

A Framework To Facilitate the Use of Systematic Reviews and Meta-analyses in the Design of Primary Research Studies



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A Framework To Facilitate the Use of Systematic Reviews and Meta-analyses in the Design of Primary Research Studies

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers; as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives. Systematic reviews are currently used by only a minority of researchers to inform the design of research studies. This may lead to inefficient and potentially wasteful research. We aimed to develop a framework which clinical researchers can apply to existing systematic reviews in order to effectively inform the design of proposed new clinical research studies.

Data Sources. Published frameworks or models designed to use results of systematic reviews or meta-analyses in new research study design.

Review Methods. A multiphase iterative process was used to develop the framework. Phase 1 involved a focused literature search to identify existing frameworks and processes that have been proposed as methods to identify research gaps by systematic reviews. In phase 2, we convened a multidisciplinary group with varied expertise to develop a stepwise framework. In phase 3, we identified two systematic reviews and applied this framework to their results. Phase 4 invited external opinions from additional experts to further refine the framework.

Results. We developed a four-step framework designed to be useable by primary researchers: Step 1 involves clearly laying out the crucial design elements of the proposed study using PICOTS (populations, interventions, comparators, outcomes, timing, and setting) elements. Step 2 provides a simple method to identify an existing systematic review which is current, valid, and relevant enough to the proposed research study to inform its design. In Step 3, the details of the systematic review are examined to determine the extent to which it has already addressed the questions proposed by the new study, and uses the PICOTS elements of the primary studies included in the systematic review to modify the design of the proposed study. Finally, Step 4 establishes the need (or otherwise) for the proposed study, and prioritizes modifications to the research design.

Conclusions. The four-step framework proposes a practical method which can be used by clinical researchers who are not experts in systematic reviews to determine whether further research studies are needed and suggest ways that the primary literature identified by the systematic review can be used to modify the design of further research studies. Further research needs to determine how useful and practical this proposed framework is for researchers, and attempt to measure its value in modifying research designs and optimizing research efficiency.

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Systematic Review and Meta-analysis

Introduction

Background

The Role of Systematic Reviews in Guiding Future Research

It is well established that systematic reviews (SRs) may provide comprehensive summaries of existing evidence using structured and robust methods. Consequently, SRs have achieved a central place in informing decision making from the level of individual patient care to health care policymakers.¹ By identifying and summarizing the existing state of evidence within a given clinical area, SRs also serve to identify existing gaps in a body of evidence. Such gaps have a number of important implications, particularly in highlighting the limitations in the conclusions that can be drawn from the SRs for patients, clinicians, and policymakers.

SRs and meta-analyses are also a potentially valuable resource for clinical researchers in the process of designing or proposing new research studies. Arguably, for maximum efficiency, new primary research studies should specifically answer those gaps identified in an existing body of evidence which are of greatest priority to clinicians, patients, and health care policymakers. By addressing established and important research gaps, new research studies would be expected to provide the greatest impact on health care. However, while optimal, we suggest that this is currently not standard practice for many clinical researchers proposing new research studies. One reason may be that the approaches and methods of systematic reviewers and primary researchers are fundamentally different. The focus of the former is identifying and summarizing “what has been found,” whereas the latter may have much more diverse reasons to design or propose new research studies: clinical experience, perceived or real gaps in clinical practice, or in response to new interventions.²

This working paper therefore describes the development of a proposed new framework that is intended to be used by researchers when designing new clinical research studies. The framework is intended to provide structured guidance to allow clinical researchers to compare the essential elements of possible new studies with the findings of prior related SRs. It provides a structured approach to considering possible implications of information typically reported in well-done published SRs for the design of new study proposals. The overall aim is to help reduce proposals that are redundant on the basis of existing research; help refine the focus of proposals on the most relevant populations, interventions, comparators, outcomes and settings; and help to assure that research addresses clearly established and important gaps in the existing evidence.

The target users of the framework are clinical researchers involved in the early design or protocol writing phases of new trials of interventions. This is a different focus from previous attempts to determine research gaps from SRs, which have been primarily aimed at those who conduct or routinely use systematic/comparative effectiveness reviews. Indeed, the proposed framework is intended to be applied by those who have limited experience in critically appraising SRs or meta-analyses, but who have a high level of content expertise in their particular area of research.

Suboptimal Use of Research Funding: “Research Wastage”

The concept that a proportion of the current biomedical research budget (approximately \$100 billion in the United States alone) may not be used optimally (i.e., is “wasted”), has been raised by Chalmers and Glasziou.³ The authors suggest at least four areas in the production and reporting of research in which this might occur. First, research questions posed may lack relevance to clinicians and patients. Second, studies may be conducted that do not consider the prior existing evidence as summarized and assessed in previously conducted SRs or may be poorly designed. Third, results of studies may not be accessible or published. Fourth, published reports may be biased and not useable, for example by failing to describe interventions adequately or all study outcomes, and may not interpret them in the context of existing SRs. Across these main categories the authors note the central role of SRs: informing the need for, or designing of new research studies, and interpreting the findings of new research studies in the light of existing SRs.

