Synthesising quantitative and qualitative evidence to inform guidelines on complex interventions: clarifying the purposes, designs and outlining some methods

Jane Noyes,1 Andrew Booth,2 Graham Moore,3 Kate Flemming,4 Özge Tunçalp,5 Elham Shakibazadeh6


ABSTRACT
Guideline developers are increasingly dealing with more difficult decisions concerning whether to recommend complex interventions in complex and highly variable health systems. There is greater recognition that both quantitative and qualitative evidence can be combined in a mixed-method synthesis and that this can be helpful in understanding how complexity impacts on interventions in specific contexts. This paper aims to clarify the different purposes, review designs, questions, synthesis methods and opportunities to combine quantitative and qualitative evidence to explore the complexity of complex interventions and health systems. Three case studies of guidelines developed by WHO, which incorporated quantitative and qualitative evidence, are used to illustrate possible uses of mixed-method reviews and evidence. Additional examples of methods that can be used or may have potential for use in a guideline process are outlined. Consideration is given to the opportunities for potential integration of quantitative and qualitative evidence at different stages of the review and guideline process. Encouragement is given to guideline commissioners and developers and review authors to consider including quantitative and qualitative evidence. Recommendations are made concerning the future development of methods to better address questions in systematic reviews and guidelines that adopt a complexity perspective.

INTRODUCTION
Recognition has grown that while quantitative methods remain vital, they are usually insufficient to address complex health systems related research questions.1 Quantitative methods rely on an ability to anticipate what must be measured in advance. Introducing change into a complex health system gives rise to emergent reactions, which cannot be fully predicted in advance. Emergent reactions can often only be understood through combining quantitative methods with a more flexible qualitative lens.2 Adopting a more pluralist position enables a diverse range of research options to the researcher depending on the research question being investigated.3–5 As a consequence, where a research study sits within the multitude of methods available is driven by the question being asked, rather than any particular methodological or philosophical stance.6

Publication of guidance on designing complex intervention process evaluations and other works advocating mixed-methods approaches to intervention research have stimulated better quality evidence for synthesis.1 7–13 Methods for synthesising

Summary box
► When combined in a mixed-method synthesis, quantitative and qualitative evidence can potentially contribute to understanding how complex interventions work and for whom, and how the complex health systems into which they are implemented respond and adapt.
► The different purposes and designs for combining quantitative and qualitative evidence in a mixed-method synthesis for a guideline process are described.
► Questions relevant to gaining an understanding of the complexity of complex interventions and the wider health systems within which they are implemented that can be addressed by mixed-method syntheses are presented.
► The practical methodological guidance in this paper is intended to help guideline producers and review authors commission and conduct mixed-method syntheses where appropriate.
► If more mixed-method syntheses are conducted, guideline developers will have greater opportunities to access this evidence to inform decision-making.
Box 1 Defining mixed-method research and reviews

Pluye and Hong define mixed-methods research as “a research approach in which a researcher integrates (a) qualitative and quantitative research questions, (b) qualitative research methods and quantitative research designs, (c) techniques for collecting and analyzing qualitative and quantitative evidence, and (d) qualitative findings and quantitative results”. A mixed-method synthesis can integrate qualitative, quantitative and mixed-method evidence or data from primary studies; Mixed-method primary studies are usually disaggregated into quantitative and qualitative evidence and data for the purposes of synthesis. Thomas and Harden further define three ways in which reviews are mixed:

1. The types of studies included and hence the type of findings to be synthesised (ie, qualitative/textual and quantitative/numerical).
2. The types of synthesis method used (eg, statistical meta-analysis and qualitative synthesis).
3. The mode of analysis: theory testing AND theory building.

“A qualitative study is one that uses qualitative methods of data collection and analysis to produce a narrative understanding of the phenomena of interest. Qualitative methods of data collection may include, for example, interviews, focus groups, observations and analysis of documents.

The Cochrane Qualitative and Implementation Methods Group coined the term ‘qualitative evidence synthesis’ to mean that the synthesis could also include qualitative data. For example, qualitative data from case studies, grey literature reports and open-ended questions from surveys. ‘Evidence’ and ‘data’ are used interchangeably in this paper.

Taking a complexity perspective

The first paper in this series outlines aspects of complexity associated with complex interventions and health systems that can potentially be explored by different types of evidence, including synthesis of quantitative and qualitative evidence. Petticrew et al distinguish between a complexity interventions perspective and a complex systems perspective. A complex interventions perspective defines interventions as having “implicit conceptual boundaries, representing a flexible, but common set of practices, often linked by an explicit or implicit theory about how they work”. A complex systems perspective differs in that “complexity arises from the relationships and interactions between a system’s agents (eg, people, or groups that interact with each other and their environment), and its context. A system perspective conceives the intervention as being part of the system, and emphasises changes and interconnections within the system itself”. Aspects of complexity associated with implementation of complex interventions in health systems that could potentially be addressed with a synthesis of quantitative and qualitative evidence are summarised in table 2. Another paper in the series outlines criteria used in a new evidence to decision framework for making decisions about complex interventions implemented in complex systems, against which the need for quantitative and qualitative evidence can be mapped. A further paper explores how context is dealt with in guidelines and reviews taking a complexity perspective also recommends using both quantitative and qualitative evidence to better understand context as a source of complexity. Mixed-method syntheses of quantitative and qualitative evidence can also help with understanding of whether there has been theory failure and or implementation failure. The Cochrane Qualitative and Implementation Methods Group provide additional guidance on exploring implementation and theory failure that can be adapted to address aspects of complexity of complex interventions when implemented in health systems.

