



Finding What Works in Health Care: Standards for Systematic Reviews

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Summary¹

Healthcare decision makers in search of the best evidence to inform clinical decisions have come to rely on systematic reviews (SRs) of comparative effectiveness research (CER) to learn what is known and not known about the potential benefits and harms of alternative drugs, devices, and other healthcare services. An SR is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data. Although the importance of SRs is increasingly appreciated, the quality of published SRs is variable and often poor. In many cases, the reader is unable to judge the quality of an SR because the methods are poorly documented, and even if methods are described, they may be used inappropriately, for example, in meta-analyses. Many reviews fail to assess the quality of the underlying research and also neglect to report funding sources. A plethora of conflicting approaches to evidence hierarchies and grading schemes for bodies of evidence is a further source of confusion.

In the 2008 report, *Knowing What Works in Health Care: A Roadmap for the Nation*, the Institute of Medicine (IOM) recommended that methodological standards be developed for both SRs and clini-

¹This summary does not include references. Citations for the findings presented in the Summary appear in the subsequent chapters.

cal practice guidelines (CPGs). The report was followed by a congressional mandate in the *Medicare Improvements for Patients and Providers Act of 2008* for two follow-up IOM studies: one to develop standards for conducting SRs, and the other to develop standards for CPGs. This is the report of the IOM Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. A companion report by the IOM Committee on Standards for Developing Trustworthy Clinical Practice Guidelines is being released in conjunction with this report.

The charge to this IOM committee was twofold: first, to assess potential methodological standards that would assure objective, transparent, and scientifically valid SRs of CER and, second, to recommend a set of methodological standards for developing and reporting such SRs (Box S-1). The boundaries of this study were defined in part by the work of the companion CPG study. The SR committee limited its focus to the development of SRs. At the same time, the CPG committee worked under the assumption that guideline developers have access to and use high-quality SRs (as defined by the standards recommended in this report).

This report presents methodological standards for SRs that are designed to inform everyday healthcare decision making, especially for patients, clinicians and other healthcare providers, and devel-

BOX S-1
Charge to the Committee on Standards
for Systematic Reviews of Comparative
Effectiveness Research

An ad hoc committee will conduct a study to recommend methodological standards for systematic reviews (SRs) of comparative effectiveness research (CER) on health and health care. The standards should ensure that the reviews are objective, transparent, and scientifically valid, and require a common language for characterizing the strength of the evidence. Decision makers should be able to rely on SRs of comparative effectiveness to determine what is known and not known and to describe the extent to which the evidence is applicable to clinical practice and particular patients. In this context, the committee will:

1. Assess whether, if widely adopted, any existing set of standards would assure that SRs of comparative effectiveness research are objective, transparent, and scientifically valid.
2. Recommend a set of standards for developing and reporting SRs of CER.

opers of CPGs. The focus is on the development and reporting of comprehensive, publicly funded SRs of the comparative effectiveness of therapeutic medical or surgical interventions. The recent health reform legislation underscores the imperative for establishing standards to ensure the highest quality SRs. The *Patient Protection and Affordable Care Act of 2010* (ACA) created the nation's first nonprofit, public-private Patient-Centered Outcomes Research Institute (PCORI). PCORI will be responsible for establishing and implementing a research agenda—including SRs of CER—to help patients, clinicians and other healthcare providers, purchasers, and policy makers make informed healthcare decisions. As this report was being developed, planning for PCORI was underway. An initial task of the newly appointed governing board of the institute is to establish a standing methodology committee charged with developing and improving the science and methods of CER.

The IOM committee undertook its work with the intention to inform the PCORI methodology committee's own standards development. The IOM committee also views other public sponsors of SRs of CER as key audiences for this report, including the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program, the Centers for Medicaid and Medicare Coverage Advisory Committee, the Drug Effectiveness Research Project, the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the U.S. Preventive Services Task Force.

PURPOSE OF SETTING STANDARDS

Organizations establish standards to set performance expectations and to promote accountability for meeting these expectations. For SRs in particular, the principal objective of setting standards is to minimize bias in identifying, selecting, and interpreting evidence. For the purposes of this report, the committee defined an SR "standard" as a process, action, or procedure that is deemed essential to producing scientifically valid, transparent, and reproducible SRs. A standard may be supported by scientific evidence, by a reasonable expectation that the standard helps achieve the anticipated level of quality in an SR, or by the broad acceptance of the practice by authors of SRs.

The evidence base for many of the steps in the SR process is sparse, especially with respect to linking characteristics of SRs to clinical outcomes, the ultimate test of quality. The committee developed its standards and elements of performance based on available research evidence and expert guidance from the AHRQ Effective

Health Care Program; the Centre for Reviews and Dissemination (CRD) (University of York, United Kingdom); the Cochrane Collaboration; the Grading of Recommendations Assessment, Development, Evaluation (GRADE) Working Group²; and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group (PRISMA).