Research wastage has financial and ethical implications.⁴ From the perspective of funders of research, it implies that at least a proportion of biomedical research budgets may be used inefficiently (or even inappropriately), diverting resources from other research priorities or other budgets. From patient perspectives, it implies that patients may be subject to research studies which may not be necessary, may be harmful because previous studies have already shown they are not beneficial, or use interventions which have not been adequately studied due to the fact that research resources have been utilized elsewhere. From an overall societal perspective, it implies that a proportion of efforts and resources may not be applied as effectively as possible for the maximum benefit.

Frequency of Use of Systematic Reviews in Research Design

SRs are used infrequently in the design of new research studies. Goudie, et al. assessed a sample of randomized controlled trials (RCTs) published in leading medical journals in 2007 to determine whether or not “authors had considered previous trials in design of their trial.”⁵ Only 6 of the 27 RCTs examined (22 percent) reported that they had used the findings of previous RCTs in sample size calculations, and only 10 of the 27 RCTs (37 percent) related the results of the new trial in the light of meta-analyses in the trial discussion sections. Cooper, et al. contacted authors of all trials added to the 2002 or 2003 updates of Cochrane SRs originally published in 1996, to determine how frequently the results of the 1996 Cochrane reviews had been used in the design of the subsequent studies.⁶ They received responses from 24 authors of the 32 studies which were newly included in the 2002/2003 Cochrane reviews (75 percent response rate). Less than half (11; 46 percent) of respondents were aware of the relevant Cochrane review when they had designed their new study, and in only a third (8; 33 percent) was the design of the new study influenced by the review.⁶

Clarke, et al. assessed reports of 18 RCTs published in the five leading medical journals in 2005.⁷ Only 5 (27 percent) of published trials referred to existing SRs in their introduction sections. Moreover, the authors noted that “none of the 15 trials which were not the first published trials in their area placed the results of the new trial in the context of an updated SR or other research.” In addition, when the same authors compared these results to a previous assessment of the 55 reports of RCTs carried out in 1997 and 2001, only 2 placed the new results in the context of SRs, and only 7 referred to SRs in the discussion sections of the published

trials.⁷ This suggests there has been no improvement in the use of SRs in design of RCTs over the decade.

Potential Reasons Why Systematic Reviews May Not Be Used When Designing New Studies

There are several reasons why the results of SRs may not currently be used by researchers to inform the design of proposed new research studies:

Systematic Review May Not Exist

Despite the growing pool of SRs, they still only address a limited proportion of all trials of interventions. In part this reflects the challenges in not only conducting, but also updating SRs. However, for other types of study, such as diagnostic test accuracy studies, the methodology for conducting SRs is less established, and a far smaller proportion of such studies are likely to have been included in SRs.

Unaware of Existence of Systematic Reviews

The researcher may be unaware of the existence of relevant SRs in the particular research area in which they are interested. Currently the majority of SRs of interventions can be identified readily using several different searching tools, but this requires at least some degree of proficiency in searching and retrieval of relevant reviews.

Inadequate Critical Appraisal Skills

Researchers may vary in their ability to critically appraise the relevance and internal validity of SRs. This is important because the results of reviews which have been conducted systematically using accepted standards may differ from those which have not and which may present partial or biased summaries of the literature. There are multiple tools that have been designed to facilitate the appraisal of SRs. These include checklists designed predominantly for clinical users^{8,9} as well as more complex checklists and quality rating systems.¹⁰ However, researchers may be unaware of these instruments or may lack the skills to use them.

Systematic Reviews Do Not Use a Defined or Transparent Process for Reporting the Evidence Gaps

The majority (if not all) of SRs highlight research gaps in the body of evidence included in the SR, although the process used by the review authors to identify (or prioritize) them may be opaque and potentially open to bias.

A survey of all 2,535 reviews published in the Cochrane Library in 2007 found that only 3.2 percent stated explicitly that no more research was needed, whereas 82.0 percent of reviews made suggestions regarding the interventions that needed evaluating, 30.2 percent suggested the appropriate participants that needed studying, and 51.9 percent suggested the outcome measures.¹¹ However, it is unclear the extent to which this occurs in other (non-Cochrane) SRs.

Evidence gaps are seldom reported explicitly, but rather they may be reported under the heading “implications for research” or more generally in the sentence “more research is needed,” following the guidelines of the QUORUM statement on the quality of reporting of meta-analyses.¹² These guidelines have now been updated to PRISMA¹³ which also includes an item

for reporting in the conclusion, “a general interpretation of the results in the context of other evidence, and implications for future research.”

Often, authors focus on what is available and do not explicitly report what is not available.² A failure to identify evidence gaps may be caused by inadequate reporting overall. A meta-review including 15 SRs on heart failure disease management programs found that populations, intervention components, comparator groups, and other important characteristics were inadequately reported.¹⁴ A review of 192 trials from seven different medical areas found that safety reporting was inadequate in the entire sample.¹⁵

Deliberately Ignoring Systematic Reviews

The deliberate selection of evidence has been described as cherry picking: selecting only the juiciest and ripest fruit. In science this may be done to support a researcher’s view and justify a new research proposal. A famous example is that of Linus Pauling describing the effects of vitamin C on the common cold.¹⁶ In his book *How to Live Longer and Feel Better*, he cites more than 30 studies, nearly all with positive results, when in fact there were 61 trials showing vitamin C cannot prevent colds and has only minimal effects on duration and severity.¹⁷ The extent to which this occurs in current research proposals is not known.