It may not be apparent which aspects of complexity or which elements of the complex intervention or health system can be explored in a guideline process, or whether combining qualitative and quantitative evidence in a mixed-method synthesis will be useful, until the available evidence is scoped and mapped. A more extensive lead in phase is typically required to scope the available evidence, engage with stakeholders and to refine the review parameters and questions that can then be mapped against potential review designs and methods.
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<tr>
<th>Case study examples and references</th>
<th>Complexity-related questions of interest in the guideline</th>
<th>Types of synthesis used in the guideline</th>
<th>Mixed-method review design and integration mechanisms</th>
<th>Observations, concerns and considerations</th>
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<tr>
<td>Antenatal Care (ANC) guidelines (online supplementary file 1)</td>
<td>What do women in high-income, medium-income and low-income countries want and expect from antenatal care (ANC), based on their own accounts of their beliefs, views, expectations and experiences of pregnancy?</td>
<td>Qualitative synthesis Framework synthesis Meta-ethnography</td>
<td>Segregated and contingent design and sequential synthesis</td>
<td>An innovative approach to guideline development No formal cross-study synthesis process and limited testing of theory. The hypothetical nature of meta-ethnography findings may be challenging for guideline panel members to process without additional training See Flemming et al. for considerations when selecting meta-ethnography</td>
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<td></td>
<td>What are the evidence-based practices during ANC that improved outcomes and lead to positive pregnancy experience and how should these practices be delivered?</td>
<td>Quantitative review of trials</td>
<td>Integration: quantitative and qualitative findings were brought together in a series of DECIDE frameworks Tools included: Psychological theory SURE framework conceptual framework for implementing policy options Conceptual framework for analysing integration of targeted health interventions into health systems to analyse contextual health system factors</td>
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<td></td>
<td>Factors that influence the uptake of routine antenatal services by pregnant women Views and experiences of maternity care providers</td>
<td>Qualitative synthesis Framework synthesis Meta-ethnography</td>
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<td>Task shifting guidelines (online supplementary file 2)</td>
<td>What are the effects of lay health worker interventions in primary and community healthcare on maternal and child health and the management of infectious diseases?</td>
<td>Quantitative review of trials</td>
<td>Combination of a segregated design and sequential synthesis Several published quantitative reviews were used (eg, Cochrane review of lay health worker interventions) Additional new qualitative evidence syntheses were commissioned (segregated)</td>
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<td>What factors affect the implementation of lay health worker programmes for maternal and child health?</td>
<td>Qualitative evidence synthesis Framework synthesis</td>
<td>Integration: quantitative and qualitative review findings on lay health workers were brought together in several DECIDE frameworks. Tools included adapted SURE Framework and post hoc logic model</td>
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<tr>
<td>Risk communication guideline (online supplementary file 3)</td>
<td></td>
<td>Quantitative review of quantitative evidence (descriptive) Qualitative using framework synthesis</td>
<td>Results based convergent synthesis A knowledge map of studies was produced to identify the method, topic and geographical spread of evidence. Reviews first organised and synthesised evidence by method-specific streams and reported method-specific findings. Then similar findings across method-specific streams were grouped and further developed using all the relevant evidence Integration: where possible, quantitative and qualitative evidence for the same intervention and question was mapped against core DECIDE domains. Tools included framework using public health emergency model and disaster phases Very few trials were identified. Quantitative and qualitative evidence was used to construct a high level view of what appeared to work and what happened when similar broad groups of interventions or strategies were implemented in different contexts</td>
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<td>Factors influencing children’s optimal fruit and vegetable consumption</td>
<td>Potential to explore theoretical, intervention and implementation complexity issues New question(s) of interest are developed and tested in a cross-study synthesis</td>
<td>Mixed-methods synthesis Each review typically has three syntheses: Statistical meta-analysis Qualitative thematic synthesis Cross-study synthesis</td>
<td>Parallel-results convergent synthesis design or a segregated or sequential synthesis design Aim is to generate and test theory from diverse body of literature Integration: used integrative matrix based on programme theory</td>
<td>Can be used in a guideline process as it fits with the current model of conducting method specific reviews separately then bringing the review products together</td>
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### Table 1 Continued