The committee faced a difficult task in proposing a set of standards where in general the evidence is thin and expert guidance varies. Yet the evidence that is available does not suggest that high-quality SRs can be done quickly and cheaply. SRs conducted with methods prone to bias do indeed often miss the boat, leading to clinical advice that may in the end harm patients. All of the committee's recommended standards are based on current evidence, expert guidance, and thoughtful reasoning, and are actively used by many experts, and thus are reasonable "best practices" for reducing bias and for increasing the scientific rigor of SRs of CER. However, all of the recommended standards must be considered provisional pending better empirical evidence about their scientific validity, feasibility, efficiency, and ultimate usefulness in medical decision making.

The committee recommends 21 standards with 82 elements of performance, addressing the entire SR process, from the initial steps of formulating the topic, building a review team, and establishing a research protocol, to finding and assessing the individual studies that make up the body of evidence, to producing qualitative and quantitative syntheses of the body of evidence, and, finally, to developing the final SR report. Each standard is articulated in the same format: first, a brief statement of the step in the SR process (e.g., in Chapter 3, Standard 3.1. Conduct a comprehensive systematic search for evidence) followed by a series of elements that are essential components of the standard. These "elements" are steps that should be taken for all publicly funded SRs of CER.

Collectively the standards and elements present a daunting task. Few, if any, members of the committee have participated in an SR that fully meets all of them. Yet the evidence and experience are strong enough that it is impossible to ignore these standards or hope that one can safely cut corners. The standards will be especially valuable for SRs of high-stakes clinical questions with broad population impact, where the use of public funds to get the right answer justifies careful attention to the rigor with which the SR is conducted. Individuals involved in SRs should be thoughtful about all of the

²GRADE was a primary source for Chapter 4 only. PRISMA was a primary source for Chapter 5 only.

standards and elements, using their best judgment if resources are inadequate to implement all of them, or if some seem inappropriate for the particular task or question at hand. Transparency in reporting the methods actually used and the reasoning behind the choices are among the most important of the standards recommended by the committee.

Initiating the SR Process

The first steps in the SR process define the focus and methods of the SR and influence its ultimate utility for clinical decisions. Current practice falls far short of expert guidance; well-designed, well-executed SRs are the exception. (Note that throughout this report reference to “expert guidance” refers to the published methodological advice of the AHRQ Effective Health Care Program, CRD, and the Cochrane Collaboration.) The committee recommends eight standards for initiating the SR process, minimizing potential bias in the SR’s design and execution. The standards address the creation of the SR team, user and stakeholder input, managing bias and conflict of interest (COI), topic formulation, and development of the SR protocol (Box S-2). The SR team should include individuals with appropriate expertise and perspectives. Creating a mechanism for users and stakeholders—consumers, clinicians, payers, and members of CPG panels—to provide input into the SR process at multiple levels helps to ensure that the SR is focused on real-world health-care decisions. However, a process should be in place to reduce the risk of bias and COI from stakeholder input and in the SR team. The importance of the review questions and analytic framework in guiding the entire review process demands a rigorous approach to formulating the research questions and analytic framework. Requiring a research protocol that prespecifies the research methods at the outset of the SR process helps to prevent the effects of author bias, allows feedback at an early stage in the SR, and tells readers of the review about protocol changes that occur as the SR develops.

Finding and Assessing Individual Studies

The committee recommends six standards for identifying and assessing the individual studies that make up an SR’s body of evidence, including standards addressing the search process, screening and selecting studies, extracting data, and assessing the quality of individual studies (Box S-3). The objective of the SR search is to identify all the studies (and all the relevant data from the studies) that

BOX S-2
**Recommended Standards for Initiating
a Systematic Review**

Standard 2.1 Establish a team with appropriate expertise and experience to conduct the systematic review

Required elements:

- 2.1.1 Include expertise in the pertinent clinical content areas
- 2.1.2 Include expertise in systematic review methods
- 2.1.3 Include expertise in searching for relevant evidence
- 2.1.4 Include expertise in quantitative methods
- 2.1.5 Include other expertise as appropriate

Standard 2.2 Manage bias and conflict of interest (COI) of the team conducting the systematic review

Required elements:

- 2.2.1 Require each team member to disclose potential COI and professional or intellectual bias
- 2.2.2 Exclude individuals with a clear financial conflict
- 2.2.3 Exclude individuals whose professional or intellectual bias would diminish the credibility of the review in the eyes of the intended users