Aim of Study

We therefore aimed to develop a pragmatic framework to help researchers use findings from SRs in designing and conducting new clinical research studies. This framework is intended to provide a structured process for researchers to identify SRs which are relevant to their proposed new study, identify gaps, and use study design features from studies included in the SR to inform the design of a new research study.

Methods

Design of Framework

We used a multiphase process to identify existing and relevant materials related to the identification of research gaps, adapted some of them in the development of the framework and attempted to apply it to existing systematic reviews (SRs). In a final step we sought external feedback from several experts in this field.

Phase 1

We used a focused literature search to identify and critique existing frameworks and processes that have been proposed as methods to identify research gaps in SRs. Within this search we examined all Future Research Needs (FRN) methods working papers for work relevant to our aim.^{18,19-24} We also searched for relevant checklists and tools with the explicit aim of incorporating these where appropriate. For example we incorporated checklists and tools published by the FRN methods project related to identifying research gaps,¹⁸ tools that have been designed for rapid appraisal of SRs,⁸ principles identified regarding the applicability of SRs for clinical populations,²⁵ and methods used by a non-United States research funding agency²⁶ to critically assess proposed trials of interventions.

Phase 2

We then convened a multidisciplinary group with expertise in evidence synthesis, primary research, biostatistics, and clinical epidemiology. Over a series of meetings, this group used an iterative process to develop a stepwise framework. We explicitly attempted to include existing published materials to inform sections of the framework.

Phase 3

We then attempted to apply the framework to specifically proposed clinical research questions. We identified two current SRs and came up with corresponding pseudo research questions. We then applied the draft versions of the framework to the combination of the research question and the contemporaneous SR and applied these to draft versions of the framework. See Appendixes A and B.

Phase 4

In a final phase, we invited external opinions from four additional experts with experience in clinical epidemiology, health technology assessment, medical statistics, clinical trials, and Cochrane reviews in order to further modify the content and structure of the proposed framework.

Based on the four-phase process, a final version of the framework was produced.

Results

Existing Literature on Improving the Use of Systematic Reviews To Inform Study Designs

We identified several studies, which have attempted to provide frameworks or conceptual models in order to improve the use of systematic reviews (SRs) in the design of future research studies, as well as additional material of relevance to our aim.

A series of eight Future Research Needs (FRN) projects funded by the Agency for Healthcare Research and Quality have aimed to propose new methods and tools for identifying and prioritizing research gaps using SRs. The eight documents address different aspects of identification of research gaps. These were intended to be used both by systematic reviewers, new researchers, and funders to improve the efficiency of evidence generation. Of the existing FRN methods studies, the most pertinent to the current proposal is “Frameworks for Determining Research Gaps.”¹⁸ The authors of this study contacted all the Evidence-based Practice Centers and various other organizations around the world to develop a framework to identify and categorize the evidence gaps from SRs. The proposed framework tool characterizes the gaps using the PICOTS (populations, interventions, comparators, outcomes, timing and setting) elements and identifies the reasons by using the following four categories:

1. Insufficient or imprecise information
2. Biased information
3. Inconsistency or unknown consistency
4. Not the right information.

This framework provides a useful method for identifying and characterizing evidence gaps from SRs, and we draw on its findings in the current project. It differs from the current study in that its focus is primarily from the perspective of systematic reviewers, rather than clinical researchers proposing new studies.

Sutton et al.²⁷ proposed a conceptual model with the intention of “making better use of information contained within the existing evidence base when designing future studies, and maximizing the information so gained and thus potentially reducing the need for future RCTs.” Their framework depends on the existence of a current SR and meta-analysis, and proposes several ways that evidence synthesis models can potentially be applied to existing data in these meta-analyses. These might include using individual patient data meta-analyses to address uncertainty in population subgroups and mixed treatment comparison modeling to synthesize competing interventions. Their framework suggests that further trials should only be conducted when these advanced synthesis methods do not provide a conclusive answer, and that the design of such trials should be based on the existing evidence. However, the latter focuses several methods to estimate the power of a new trial based on the results of the existing meta-analysis, either in isolation or to update the existing meta-analysis. The limitations of this framework are that it focuses only on the quantitative findings from meta analyses, implies the need for meta analyses for the application of advanced synthesis methods, and does not provide guidance about how existing trials can be used to inform design of further studies aside from power and sample size.