<table>
<thead>
<tr>
<th>Case study examples and references</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions to promote smoke alarm ownership and function</strong></td>
<td>Intervention effect and/or intervention implementation related questions within a system</td>
<td>Narrative synthesis (specifically Popay's methodology)</td>
<td>Can be accommodated within various review designs</td>
<td>Few published examples with the exception of Rodgers, who reinterpreted a Cochrane review on the same topic with narrative synthesis methodology. Methodology is complex. Most subsequent examples have only partially operationalised the methodology. An intervention effect review will still be required to feed into the guideline process.</td>
</tr>
<tr>
<td><strong>Factors affecting childhood immunisation</strong></td>
<td>What factors explain complexity and causal pathways?</td>
<td>Bayesian synthesis of qualitative and quantitative evidence</td>
<td>Can be accommodated within various review designs</td>
<td>Not yet used in a guideline context. Complex methodology. Undergoing development and testing for a health context. The end product may not easily ‘fit’ into an evidence to decision framework and an effect review will still be required.</td>
</tr>
<tr>
<td><strong>Providing effective and preferred care closer to home: a realist review of intermediate care.</strong></td>
<td>Developing and testing theories of change underpinning complex policy interventions What works for whom in what contexts and how?</td>
<td>Realist synthesis NB. Other theory-informed synthesis methods follow similar processes</td>
<td>Can be accommodated within various review designs</td>
<td>May be useful where there are few trials. The hypothetical nature of findings may be challenging for guideline panel members to process without additional training. The end product may not easily ‘fit’ into an evidence to decision framework and an effect review will still be required.</td>
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<tr>
<td><strong>Use of morphine to treat cancer-related pain</strong></td>
<td>Any aspect of complexity could potentially be explored How does the context of morphine use affect the established effectiveness of morphine?</td>
<td>Critical interpretive synthesis</td>
<td>Can be accommodated within various review designs</td>
<td>There are few examples and the methodology is complex. The hypothetical nature of findings may be challenging for guideline panel members to process without additional training. The end product would need to be designed to feed into an evidence to decision framework and an intervention effect review will still be required.</td>
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<tr>
<td><strong>Food sovereignty, food security and health equity</strong></td>
<td>Examples have examined health system complexity To understand the state of knowledge on relationships between health equity health inequalities that are socially produced—and food systems, where the concepts of ‘food security’ and ‘food sovereignty’ are prominent Focused on eight pathways to health (in)equity through the food system: (1) Multi-Scalar Environmental, Social Context; (2) Occupational Exposures; (3) Environmental Change; (4) Traditional Livelihoods, Cultural Continuity; (5) Intake of Contaminants; (6) Nutrition; (7) Social Determinants of Health; (8) Political, Economic and Regulatory context</td>
<td>Meta-narrative</td>
<td>Aim is to review research on diffusion of innovation to inform healthcare policy</td>
<td>Not yet used in a guideline context. The originators are calling for meta-narrative reviews to be used in a guideline process. Potential to provide a contextual overview within which to interpret other types of reviews in a guideline process. The meta-narrative review findings may require tailoring to ‘fit’ into an evidence to decision framework and an intervention effect review will still be required. Few published examples and the methodology is complex.</td>
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### Table 2  Health-system complexity-related questions that a synthesis of quantitative and qualitative evidence could address (derived from Petticrew et al17)

<table>
<thead>
<tr>
<th>Aspect of complexity of interest</th>
<th>Examples of potential research question(s) that a synthesis of qualitative and quantitative evidence could address</th>
<th>Types of studies or data that could contribute to a review of qualitative and quantitative evidence</th>
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<tr>
<td>What ‘is’ the system? How can it be described?</td>
<td>What are the main influences on the health problem? How are they created and maintained? How do these influences interconnect? Where might one intervene in the system?</td>
<td>Quantitative: previous systematic reviews of the causes of the problem; epidemiological studies (eg, cohort studies examining risk factors of obesity); network analysis studies showing the nature of social and other systems. Qualitative data: theoretical papers; policy documents.</td>
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<td>Interactions of interventions with context and adaptation</td>
<td>1. For a research question about Implementation: (How and why) does the implementation of this intervention vary across contexts?  2. For an effectiveness review: Do the effects of the intervention appear to be context dependent?</td>
<td>Qualitative: (1) eg, qualitative studies; case studies. Quantitative: (2) trials or other effectiveness studies from different contexts; multicentre trials, with stratified reporting of findings; other quantitative studies that provide evidence of moderating effects of context.</td>
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<tr>
<td>System adaptivity (how does the system change?)</td>
<td>(How) does the system change when the intervention is introduced? Which aspects of the system are affected? Does this potentiate or dampen its effects?</td>
<td>Quantitative: longitudinal data; possibly historical data; effectiveness studies providing evidence of differential effects across different contexts; system modelling (eg, agent-based modelling). Qualitative: qualitative studies; case studies.</td>
</tr>
<tr>
<td>Emergent properties</td>
<td>What are the effects (anticipated and unanticipated) which follow from this system change?</td>
<td>Quantitative: prospective quantitative evaluations; retrospective studies (eg, case–control studies, surveys) may also help identify less common effects; dose–response evaluations of impacts at aggregate level in individual studies or across studies included with systematic reviews (see suggested examples). Qualitative: qualitative studies.</td>
</tr>
<tr>
<td>Positive (reinforcing) and negative (balancing) feedback loops</td>
<td>What explains change in the effectiveness of the intervention over time? Are the effects of an intervention are damped/suppressed by other aspects of the system (eg, contextual influences?)</td>
<td>Quantitative: studies of moderators of effectiveness; long-term longitudinal studies. Qualitative: studies of factors that enable or inhibit implementation of interventions.</td>
</tr>
<tr>
<td>Multiple (health and non-health) outcomes</td>
<td>What changes in processes and outcomes follow the introduction of this system change? At what levels in the system are they experienced?</td>
<td>Quantitative: studies tracking change in the system over time. Qualitative: studies exploring effects of the change in individuals, families, communities (including equity considerations and factors that affect engagement and participation in change).</td>
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</table>
of synthesis. At the scoping stage, it is also common to
decide on a theoretical perspective or undertake further
work to refine a theoretical perspective. This is also
the stage to begin articulating the programme theory of
the complex intervention that may be further developed to
refine an understanding of complexity and show how
the intervention is implemented in and impacts on the
wider health system. In practice, this process can
be lengthy, iterative and fluid with multiple revisions to
the review scope, often developing and adapting a logic model as the available evidence becomes known and the
total potential to incorporate different types of review designs
and syntheses of quantitative and qualitative evidence
becomes better understood. Further questions, propositions or hypotheses may emerge as the reviews progress
and therefore the protocols generally need to be developed iteratively over time rather than a priori.