Standard 2.3 Ensure user and stakeholder input as the review is designed and conducted

Required element:

- 2.3.1 Protect the independence of the review team to make the final decisions about the design, analysis, and reporting of the review

Standard 2.4 Manage bias and COI for individuals providing input into the systematic review

Required elements:

- 2.4.1 Require individuals to disclose potential COI and professional or intellectual bias
- 2.4.2 Exclude input from individuals whose COI or bias would diminish the credibility of the review in the eyes of the intended users

Standard 2.5 Formulate the topic for the systematic review

Required elements:

- 2.5.1 Confirm the need for a new review

may pertain to the research question and analytic framework. The search should be systematic, use prespecified search parameters, and access an array of information sources that provide both published and unpublished research reports. Screening and selecting

- 2.5.2 Develop an analytic framework that clearly lays out the chain of logic that links the health intervention to the outcomes of interest and defines the key clinical questions to be addressed by the systematic review
- 2.5.3 Use a standard format to articulate each clinical question of interest
- 2.5.4 State the rationale for each clinical question
- 2.5.5 Refine each question based on user and stakeholder input

Standard 2.6 Develop a systematic review protocol

Required elements:

- 2.6.1 Describe the context and rationale for the review from both a decision-making and research perspective
- 2.6.2 Describe the study screening and selection criteria (inclusion/exclusion criteria)
- 2.6.3 Describe precisely which outcome measures, time points, interventions, and comparison groups will be addressed
- 2.6.4 Describe the search strategy for identifying relevant evidence
- 2.6.5 Describe the procedures for study selection
- 2.6.6 Describe the data extraction strategy
- 2.6.7 Describe the process for identifying and resolving disagreement between researchers in study selection and data extraction decisions
- 2.6.8 Describe the approach to critically appraising individual studies
- 2.6.9 Describe the method for evaluating the body of evidence, including the quantitative and qualitative synthesis strategies
- 2.6.10 Describe and justify any planned analyses of differential treatment effects according to patient subgroups, how an intervention is delivered, or how an outcome is measured
- 2.6.11 Describe the proposed timetable for conducting the review

Standard 2.7 Submit the protocol for peer review

Required element:

- 2.6.9 Provide a public comment period for the protocol and publicly report on disposition of comments

Standard 2.8 Make the final protocol publicly available, and add any amendments to the protocol in a timely fashion

studies should use methods that address the pervasive problems of SR author bias, errors, and inadequate documentation of the study selection process in SRs. Study methods should be reported in sufficient detail so that searches can be replicated and appraised. Qual-

BOX S-3
**Recommended Standards for Finding
and Assessing Individual Studies**

Standard 3.1 Conduct a comprehensive systematic search for evidence

Required elements:

- 3.1.1 Work with a librarian or other information specialist trained in performing systematic reviews to plan the search strategy
- 3.1.2 Design the search strategy to address each key research question
- 3.1.3 Use an independent librarian or other information specialist to peer review the search strategy
- 3.1.4 Search bibliographic databases
- 3.1.5 Search citation indexes
- 3.1.6 Search literature cited by eligible studies
- 3.1.7 Update the search at intervals appropriate to the pace of generation of new information for the research question being addressed
- 3.1.8 Search subject-specific databases if other databases are unlikely to provide all relevant evidence
- 3.1.9 Search regional bibliographic databases if other databases are unlikely to provide all relevant evidence

Standard 3.2 Take action to address potentially biased reporting of research results

Required elements:

- 3.2.1 Search grey-literature databases, clinical trial registries, and other sources of unpublished information about studies
- 3.2.2 Invite researchers to clarify information about study eligibility, study characteristics, and risk of bias
- 3.2.3 Invite all study sponsors and researchers to submit unpublished data, including unreported outcomes, for possible inclusion in the systematic review
- 3.2.4 Handsearch selected journals and conference abstracts
- 3.2.5 Conduct a web search
- 3.2.6 Search for studies reported in languages other than English if appropriate

Standard 3.3 Screen and select studies

Required elements:

- 3.3.1 Include or exclude studies based on the protocol's prespecified criteria
- 3.3.2 Use observational studies in addition to randomized clinical trials to evaluate harms of interventions

- 3.3.3 Use two or more members of the review team, working independently, to screen and select studies
- 3.3.4 Train screeners using written documentation; test and retest screeners to improve accuracy and consistency
- 3.3.5 Use one of two strategies to select studies: (1) read all full-text articles identified in the search or (2) screen titles and abstracts of all articles and then read the full texts of articles identified in initial screening
- 3.3.6 Taking account of the risk of bias, consider using observational studies to address gaps in the evidence from randomized clinical trials on the benefits of interventions

