance needs to be adaptable to real-world practice scenarios, which often requires combined information from multiple sources of evidence.⁵

To plug the evidence-to-practice translational gap, review methods are evolving beyond conventional 'what works' systematic reviews. Broader forms of evidence synthesis have emerged, such as network meta-analysis, scoping reviews, realist reviews, umbrella and meta-narrative reviews, meta-synthesis, and several others.^{6,7} Cochrane groups have expanded, with the creation of specific methods groups to reflect the growing number of review types.

The recognition that complex clinical and policy questions require more advanced methods of evidence synthesis to answer them has led to the term 'complex review', which is used to cover a wide range of evolving methods. However, there is some uncertainty as to what a complex systematic review is.

Defining 'complex systematic reviews'

There is a tried and tested method of defining scientific terms, by exploring their etymology, usages, and previous definitions, and considering the elements of which the relevant processes consist.

Etymology and usage

The word 'complex' derives from an ancient linguistic root, PLEK, which implies weaving, giving words such as plait, pleat, pliant, and plicate. Adding the prefix 'com' (Latin cum, meaning 'with') to the basic root implies

interweaving of several elements, making things complicated, literally woven together. Reflecting this, 'complex' is defined in the *Oxford English Dictionary* as 'consisting of parts or elements not simply co-ordinated, but some of them involved in various degrees of subordination; complicated, involved, intricate; not easily analysed or disentangled'. No other usages of the word have emerged since it entered English in this form in the 17th century.

Previous definitions

Seeking previous definitions of complex systematic reviews, we did a rapid scope of the literature, with the following results:

- ▶ First, we identified a need for distinction between a systematic review of complex interventions and a complex systematic review. Petticrew and colleagues have argued 'that reviews of complex interventions can themselves be simple or complex, depending on the question to be answered'.⁸ As outlined below, we argue that a complex systematic review may be designated as such for a variety of reasons, regardless of how complex the unit of analysis is (eg, the intervention(s), procedures, and tests).
- ▶ We looked for definitions on the National Institute for Health Research Complex Reviews Unit website, but could not find any, although we did find a list of reasons for the increasing complexity of reviews.⁹
- ▶ Gough and colleagues described 'multi-component reviews' as a strategy for dealing with complex review questions, but we were still unable to identify an explicit definition of a complex review.¹⁰
- ▶ We found a definition of a 'comprehensive review' in the Joanna Briggs Methods Manual: 'A systematic review is considered to be a comprehensive systematic review when it includes two or more types of evidence, such as both qualitative and quantitative, in order to address a particular review objective.'¹¹
- ▶ We identified an excellent series of articles under the banner 'Considering Complexity in Systematic Reviews of Interventions' in *The Journal of Clinical Epidemiology*, although we were unable to identify an explicit definition of a complex review.¹²
- ▶ We identified a paper by Whitlock and colleagues, who described a complex review as one that 'evaluate(s) a number of linked clinical questions, multiple interventions or diag-