Following a scoping exercise and definition of key
questions, the next step in the guideline development process is to identify existing or commission new systematic reviews to locate and summarise the best available evidence in relation to each question. For example, case study 2, ‘Optimising health worker roles for maternal and newborn health through task shifting’, included qualitative reviews that did and did not take an additional complexity perspective, and qualitative evidence syntheses that were able to explain how specific elements of complexity impacted on intervention outcomes within the wider health system. Further understanding of health system complexity was facilitated through the conduct of additional country-level case studies that contributed to an overall understanding of what worked and what happened when lay health worker interventions were implemented. See table 1 online supplementary file 2.

There are a few existing examples, which we draw on
in this paper, but integrating quantitative and qualitative evidence in a mixed-method synthesis is relatively uncommon in a guideline process. Box 2 includes a set of key questions that guideline developers and review authors contemplating combining quantitative and qualitative evidence in mixed-methods design might ask. Subsequent sections provide more information and signposting to further reading to help address these key questions.

### Complexity-related questions that a synthesis of quantitative and qualitative evidence can potentially address

Petticrew et al define the different aspects of complexity and examples of complexity-related questions that can potentially be explored in guidelines and systematic reviews taking a complexity perspective. Relevant aspects of complexity outlined by Petticrew et al are summarised in table 2 below, together with the corresponding questions that could be addressed in a synthesis combining qualitative and quantitative evidence. Importantly, the aspects of complexity and their associated concepts of interest have however yet to be translated fully in primary health research or systematic reviews. There are few known examples where selected complexity concepts have been used to analyse or reanalyse a primary intervention study. Most notable is Chandler et al who specifically set out to identify and translate a set of relevant complexity theory concepts for application in health systems research. Chandler then reanalysed a trial process evaluation using selected complexity theory concepts to better understand the complex causal pathway in the health system that explains some aspects of complexity in table 2.

Rehfeuss et al also recommends upfront consideration of the WHO-INTEGRATE evidence to decision criteria when planning a guideline and formulating questions. The criteria reflect WHO norms and values and take
account of a complexity perspective. The framework can be used by guideline development groups as a menu to decide which criteria to prioritise, and which study types and synthesis methods can be used to collect evidence for each criterion. Many of the criteria and their related

### Box 2 Key questions that guideline developers and review authors contemplating combining quantitative and qualitative evidence in a mixed-methods design might ask

1. Why: Why is a mixed-method synthesis being planned? To answer compound questions requiring both quantitative and qualitative evidence?
   - Questions requiring mixed-methods studies?
   - Separate quantitative and qualitative questions?
2. What: What type of evidence is likely to be available?
   - Separate quantitative and qualitative research studies?
   - Related quantitative and qualitative research studies?
   - Mixed-methods studies?
   - Quantitative unpublished data and/or qualitative unpublished data, eg, narrative survey data?
3. When: At what point will quantitative and qualitative evidence be integrated?
   - Throughout the review?
   - Following separate reviews?
   - At the question point?
   - At the synthesis point?
   - At the evidence to recommendations stage?
   - Or a combination?
4. How: How easy is it to disaggregate quantitative and qualitative data from mixed-method studies? How will quantitative and qualitative evidence be integrated? Through a:
   - Narrative synthesis or summary?
   - Quantitising approach, eg, frequency analysis?
   - Qualitising approach, eg, thematic synthesis?
   - Tabulation?
   - Logic model?
   - Conceptual model/framework?
   - Matrix?
   - Graphical approach?
   - Or a combination?
5. Which: Which mixed-method designs, methodologies and methods best fit into a guideline process to inform recommendations?
questions can be addressed using a synthesis of quantitative and qualitative evidence: the balance of benefits and harms, human rights and sociocultural acceptability, health equity, societal implications and feasibility (see table 3). Similar aspects in the DEcIDE framework could also be addressed using synthesis of qualitative and quantitative evidence.