Several publications have proposed methods which can be used to simulate sample size calculations and power calculations, based the findings from existing meta-analyses.²⁸ We

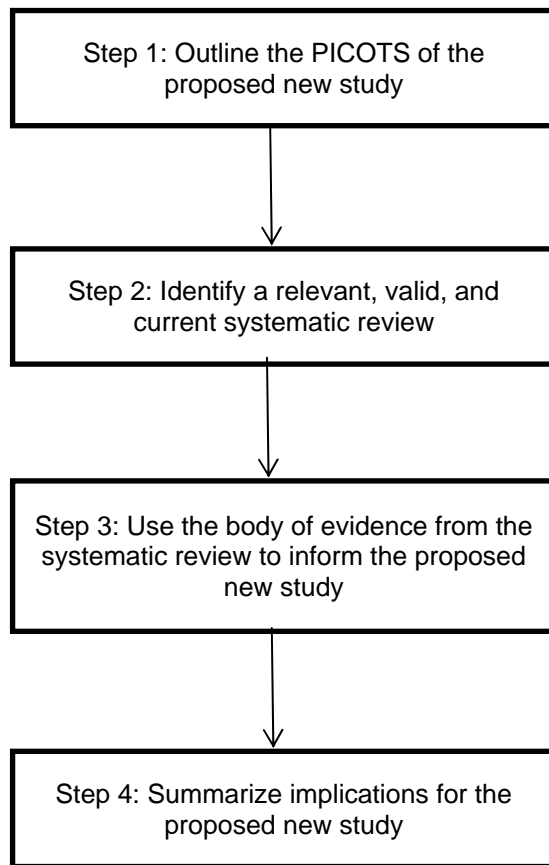
identified several articles which outlined various models that can be used by statisticians to provide more accurate estimates in the design phase of new trials.^{5, 29} We also examined the literature on value of information (VOI) also known as value of research studies which attempt to provide a systematic approach to informing the optimal design of research studies and their prioritization.³⁰ These models calculate the probability that research would provide evidence for an improved treatment decision and the gains that are to be expected from this improved treatment decision.³¹ Such VOI studies have been used to justify the importance of proposed studies, and can compare study designs in terms of net benefit given the costs of studies. Although a minimal modeling approach to using VOI has been proposed, we considered that these approaches would be too complex for most clinical researchers, given the decision analytic modeling involved.²¹

We also identified principles which had originally been developed to help systematically assess applicability of an SR for informing practice and policy.²⁵ This study suggested a framework for identifying and organizing the details of the PICOTS elements which need to be examined in detail in order to assess applicability. However, this framework was not designed for use by clinical researchers proposing new studies.

Proposed Four-Step Framework

The four-step process for researchers who are in the design phase of study proposal or protocol writing is outlined in the Figure 1. Step 1 involves laying out the crucial design elements of the proposed study using PICOTS elements. Step 2 uses a simple method to identify an existing SR which is current, valid and relevant enough to the proposed research study to inform its design. In Step 3, the details of the SR are examined to determine the extent to which it has already addressed the questions proposed by the new study, and identifies the PICOTS elements of the primary studies included in the SR which can be used to modify the design of the proposed study. Finally, Step 4 establishes the need (or otherwise) for the proposed study, and prioritizes modifications to research design based framework.

Figure 1. Proposed four-step framework



PICOTS = populations, interventions, comparators, outcomes, timing, and setting

Step 1: Outline the PICOTS of the Proposed New Study

For all trials of interventions, the key questions can be described using the PICOTS elements, which include patient group, intervention, control or comparators, outcomes of the study (main or important ones), timing (or duration of follow-up), and study design. (**Box 1**). Therefore the aim of Step 1 is to clearly delineate these basic elements, in addition to other study characteristics, and lay out each component discretely. Some trials will have several interventions (e.g. different medications, different doses), and most trials will have multiple outcomes. The reason for outlining each of the PICOTS elements is to facilitate all subsequent phases of the proposed framework, where the PICOTS of the proposed study will be compared with SRs, and then with the body of evidence identified from the SR.

Box 1: Outlining the main elements of a proposed study

1. Patient group
2. Intervention
3. Control or comparator
4. Outcomes (main/important outcomes)
5. Timing (duration of followup)
6. Setting
7. Study design

Step 2: Identify a Relevant, Valid, and Current Systematic Review

The aim of Step 2 is to identify one (or more) existing SR which is sufficiently relevant, valid, and current in relation to the proposed research study and assess its internal validity and whether it is current. The process of searching and retrieval of SR is well established, and researchers have access to numerous free search engines (e.g., TRIP, Pub Med, etc), which for most research institutions will then provide full text online access to identified SRs. In some cases, information specialists may improve the efficiency and success of searches for SRs.

For some clinical questions, there may be no SR available. If the researcher is aware of or identifies a large body of primary studies which have not be summarized into a SR, we suggest that a formal SR may be a greater priority than embarking on a primary research study.

A. Is It relevant?

Identifying a SR that is sufficiently relevant to the proposed research study involves initially examining only the title and/or abstract of SRs identified by a search to allow those that are clearly irrelevant to be immediately discarded. Then, a more detailed assessment of the abstract and if necessary full text of SRs can be used to identify one (or more) which is sufficiently similar or relevant to the proposed research study.

There is no quantitative or objective way to assess the relevance of a SR in relation to a proposed research question; this is inevitably a subjective decision. If too narrow relevance criteria are applied then it might be impossible to identify any qualifying SR, while if criteria are too broad then SRs with very limited relevance may be identified and be of little value to the researcher.

We therefore suggest a pragmatic approach by comparing the PICOTS elements from the SRs to those from the proposed study. For researchers the key question is whether the SR is relevant enough (or similar enough) to their proposed research question. For some clinical areas where there are numerous SR of interventions it will be possible (and necessary) to be more selective and attempt to find a SR that matches on several PICOTS elements. In other clinical areas where there are fewer SRs it will be necessary to be more inclusive, and include for example a SR that “matches” on only patient group and intervention.