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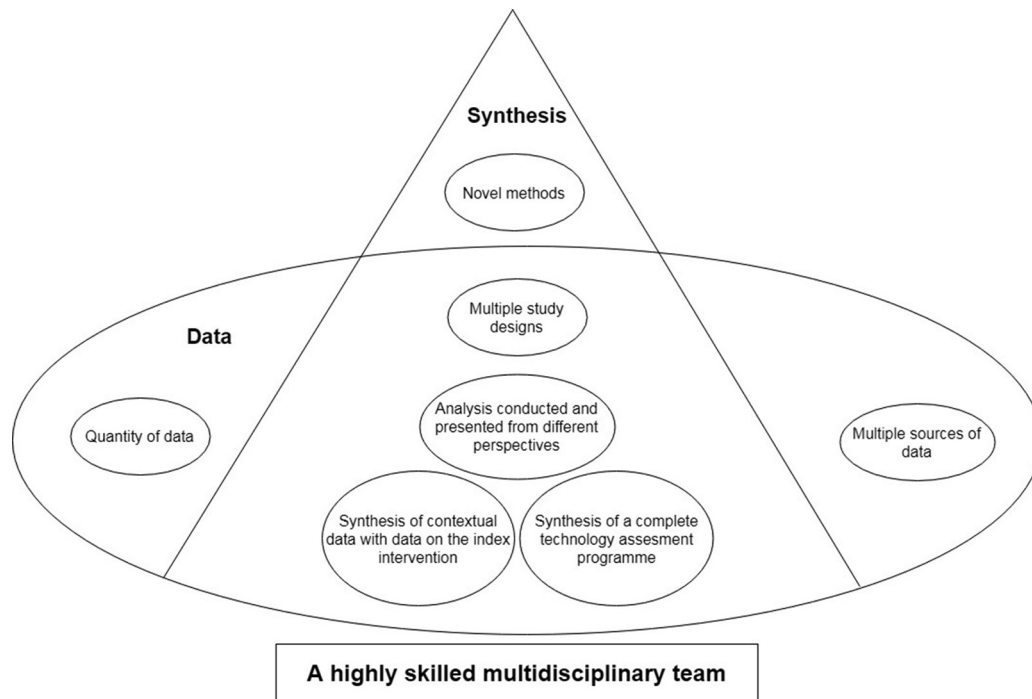


Figure 1 Proposed elements of a complex systematic review.

nostic tests, different or distinct population groups, and/or many outcomes.¹³

Elements of the process

Considering how complex reviews are carried out, we propose that for a systematic review to be designated as 'complex', it should demonstrate exceptional aspects in two broad domains: the *nature and sources of the data* included in the review and the *processes of synthesis* involved in their interpretation. We have identified eight aspects of complex reviews that underpin these domains, described in the text below and illustrated in [figure 1](#).

Several of these aspects reflect the interweaving of disparate elements implied by the origin of the word 'complex'. We suggest that a complex systematic review should primarily fulfil the following criterion:

- ▶ The need for a highly skilled and multidisciplinary team to complete the review. Although the Cochrane Handbook alludes to this,¹⁴ we extend this absolute requirement by stating that: the skill mix needed to complete a complex review should include a breadth of content expertise, including end-users of the research, to shape and contextualise the relevance and implications of the review findings. The success of a complex review should depend on highly skilled methodological expertise, without which it would be impossible to complete the review.

This is the only absolute criterion. The other elements (below) are optional, but we suggest that a requirement of any complex systematic review is that any two should be included.

- ▶ The use of more than one type of study design (eg, qualitative and quantitative) and more than one type of synthesis approach. Gough and colleagues describe a continuum in synthesis approaches that may, at one end, use a predefined method to aggregate existing data and test a theory, or at the other, use a more iterative synthesis approach and configure existing data to generate a new theory.¹⁰ A complex review may do both.

- ▶ The inclusion of a large quantity of data. This could include, for example, clinical study reports (CSRs), large and highly detailed documents written for regulators as part of licensing applications for medicinal products.¹⁵ However, we are not proposing an arbitrary cut-off for what would constitute a large quantity of data. A systematic review of over 100 published randomised controlled trials might provide as much relevant data as two CSRs, each over 4000 pages long. Context is important. Instead, we propose that researchers should justify whether their review qualifies under this heading and why.
- ▶ Assessment of a complete evidence development programme. This cumulative collection of data may be presented chronologically, providing greater insights into the origins and purpose of a technology. For example, combined assessment of preclinical, phase I–IV studies of a technology or evidence of the development of a complex instrument or a large diagnostic tool from the horizon-scanning phase to the postmarketing phase, perhaps starting with a definition of its predicate (ie, the index molecule, instrument, or device from which all other versions and medicinal products have evolved).
- ▶ Systematic inclusion of data from several different sources. Most systematic reviews source data from the existing published literature and sometimes from the grey (ie, unpublished) literature as well. However, the validity of a systematic review is threatened by the scope of the data it includes. Problems with publication bias, particularly in relation to pharmaceuticals, are well documented.⁴ These problems have led to calls for inclusion of data from sources other than just the aggregative summaries in the published literature.² Including individual participant or patient data may mitigate this to some degree.¹⁶ Other sources could include regulatory or registry data, where additional information, for example, on adverse events, may be found.¹⁷
- ▶ An evaluation of an intervention in relation to the contexts in which it is set, for example, information to describe the