Questions as anchors or compasses
Questions can serve as an ‘anchor’ by articulating the specific aspects of complexity to be explored (eg, Is successful implementation of the intervention context dependent?). Anchor questions such as “How does intervention x impact on socioeconomic inequalities in health behaviour/outcome x” are the kind of health system question that requires a synthesis of both quantitative and qualitative evidence and hence a mixed-methods synthesis. Quantitative evidence can quantify the difference in effect, but does not answer the question of how. The ‘how’ question can be partly answered with quantitative and qualitative evidence. For example, quantitative evidence may reveal where socioeconomic status and inequality emerges in the health system (an emergent property) by exploring questions such as “Does patterning emerge during uptake because fewer people from certain groups come into contact with an intervention in the first place?” or “are people from certain backgrounds more likely to drop out, or to maintain effects beyond an intervention differently?” Qualitative evidence may help understand the reasons behind all of these mechanisms. Alternatively, questions can act as ‘compasses’ where a question sets out a starting point from which to explore further and to potentially ask further questions or develop propositions or hypotheses to explore through a complexity perspective (eg, What factors enhance or hinder implementation?).

Other papers in this series provide further guidance on developing questions for qualitative evidence syntheses and guidance on question formulation. For anchor and compass questions, additional application of a theory (eg, complexity theory) can help focus evidence synthesis and presentation to explore and explain complexity issues. Development of a review specific logic model(s) can help to further refine an initial understanding of any complexity-related issues of interest associated with a specific intervention, and if appropriate the health system or section of the health system within which to contextualise the review question and analysis data. Specific tools are available to help clarify context and complex interventions.

If a complexity perspective, and certain criteria within evidence to decision frameworks, is deemed relevant and desirable by guideline developers, it is only possible to pursue a complexity perspective if the evidence is available. Careful scoping using knowledge maps or scoping reviews will help inform development of questions that are answerable with available evidence. If evidence of effect is not available, then a different approach to develop questions leading to a more general narrative understanding of what happened when complex interventions were implemented in a health system will be required (such as in case study 3—risk communication guideline). This should not mean that the original questions developed for which no evidence was found when scoping the literature were not important. An important function of creating a knowledge map is also to identify gaps to inform a future research agenda.

Table 2 and online supplementary files 1–3 outline examples of questions in the three case studies, which were all ‘COMPASS’ questions for the qualitative evidence syntheses.

Types of integration and synthesis designs in mixed-method reviews
The shift towards integration of qualitative and quantitative evidence in primary research has, in recent years, begun to be mirrored within research synthesis. The natural extension to undertaking quantitative or qualitative reviews has been the development of methods for integrating qualitative and quantitative evidence within reviews, and within the guideline process using evidence to decision-frameworks. Advocating the integration of quantitative and qualitative evidence assumes a complementarity between research methodologies, and a need for both types of evidence to inform policy and practice. Below, we briefly outline the current designs for integrating qualitative and quantitative evidence within a mixed-method review or synthesis.

One of the early approaches to integrating qualitative and quantitative evidence detailed by Sandelowski et al advocated three basic review designs: segregated, integrated and contingent designs, which have been further developed by Heyvaert et al.

A recent review of more than 400 systematic reviews combining quantitative and qualitative evidence identified two main synthesis designs—convergent and sequential. In a convergent design, qualitative and quantitative evidence is collated and analysed in a parallel or complementary manner, whereas in a sequential synthesis, the collation and analysis of quantitative and qualitative evidence takes place in a sequence with one synthesis informing the other. These designs can be seen to build on the work of Sandelowski et al, particularly in relation to the transformation of data from qualitative to quantitative (and vice versa) and the sequential synthesis design, with a cyclical approach to reviewing that evokes Sandelowski’s contingent design.

The three case studies (table 1, online supplementary files 1–3) illustrate the diverse combination of review designs and synthesis methods that were considered the most appropriate for specific guidelines.