Assessing whether a SR is relevant can usually be achieved by looking at the aims and methods (in particular inclusion and exclusion criteria) of the SR. It is not necessary for the researcher to examine the findings of the SR at this stage. **Box 2** is intended to facilitate this process: the PICOTS elements from the proposed study (i.e., those already outlined in Step 1) are compared with the corresponding elements obtained from methods section of the SR.

For some proposed research questions, there may be no relevant SRs identified. In these cases it may be valuable to broaden the search criteria and conduct another cycle of searching and assessment.

Box 2: Assessing relevance of a SR for the proposed study

1. **Patient group in the SR:** Are they relevant to proposed study?
2. **Intervention(s) in SR:** Are they relevant to proposed study?
3. **Control or comparator in the SR:** Are they relevant to proposed study?
4. **Outcomes (main/important outcomes) in the SR:** Are they relevant to proposed study?
5. **Timing (duration of followup) in the SR:** Are they relevant to proposed study?
6. **Setting in the SR:** Are they relevant to proposed study?
7. **Study design in the SR:** Are they relevant to proposed study?

B. Is It Valid?

Even if a SR appears sufficiently relevant to the proposed research study, it is important to critically appraise key areas of its internal validity in order to determine whether its findings are likely to be biased.

There are multiple possible elements of internal validity (or methodological quality) that can be assessed in SRs, and multiple tools have been proposed to facilitate their appraisal including several checklists.¹⁰ Another pragmatic appraisal tool that was developed by the Centre for Evidence-Based Medicine (**Box 3**) is available for clinicians.³² It assesses the four main areas of internal validity of SRs: comprehensiveness of literature search, criteria used to select articles, sufficient validity of included studies, and similarity of included studies.

Box 3: Assessing internal validity of an existing SR

1. **Comprehensiveness of literature search**
2. **Criteria used to select articles**
3. **Included studies of sufficient validity and quality**
4. **Similarity, or degree of homogeneity, of included studies**

The sections of the SR which a researcher needs to look at in order to assess the elements of internal validity, will include the methods section to identify the search strategy and inclusion and exclusion criteria; the results section to examine the characteristics of included studies to assess the similarity (i.e., homogeneity/heterogeneity) of included studies; where meta-analyses have been performed; and the statistical measures of heterogeneity.³³

Having identified these elements, it is necessary for the researcher to assess their impact on the validity of the SR and its findings. This is a subjective process. If the SR lacks sufficient internal validity, then it may not be possible to trust its findings and it should not be used to further inform the design and conduct of the proposed study.

C. Is It Current?

The search date of the SR identified indicates how current the SR is. There is no objective period of time beyond which all SR require updating. Guidelines for example are generally considered out of date after 5 years, while the interval for updating reviews median duration of time before signals that the evidence had changed was 5.5 years (but was as short as 2 years for some clinical areas).³⁴ Assessing how current a SR is depends on the clinical topic—if this is likely to be changing rapidly, then a very recent search date is important, whereas for other clinical areas, a less current SR is likely still to be of value.

If there is sufficient uncertainty regarding whether the SR identified is sufficiently current for the proposed research topic, then an information specialist can be used to search for articles published between the last date of search of the SR and the present day. If this search indicates that there are potentially additional primary research papers, the researcher may consider their impact on the existing SR and whether it needs updating.

Step 3: Use the Body of Evidence Assessed in the Systematic Review To Inform the Proposed Research Study

A. What can be Learned From the Primary Studies Included in the Systematic Review?

The aim of this step is to assess whether the design of the proposed study should be modified based on the details of the study designs of previous studies, and in what ways (**Box 4**). Identifying similarities as well as differences of the studies included in the SR to the proposed research study may be useful. Similarities between the proposed study and the primary studies included in the SR may reinforce the importance of such design features for the proposed study. Differences however may serve to highlight features where the researcher may have to justify/explain such differences and whether or not their study design should be modified. The researcher can use these to inform design of the proposed study by justifying why proposed PICOTS elements are different from those in primary studies, gaining new information on PICOTS elements that were not known to the researcher previously, and highlighting gaps in the existing primary studies which the proposed study aims to address.

For most SRs this information can be identified in the results sections where there is a narrative description of included studies, or can be found in the “characteristics of included studies” tables.

Box 4: Comparing the details of the primary studies and the proposed study

1. **Patient group:** Compare details of planned included population, eligibility, and exclusion criteria.
2. **Intervention:** Compare details of planned intervention in terms of type, dose, intensity, delivery of intervention, monitoring of intervention, presence of cointerventions, feasibility in planned settings, and run-in periods.
3. **Control or comparators:** Compare similarity of placebo planned and description of standard care.
4. **Main/important outcomes:** Compare primary and secondary outcomes, short term or surrogate outcomes, composite outcomes, and clinically relevant outcomes.
5. **Duration of followup:** Compare details of duration and process for followup and linearity of outcome with time (i.e. fewer measures may be needed).
6. **Setting:** Compare details of setting (primary and secondary care, etc.)
7. **Study design:** Compare study designs, sources of bias of included studies, feasibility of study designs higher in hierarchy, sample sizes and power calculations used, and feasibility of using data to assist with simulation for proposed study sample size or power calculations.