Table 1 Examples of complex systematic reviews that fit our criteria

Title of review	Justification for inclusion
Community engagement to reduce inequalities in health: a systematic review, meta-analysis and economic analysis. ¹⁹	This review incorporated different perspectives and viewpoints into the synthesis, presenting its findings in the context of service, social and health perspectives. The study used a mixture of quantitative and qualitative data.
Diffusion of innovations in service organisations: systematic review and recommendations. ²⁰	Developed a new evidence synthesis technique, which the authors called a meta-narrative review. The study used a mixture of quantitative and qualitative data.
Comparison of treatment effects between animal experiments and clinical trials: systematic review. ²¹	This review systematically included data from several different sources: comparing human and animal data from the same design for the same outcome. A large quantity of data was analysed (over 200 primary animal studies).
Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. ²²	This was the first review to base its synthesis on regulatory evidence only. The highly skilled and multidisciplinary team developed new methods of synthesis for this type of primary data.
Non-pharmacological treatments for stuttering in children and adults: a systematic review and evaluation of clinical effectiveness and exploration of barriers to successful outcomes. ²³	A systematic review of quantitative and qualitative literature, which identified over 100 unique papers for inclusion. Presented quantitative data on clinical effectiveness as well as qualitative data on barriers and facilitators to effectiveness. Presented perspectives of participants with the condition and their carers.

process through which the intervention is being implemented or to explain the rationale for the choice of study design, in the light of current knowledge. Both of these types could also include timelines.

- ▶ Reviews that simultaneously answer questions from different perspectives and viewpoints: societal, healthcare, funders, patients and carers, healthcare workers, and manufacturers. These could include multiple evaluations and comparisons using different evaluation methods consistent with the different perspectives.
- ▶ The use of a particular evidence synthesis method for the first time. A review of evidence synthesis methods used across the fields of nursing, healthcare science and services, and health policy found that many methods were contemporary and probably emerging, implying that more detailed descriptions and validation studies were likely to appear in future.⁶

Here we provide examples of systematic reviews that can justifiably be termed complex (table 1). All involved a multidisciplinary team.

Thus, based on etymology, usage, previous definitions, and considerations of the elements of which a complex systematic review consists, we propose the following definition:

Complex systematic review n. *A systematic review, performed by a multidisciplinary team, consisting of multiple components, large amounts of data from different sources or different perspectives, collectively contributing more than would be expected from their individual contributions, the individual components not being easily coordinated, analysed or disentangled.*

Conclusion

Systematic reviews play a pivotal role in the translation of research findings into practice and policy.¹⁸ However, the field is moving beyond traditional 'what works' reviews to more complex reviews, which may make a greater contribution to healthcare decision making. In this commentary, we seek to advance the field by presenting a definition of a complex systematic review to provide clarity in the field and to stimulate further thought and discussion.

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Care Research, The Wellcome Trust, and the WHO. He has also received income from the publication of a series of toolkit books published by Blackwells. CEBM jointly runs the EvidenceLive Conference with the *BMJ* and the Overdiagnosis Conference with some international partners which are based on a non-profit model. DN has received expenses and fees for his media work. He holds grant funding from the NIHR School of Primary Care Research and the Royal College of General Practitioners. JKA is a member of the CEBM, with similar potential conflicts to those outlined above.

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