Methods for conducting mixed-method reviews in the context of guidelines for complex interventions
In this section, we draw on examples where specific review designs and methods have been or can be used to explore selected aspects of complexity in guidelines or systematic reviews. We also identify other review...
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<th>Domains of the WHO-INTEGRATE EtD framework</th>
<th>Examples of potential research question(s) that a synthesis of qualitative and/or quantitative evidence could address</th>
<th>Types of studies that could contribute to a review of qualitative and quantitative evidence</th>
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<tbody>
<tr>
<td>Balance of benefits and harms</td>
<td>To what extent do patients/beneficiaries value different health outcomes?</td>
<td>Qualitative: studies of views and experiences</td>
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<td>Quantitative: Questionnaire surveys</td>
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<td>Human rights and sociocultural acceptability</td>
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<td>Qualitative: discourse analysis, qualitative studies (ideally longitudinal to examine changes over time)</td>
</tr>
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<td></td>
<td>To what extent do patients/beneficiaries value different non-health outcomes?</td>
<td>Quantitative: pro et contra analysis, discrete choice experiments, longitudinal quantitative studies (to examine changes over time), cross-sectional studies</td>
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<td>How does the intervention affect an individual’s, population group’s or organisation’s autonomy, that is, their ability to make a competent, informed and voluntary decision?</td>
<td>Mixed-method studies; case studies</td>
</tr>
<tr>
<td>Health equity, equality and non-discrimination</td>
<td>How affordable is the intervention for individuals, households or communities?</td>
<td>Qualitative: studies of views and experiences</td>
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<td>How accessible—in terms of physical as well as informational access—is the intervention across different population groups?</td>
<td>Quantitative: cross-sectional or longitudinal observational studies, discrete choice experiments, health expenditure studies; health system barrier studies, cross-sectional or longitudinal observational studies, discrete choice experiments, ethical analysis, GIS-based studies</td>
</tr>
<tr>
<td>Societal implications</td>
<td>What is the social impact of the intervention: are there features of the intervention that increase or reduce stigma and that lead to social consequences? Does the intervention enhance or limit social goals, such as education, social cohesion and the attainment of various human rights beyond health? Does it change social norms at individual or population level? What is the environmental impact of the intervention? Does it contribute to or limit the achievement of goals to protect the environment and efforts to mitigate or adapt to climate change?</td>
<td>Qualitative: studies of views and experiences</td>
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<td></td>
<td></td>
<td>Quantitative: RCTs, quasi-experimental studies, comparative observational studies, longitudinal implementation studies, case studies, power analyses, environmental impact assessments, modelling studies</td>
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<tr>
<td>Feasibility and health system considerations</td>
<td>Are there any legal factors that impact on implementation of the intervention?</td>
<td>Non-research: policy and regulatory frameworks</td>
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<td>How might governance aspects, such as past decisions and strategic considerations, positively or negatively impact the implementation of the intervention?</td>
<td>Qualitative: studies of views and experiences</td>
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<td></td>
<td>How does the intervention interact with the existing health system? Is it likely to fit well or not, is it likely to impact on it in positive or negative ways?</td>
<td>Mixed-method: health systems research, situation analysis, case studies</td>
</tr>
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<td>How does the intervention interact with the need for and usage of the existing health workforce and broader human resources, at national and subnational levels?</td>
<td>Quantitative: cross-sectional studies</td>
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<tr>
<td></td>
<td>How does the intervention interact with the need for and usage of the existing health system infrastructure as well as other relevant infrastructure, at national and subnational levels?</td>
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GIS, Geographical Information System; RCT, randomised controlled trial.
methods that could potentially be used to explore aspects of complexity. Of particular note, we could not find any specific examples of systematic methods to synthesise highly diverse research designs as advocated by Petticrew et al. and summarised in Tables 2 and 3. For example, we could not find examples of methods to synthesise qualitative studies, case studies, quantitative longitudinal data, possibly historical data, effectiveness studies providing evidence of differential effects across different contexts, and system modelling studies (eg, agent-based modeling) to explore system adaptivity.

There are different ways that quantitative and qualitative evidence can be integrated into a review and then into a guideline development process. In practice, some methods enable integration of different types of evidence in a single synthesis, while in other methods, the single systematic review may include a series of stand-alone reviews or syntheses that are then combined in a cross-study synthesis. Table 1 provides an overview of the characteristics of different review designs and methods and guidance on their applicability for a guideline process. Designs and methods that have already been used in WHO guideline development are described in part A of the table. Part B outlines a design and method that can be used in a guideline process, and part C covers those that have the potential to integrate quantitative, qualitative and mixed-method evidence in a single review design (such as meta-narrative reviews and Bayesian synthesises), but their application in a guideline context has yet to be demonstrated.

### Points of Integration when Integrating Quantitative and Qualitative Evidence in Guideline Development

Depending on the review design (see boxes 3 and 4), integration can potentially take place at a review team and design level, and more commonly at several key points of the review or guideline process. The following sections outline potential points of integration and associated practical considerations when integrating quantitative and qualitative evidence in guideline development.

#### Review Team Level

In a guideline process, it is common for syntheses of quantitative and qualitative evidence to be done separately by different teams and then to integrate the evidence. A practical consideration relates to the organisation, composition and expertise of the review teams and ways of working. If the quantitative and qualitative reviews are being conducted separately and then brought together by the same team members, who are equally comfortable operating within both paradigms, then a consistent approach across both paradigms becomes possible. If, however, a team is being split between the quantitative and qualitative reviews, then the strengths of specialisation can be harnessed, for example, in quality assessment or synthesis. Optimally, at least one, if not more, of the team members should be involved in both quantitative and qualitative reviews to offer the possibility of making connections throughout the review and not simply at re- agreed junctures. This mirrors O’Cathain’s conclusion that mixed-methods primary research tends to work only...
when there is a principal investigator who values and is able to oversee integration.9 10 While the above decisions have been articulated in the context of two types of evidence, variously quantitative and qualitative, they equally apply when considering how to handle studies reporting a mixed-method study design, where data are usually disaggregated into quantitative and qualitative for the purposes of synthesis (see case study 3—risk communication in humanitarian disasters).

**Question formulation**

Clearly specified key question(s), derived from a scoping or consultation exercise, will make it clear if quantitative and qualitative evidence is required in a guideline development process and which aspects will be addressed by which types of evidence. For the remaining stages of the process, as documented below, a review team faces challenges as to whether to handle each type of evidence separately, regardless of whether sequentially or in parallel, with a view to joining the two products on completion or to attempt integration throughout the review process. In each case, the underlying choice is of efficiencies and potential comparability vs sensitivity to the underlying paradigm.

**Searching**

Once key questions are clearly defined, the guideline development group typically needs to consider whether to conduct a single sensitive search to address all potential subtopics (lumping) or whether to conduct specific searches for each subtopic (splitting).12 A related consideration is whether to search separately for qualitative, quantitative and mixed-method evidence ‘streams’ or whether to conduct a single search and then identify specific study types at the subsequent sifting stage. These two considerations often mean a trade-off between a single search process involving very large numbers of records or a more protracted search process retrieving smaller numbers of records. Both approaches have advantages and choice may depend on the respective availability of resources for searching and sifting.