B. What Does the SR Answer and Where Do Gaps Remain?

This step examines the quantitative findings from the body of evidence included in a SR selected in the previous step, to determine the extent to which it answers some or all of the questions/aims of the proposed study, and where gaps still remain. In order to find this information, the researcher will need to examine the Results section of the review identified in the above steps.³³

The key goal of this step is first to assess whether or not the SR has explicitly addressed a stated outcome/aim (or more than one outcome/aim) of the proposed research study, and if so what were the findings. There are two possible scenarios:

1. **Proposed study question has been answered adequately by the SR.** In this case the aim of the proposed research study has been answered adequately by the SR. Adequately implies an effect size which demonstrates evidence of effect (or lack of effect), an effect that is clinically significant, and one where there is sufficiently narrow confidence interval. When the SR identifies a high quality of evidence and adequately answers the aims of the proposed study, there may be little justification for a further trial of efficacy. Rather, study designs which focus on implementation, translation, or dissemination may be of greater priority.
2. **Proposed study question has not been answered adequately by the SR.** In this case, the aim/outcome of the proposed research study has not been answered adequately by the SR, or has only been answered partially. “Inadequately” could mean the outcomes/aims of the SR are not similar enough to that proposed by the new research study, there is insufficient evidence of effect (or no evidence of lack of effect), there are wide confidence intervals, or there is an effect which is not clinically significant. The body of evidence of the SR can then be examined to identify explanations for the inability of the SR to answer the proposed study question. These can be grouped into four main categories (**Box 5**).¹⁸

Box 5: Reasons for failure of SR to address proposed study question

1. **Insufficient data:** too few primary studies, or studies that are too small (sample size inadequate or not adequately powered)
2. **Imprecise data:** insufficient evidence of effect or lack of effect
3. **Potentially biased information:** primary studies were of inadequate quality to address the question
4. **Inconsistency:** effect sizes from different studies go in different directions, or there are large differences between the effect sizes of different studies.

Step 4: Summarize Implications for the Proposed New Study

The aim of the final step is to summarize the findings from the previous step and provide an overall decision on the need for the proposed study and the ways in which its design may be modified based on the SR. The interpretation of the findings from this step once again requires the insight of the researcher (and funder of proposed study) in terms of the overall need for the proposed study and the modifications that could be made to the proposed study design and rationale.

1. In what ways does the proposed research study address the gaps in the evidence identified by the SR?
2. Does the proposed study have adequate sample size and power? Several studies have proposed improved ways to estimate sample size and power using existing meta-analyses. Involving a statistician to consider applying these methods may be appropriate.²⁷⁻²⁹
3. Based on the findings from the SR and the body of evidence, which of the features that have been identified as being different to the proposed study should be modified, and which can it be justified to leave unchanged?
4. Which components of the proposed study are redundant with specific aspects of the PICOTS that are already answered (as opposed to the entire question already being answered)?
5. Does the proposed study do something completely new and relevant that has not been covered in either an SR or in other original studies (and, therefore, might not have been identified using the framework)?
6. Are research studies currently underway which will address these gaps? This should involve searches for ongoing trials using databases such as clinicaltrials.gov, VA Health Services Research & Development Web site, and the meta-register of controlled clinical trials (controlled-trials.com). A search for ongoing studies may not be a standard component of all SRs (although authors of reviews may include this information), and may not be part of all research protocols, therefore it may be valuable to include a search for such ongoing trials at this stage.
7. Other considerations: Although strength (or lack of strength) of evidence existing is the most important basis on which to base decisions to propose a new clinical trial, there may be other considerations. These include a balanced assessment of the level of risk of an intervention compared with potential benefit, adverse events from proposed intervention, feasibility of intervention, generalizability of intervention, and costs.³⁵

Discussion

The proposed framework attempts to provide a practical method to improve the use of systematic review (SR) findings in the design and conduct of new research studies. The framework has been designed to be used by researchers rather than systematic reviewers, and thus provides a contrast to the perspective of many other initiatives in this area. It is not intended to be applied as a simple checklist or “tick-box exercise,” rather it requires the in depth knowledge about a particular clinical research area which only a primary research is likely to have, and requires a degree of judgment in several steps. The four-step process is intended for researchers who are in the design phase of study proposal or protocol writing, and involves: Step 1, clearly laying out the crucial design elements of the proposed study using PICOTS elements; Step 2, identifying an existing SR which is current, valid, and relevant enough to the proposed research study; Step 3, examining the details of the SR to determine the extent to which it has already addressed the questions proposed by the new study and identifying the PICOTS elements of the primary studies included in the SR which can be used to modify the design of the proposed study; and Step 4, establishing the need (or otherwise) for the proposed study and prioritizing modifications to research design.