**Screening and selecting studies**

Closely related to decisions around searching are considerations relating to screening and selecting studies for inclusion in a systematic review. An important consideration here is whether the review team will screen records for all review types, regardless of their subsequent involvement (‘altruistic sifting’), or specialise in screening for specific study types at the subsequent sifting stage. These two considerations often mean a trade-off between a single search process involving very large numbers of records or a more protracted search process retrieving smaller numbers of records. Both approaches have advantages and choice may depend on the respective availability of resources for searching and sifting.

**Assessment of methodological limitations in primary studies**

Within a guideline process, review teams may be more limited in their choice of instruments to assess methodological limitations of primary studies as there are mandatory requirements to use the Cochrane risk of bias tool37 to feed into Grading of Recommendations Assessment, Development and Evaluation (GRADE).38 or to select from a small pool of qualitative appraisal instruments in order to apply GRADE; Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual)39 to assess the overall certainty or confidence in findings. The Cochrane Qualitative and Implementation Methods Group has recently issued guidance on the selection of appraisal instruments and core assessment criteria.40 The Mixed-Methods Appraisal Tool, which is currently undergoing further development, offers a single quality assessment instrument for quantitative, qualitative and mixed-methods studies.41 Other options include using corresponding instruments from within the same ‘stable’, for example, using different Critical Appraisal Skills Programme instruments.42 While using instruments developed by the same team or organisation may achieve a degree of epistemological consonance, benefits may come more from consistency of approach and reporting rather than from a shared view of quality. Alternatively, a more paradigm-sensitive approach would involve selecting the best instrument for each respective review while deferring challenges from later heterogeneity of reporting.

**Data extraction**

The way in which data and evidence are extracted from primary research studies for review will be influenced by the type of integrated synthesis being undertaken and the review purpose. Initially, decisions need to be made regarding the nature and type of data and evidence that are to be extracted from the included studies. Method-specific reporting guidelines33 44 provide a good template as to what quantitative and qualitative data it is potentially possible to extract from different types of method-specific study reports, although in practice reporting quality varies. Online supplementary file 5 provides a hypothetical example of the different types of studies from which quantitative and qualitative evidence could potentially be extracted for synthesis.

The decisions around what data or evidence to extract will be guided by how ‘integrated’ the mixed-method review will be. For those reviews where the quantitative and qualitative findings of studies are synthesised separately and integrated at the point of findings (eg, segregated or contingent approaches or sequential synthesis design), separate data extraction approaches will likely be used.

Where integration occurs during the process of the review (eg, integrated approach or convergent synthesis design), an integrated approach to data extraction may be considered, depending on the purpose of the review. This may involve the use of a data extraction framework, the choice of which needs to be congruent with the approach to synthesis chosen for the review.10 45 The integrative or theoretical framework may be decided on a priori if a pre-developed theoretical or conceptual
framework is available in the literature. The development of a framework may alternatively arise from the reading of the included studies, in relation to the purpose of the review, early in the process. The Cochrane Qualitative and Implementation Methods Group provide further guidance on extraction of qualitative data, including use of software.

Synthesis and integration
Relatively few synthesis methods start off being integrated from the beginning, and these methods have generally been subject to less testing and evaluation particularly in a guideline context (see Table 1). A review design that started off being integrated from the beginning may be suitable for some guideline contexts (such as in case study 3—risk communication in humanitarian disasters—where there was little evidence of effect), but in general if there are sufficient trials then a separate systematic review and meta-analysis will be required for a guideline. Other papers in this series offer guidance on methods for synthesising quantitative and qualitative evidence in reviews that take a complexity perspective. Further guidance on integrating quantitative and qualitative evidence in a systematic review is provided by the Cochrane Qualitative and Implementation Methods Group.

Types of findings produced by specific methods
It is highly likely (unless there are well-designed process evaluations) that the primary studies may not themselves seek to address the complexity-related questions required for a guideline process. In which case, review authors will need to configure the available evidence and transform the evidence through the synthesis process to produce explanations, propositions and hypotheses (i.e., findings) that were not obvious at primary study level. It is important that guideline commissioners, developers and review authors are aware that specific methods are intended to produce a type of finding with a specific purpose (such as developing new theory in the case of meta-ethnography). Case study 1 (antenatal care guideline) provides an example of how a meta-ethnography was used to develop a new theory as an end product, as well as framework synthesis which produced descriptive and explanatory findings that were more easily incorporated into the guideline process. The definitions (Box 5) may be helpful when defining the different types of findings.

Bringing mixed-method evidence together in evidence to decision (EtD) frameworks
A critical element of guideline development is the formulation of recommendations by the Guideline Development Group, and EtD frameworks help to facilitate this process. The EtD framework can also be used as a mechanism to integrate and display quantitative and qualitative evidence and findings mapped against the EtD framework domains with hyperlinks to more detailed evidence summaries from contributing reviews (see Table 1). It is commonly the EtD framework that enables the findings of the separate quantitative and qualitative reviews to be brought together in a guideline process. Specific challenges when populating the DECIDE evidence to decision framework were noted in case study 3 (risk communication in humanitarian disasters) as there was an absence of intervention effect data and the interventions to communicate public health risks were context specific and varied. These problems would not, however, have been addressed by substitution of the DECIDE framework with the new INTEGRATE evidence to decision framework. A different type of EtD framework needs to be developed for reviews that do not include sufficient evidence of intervention effect.