In 2004, the Editor of the Cochrane Library, Dr. Mike Clarke, suggested that researchers should “Design your study to take account of the relevant successes and failures of the prior studies, and of the evidence within them.”⁴ As we highlighted in the introduction, currently only a minority of trials of interventions appear to incorporate the results of existing SRs in their design. We suggest that this contributes to research “wastage” or the inefficient process of conducting new research studies with insufficient attention to existing literature. Indeed, some commentators have proposed a moratorium on new efficacy randomized controlled trials to give researchers and others necessary time to “collaboratively identify and evaluation innovations that have real potential for translation.”³⁶ There are numerous reasons why SRs may not currently be used by researchers to inform study design. The proposed framework attempts to address some of these potential reasons—namely that researchers may lack critical appraisal skills in order to be able to evaluate published SRs effectively, and that SRs in their current format present findings in a way that does not make it straightforward for primary researchers to use inform their future research study.

Most of the current literature on improving the use of SRs in research study design has arisen from the perspective of statistics, and there have been several proposals for improving the use of meta-analyses in simulating sample size and power calculations. These are important, yet focus on particular findings from the meta-analysis and ignore other aspects of study design and indeed need for further studies. As Viechtbauer noted in 2010, “focus on sample size considerations should not draw our attention away from other design issues that can and should be informed by previous research.”² The Future Research Needs (FRN) methods project, “Frameworks for Determining Research Gaps During Systematic Reviews” provides a useful way of categories gaps identified in the PICOTS elements using four categories of insufficient or imprecise information, biased information, inconsistency or unknown consistency, and not the right information,¹⁸ and we have incorporated this categorization in Step 3 of the current framework. In contrast to the proposed study, the FRN project focus was primarily that of systematic reviewers, rather than clinical researchers in the process of proposing or writing the protocols for new research studies. We therefore aimed to add to this FRN project by providing a more

pragmatic “tool” that clinical researchers could use to operationalize some of the principles and initial guidance provided in the FRN project.

A possible limitation of the proposed framework is the danger in prioritizing the need for further research based solely on evidence of effect (or evidence of lack of effect). Publication bias suggests that there is a tendency to publish only when findings are significant, and only when showing positive effect. Even when there is confidence in the size and direction of an effect, it is still possible that additional trials could alter the direction of effect, and there are examples of where evidence of effective treatment based on a meta-analysis have been changed by subsequent trials. Another reason to propose further small trials is that they may demonstrate greater generalizability, which may not be possible from a single larger trial. However, this caution would apply to all frameworks, and we have attempted to use a broader perspective than merely examining the results of a SR meta-analysis in order to judge the need (or not) for a further study. A further limitation of the proposed framework is that we do not know whether most clinical researchers currently have the skill in order to use SRs in the manner in which we have proposed. In addition, we do not know if the proposed framework offers advantages over other attempts to improve the usefulness of SRs for indicating future research gaps, such as better reporting or more explicit mention of research gaps.¹¹

The following next steps could be considered in methodology research in this area. First, although the proposed framework has been designed from the perspective of the primary researcher and has received feedback from several individuals involved in trial design, we do not know how useful this framework is for primary researchers. Therefore using a wider group of stakeholders to evaluate the proposed framework, in particular engaging with researchers in the proposal phase of new research studies in order to use the framework “for real,” would be valuable. Second, one possible way of “testing” the framework would be to identify a series of trials published in a set of the main medical journals in 2011, identify the original protocols of the trials (e.g., from clinical trials.gov), and determine whether application of the framework at the time of the protocol publication would have been useful to modify the protocol, and in what ways. Third, it would be useful to consider whether the current framework could benefit from making more explicit for primary researchers the situations in which the data from meta-analyses could be used more effectively. This could include alternative methods of meta-analyses, such as individual patient data meta-analysis. Currently primary researchers would have little way of knowing the “triggers” for when to consider an individual patient data meta-analysis rather than a further primary research study.

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Acronyms and Abbreviations

| | |
|------|--|
| AHRQ | Agency for Healthcare Research and Quality |
| EPC | Evidence-based Practice Center |
| FRN | Future Research Needs |
| RCT | Randomized controlled trial |
| SR | Systematic review |
| VOI | Value of information |

Appendix A. Assessing Validity of Systematic Reviews

Comprehensive Literature Search

| What is Best? | Where is This Information? |
|--|--|
| The starting point for a comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words. | The Methods section should describe the search strategy, including the terms used, in some detail. The Results section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart. |
| Comment: | |

Criteria Used to Select Articles for Inclusion Appropriate?

| What is Best? | Where is This Information? |
|---|---|
| The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria. | The Methods section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design. |
| Comment: | |

Included Studies Sufficiently Valid for the Type of Question Asked?

| What is Best? | Where is This Information? |
|--|---|
| The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question and the study design (e.g., randomization, blinding, and completeness of follow-up) | The Methods section should describe the assessment of quality and the criteria used. The Results section should provide information on the quality of the individual studies. |
| Comment: | |

Were the Results Similar From Study to Study?

| What is Best? | Where is This Information? |
|--|---|
| Ideally, the results of the different studies should be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored. | The Results section should state whether the results are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present. |
| Comment: | |

Appendix B. Four-Step Framework Example 1: Corticosteroids for Pain Relief in Sore Throat: Systematic Review and Meta-analysis

Hayward G, Thompson M, Heneghan C, et al. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ*. 2009;339:b2976

| Step | Substeps | Proposed New Study | | Systematic Review |
|--|--|----------------------|----|--|
| Step 1: Outline the PICO of the proposed new study. | Intervention | Corticosteroids | NA | |
| | Patient group | Adults | NA | |
| | Setting | Outpatient | NA | |
| | Control or comparator | Tylenol | NA | |
| | Study design | RCT | NA | |
| | Main/important outcomes | Improvement in pain | NA | |
| | Duration of followup | 1 week | NA | |
| Step 2: Identify a relevant, valid and current systematic review. Is it relevant? | Intervention | Oral corticosteroids | | Systemic corticosteroid |
| | Patient group | Adults | | Adults and children |
| | Setting | Outpatient | | Outpatient (ambulatory) |
| | Control or comparator | Tylenol or NSAIDs | | Placebo |
| | Study design | Observational | | Randomized controlled trials |
| | Main/important outcomes | Improvement in pain | | Symptoms of sore throat |
| | Duration of followup | 1 week | | Not specified |
| Step 2: Identify a relevant, valid and current systematic review. Is it valid? | What question (PICO) did the systematic review address? | NA | | Evaluated whether systemic corticosteroids improve symptoms of sore throat in adults and children. |
| | Comprehensive Literature Search? | NA | | Yes: All major search engines were searched |
| | Criteria used to select articles for inclusion appropriate? | NA | | Yes |
| | Included studies sufficiently valid for the type of questions asked? | NA | | Unclear (8 studies included with 743 patients) |
| | Were the results similar from study to study? | NA | | No. Heterogeneity exists in setting, intervention, outcomes, and severity of illness. |

Step 2: Identify a relevant, valid and current systematic review. Is it current?

Is it Current?

NA

Yes: 2009

Intervention (type and number)

NA

Six studies used Dexamethasone (IM), one used Betamethasone (IM), and one used Prednisone (PO).
Implications: very little data on use of oral steroids, which is most likely to be the type of steroids used in ambulatory settings.

Patient group

NA

Five studies used adults (age ranges from 12 to 65) and three used children (age ranges 5 to 16).
Implications: the effect was significant in adults but not children, but 4/5 adult studies used IM steroids not oral, the only one that did was based in Israel in patients with severe sore throat.

Setting

Outpatient, variety of methods used to determine severity.
Implications: need standardized way of assessing severity of sore throat and standardize throat swabbing.
Placebo in studies was IM saline or PO placebo, but all participants were given antibiotics.

Step 3: Use the body of evidence from SR to inform the proposed research study. What can be learned from the primary studies included in the SR?

Control or comparator

NA

Implication: need for study where participants are not given antibiotics, otherwise do not know the independent effects of steroids without abx.

Study design

NA

Randomized controlled trials.
Implication: no justification for using inferior study design to this. None of the studies used pragmatic RCT, could consider this type of design.

Main/important outcomes

NA

Included studies used many different outcome measures related to pain, associated symptoms, and impact on quality of life.
Implication: select the validated visual analogue score used in several of the studies to measure pain. None of the studies examined recurrence within 1-2 weeks, or the effect on reattendance—consider adding these as secondary outcomes. None of the studies examined cost effectiveness, could add this to proposed study.

Duration of followup

NA

72 hours followup in most studies.
Implication: 72 hours was sufficient as most participants completely improved by then, no need for longer followup for efficacy, might consider whether longer followup might be useful to look for impact on recurrence (of same episode) or re attendance (with new episodes).

| | | | |
|--|---|-----|--|
| <p>Step 3: Use the body of evidence from SR to inform the proposed research study. What does the SR answer, and where do gaps remain?</p> | Proposed study questions have already been answered adequately? | No | <p>Corticosteroids provide symptomatic relief of pain in sore throat, in addition to antibiotic therapy, mainly in participants with severe or exudative sore throat.</p> <p><i>Evidence for effect on adults was significant, not for oral steroids, not for less severe sore throat.</i></p> <p>A. Insufficient data?</p> <p><i>Only 8 studies with a combined sample of 369 children and 374 adults, only 1 study of oral steroids, most participants had severe sore throat.</i></p> <p>B. Imprecise data?</p> <p><i>Limitations like antibiotic use, heterogeneity in outcome measures, imprecision for oral steroids and nonsevere sore throat</i></p> <p>C. Potentially biased information? <i>Generic drugs, but possible reporting bias as all studies positive effect, authors stated that not possible to exclude publication bias.</i></p> <p>D. Inconsistency or unknown consistency?</p> |
| | Proposed study questions have not been answered adequately? | Yes | <p>Study in adults, with range of severity of sore throat, using oral steroids is justified.</p> |
| | Does it address gaps? | NA | |
| | Which components of proposed study are redundant? | NA | None |
| <p>Step 4: Summarizing the implications for proposed study.</p> | Balance of risk/benefit? | NA | <p>Need to assess cost effectiveness. Effect size from SR is small (6 hours improvement with steroids) thus cost effectiveness may be major issue to generalizability of results.</p> |
| | Which features should be modified? | NA | <p>Select valid pain score outcome measure, consider adding recurrence or re attendance as 2 year outcomes, type and dose of steroid, and severity of sore throat in included participants.</p> |