DISCUSSION
Mixed-method review and synthesis methods are generally the least developed of all systematic review methods. It is acknowledged that methods for combining quantitative and qualitative evidence are generally poorly articulated. There are however some fairly well-established methods for using qualitative evidence to explore aspects of complexity (such as contextual, implementation and outcome complexity), which can be combined with evidence of effect (see sections A and B of Table 1).

There are good examples of systematic reviews that use these methods to combine quantitative and qualitative evidence, and examples of guideline recommendations that were informed by evidence from both quantitative...
and qualitative reviews (eg, case studies 1–3). With the exception of case study 3 (risk communication), the quantitative and qualitative reviews for these specific guidelines have been conducted separately, and the findings subsequently brought together in an EtD framework to inform recommendations.

Other mixed-method review designs have potential to contribute to understanding of complex interventions and to explore aspects of wider health systems complexity but have not been sufficiently developed and tested for this specific purpose, or used in a guideline process (section C of table 1). Some methods such as meta-narrative reviews also explore different questions to those usually asked in a guideline process. Methods for processing (eg, quality appraisal) and synthesising the highly diverse evidence suggested in tables 2 and 3 that are required to explore specific aspects of health systems complexity (such as system adaptivity) and to populate some sections of the INTEGRATE EtD framework remain underdeveloped or in need of development.

In addition to the required methodological development mentioned above, there is no GRADE approach for assessing confidence in findings developed from combined quantitative and qualitative evidence. Another paper in this series outlines how to deal with complexity and grading different types of quantitative evidence, and the GRADE CERQual approach for qualitative findings is described elsewhere, but both these approaches are applied to method-specific and not mixed-method findings. An unofficial adaptation of GRADE was used in the risk communication guideline that reported mixed-method findings. Nor is there a reporting guideline for mixed-method reviews, and for now reports will need to conform to the relevant reporting requirements of the respective method-specific guideline. There is a need to further adapt and test DECIDE, WHO-INTEGRATE and other types of evidence to decision frameworks to accommodate evidence from mixed-method syntheses which do not set out to determine the statistical effects of interventions and in circumstances where there are no trials.

When conducting quantitative and qualitative reviews that will subsequently be combined, there are specific considerations for managing and integrating the different types of evidence throughout the review process. We have summarised different options for combining qualitative and quantitative evidence in mixed-method syntheses that guideline developers and systematic reviewers can choose from, as well as outlining the opportunities to integrate evidence at different stages of the review and guideline development process.

Review commissioners, authors and guideline developers generally have less experience of combining qualitative and evidence in mixed-methods reviews. In particular, there is a relatively small group of reviewers who are skilled at undertaking fully integrated mixed-method reviews. Commissioning additional qualitative and mixed-method reviews creates an additional cost. Large complex mixed-method reviews generally take more time to complete. Careful consideration needs to be given as to which guidelines would benefit most from additional qualitative and mixed-method syntheses. More training is required to develop capacity and there is a need to develop processes for preparing the guideline panel to consider and use mixed-method evidence in their decision-making.

CONCLUSION

This paper has presented how qualitative and quantitative evidence, combined in mixed-method reviews, can help understand aspects of complex interventions and the systems within which they are implemented. There are further opportunities to use these methods, and to further develop the methods, to look more widely at additional aspects of complexity. There is a range of review designs and synthesis methods to choose from depending on the question being asked or the questions that may emerge during the conduct of the synthesis. Additional methods need to be developed (or existing methods further adapted) in order to synthesise the full range of diverse evidence that is desirable to explore the complexity-related questions when complex interventions are implemented into health systems. We encourage review commissioners and authors, and guideline developers to consider using mixed-methods review and synthesis in guidelines and to report on their usefulness in the guideline development process.

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Contributors JN, AB, GM, KF, ÖT and ES drafted the manuscript. All authors contributed to paper development and writing and agreed the final manuscript. Anayda Portela and Susan Norris from WHO managed the series. Helen Smith was series Editor. We thank all those who provided feedback on various iterations.

Funding Funding provided by the World Health Organization Department of Maternal, Newborn, Child and Adolescent Health through grants received from the United States Agency for International Development and the Norwegian Agency for Development Cooperation.

Disclaimer ÖT is a staff member of WHO. The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO.

Competing interests No financial interests declared. JN, AB and ÖT have an intellectual interest in GRADE CERQual; and JN has an intellectual interest in the iCAT_SR tool.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.
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REFERENCES

30. Thomas J, Harden A, Oakley A. Integrating Qualitative Research with trials in systematic reviews: an example review from public health shows how integration is possible and some potential benefits. BMJ 2004;328:1010–2.


52. Puyre P, Hong GN. Combining the power of stories and the power of numbers: mixed methods research and mixed studies reviews. *Annu Rev Public Health* 2014;35:29–45.