Standard 3.4 Document the search

Required elements:

- 3.4.1 Provide a line-by-line description of the search strategy, including the date of every search for each database, web browser, etc.
- 3.4.2 Document the disposition of each report identified including reasons for their exclusion if appropriate

Standard 3.5 Manage data collection

Required elements:

- 3.5.1 At a minimum, use two or more researchers, working independently, to extract quantitative and other critical data from each study. For other types of data, one individual could extract the data while the second individual independently checks for accuracy and completeness. Establish a fair procedure for resolving discrepancies—do not simply give final decision-making power to the senior reviewer
- 3.5.2 Link publications from the same study to avoid including data from the same study more than once
- 3.5.3 Use standard data extraction forms developed for the specific SR
- 3.5.4 Pilot-test the data extraction forms and process

Standard 3.6 Critically appraise each study

Required elements:

- 3.6.1 Systematically assess the risk of bias, using predefined criteria
- 3.6.2 Assess the relevance of the study's populations, interventions, and outcome measures
- 3.6.3 Assess the fidelity of the implementation of interventions

ity assurance and control are essential when data are extracted from individual studies from the collected body of evidence. A thorough and thoughtful assessment of the validity and relevance of each eligible study helps ensure scientific rigor and promote transparency.

Synthesizing the Body of Evidence

The committee recommends four standards for the qualitative and quantitative synthesis and assessment of an SR's body of evidence (Box S-4). The qualitative synthesis is an often undervalued component of an SR. Many SRs lack a qualitative synthesis altogether or simply recite the facts about the studies without examining them for patterns or characterizing the strengths and weaknesses

BOX S-4 **Recommended Standards for Synthesizing the Body of Evidence**

Standard 4.1 Use a prespecified method to evaluate the body of evidence

Required elements:

- 4.1.1 For each outcome, systematically assess the following characteristics of the body of evidence:
 - Risk of bias
 - Consistency
 - Precision
 - Directness
 - Reporting bias
- 4.1.2 For bodies of evidence that include observational research, also systematically assess the following characteristics for each outcome:
 - Dose–response association
 - Plausible confounding that would change the observed effect
 - Strength of association
- 4.1.3 For each outcome specified in the protocol, use consistent language to characterize the level of confidence in the estimates of the effect of an intervention

Standard 4.2 Conduct a qualitative synthesis

Required elements:

- 4.2.1 Describe the clinical and methodological characteristics of the included studies, including their size, inclusion or exclusion of important subgroups, timeliness, and other relevant factors

of the body of evidence as a whole. If the SR is to be comprehensible, it should use consistent language to describe the quality of evidence for each outcome and incorporate multiple dimensions of study quality. For readers to have a clear understanding of how the evidence applies to real-world clinical circumstances and specific patient populations, SRs should describe—in easy-to-understand language—the clinical and methodological characteristics of the individual studies, including their strengths and weaknesses and their relevance to particular populations and clinical settings. It should also describe how flaws in the design or execution of the individual studies could bias the results. The qualitative synthesis is more than a narrative description or set of tables that simply detail how many studies were assessed, the reasons for excluding other

- 4.2.2 Describe the strengths and limitations of individual studies and patterns across studies
- 4.2.3 Describe, in plain terms, how flaws in the design or execution of the study (or groups of studies) could bias the results, explaining the reasoning behind these judgments
- 4.2.4 Describe the relationships between the characteristics of the individual studies and their reported findings and patterns across studies
- 4.2.5 Discuss the relevance of individual studies to the populations, comparisons, cointerventions, settings, and outcomes or measures of interest

Standard 4.3 Decide if, in addition to a qualitative analysis, the systematic review will include a quantitative analysis (meta-analysis)

Required element:

- 4.3.1 Explain why a pooled estimate might be useful to decision makers

Standard 4.4 If conducting a meta-analysis, then do the following:

Required elements:

- 4.4.1 Use expert methodologists to develop, execute, and peer review the meta-analyses
- 4.4.2 Address the heterogeneity among study effects
- 4.4.3 Accompany all estimates with measures of statistical uncertainty
- 4.4.4 Assess the sensitivity of conclusions to changes in the protocol, assumptions, and study selection (sensitivity analysis)

NOTE: The order of the standards does not indicate the sequence in which they are carried out.

studies, the range of study sizes and treatments compared, or the quality scores of each study as measured by a risk of bias tool.

Meta-analysis is the statistical combination of results from multiple individual studies. Many published meta-analyses have combined the results of studies that differ greatly from one another. The assumption that a meta-analysis is an appropriate step in an SR should never be made. The decision to conduct a meta-analysis is neither purely analytical nor statistical in nature. It will depend on a number of factors, such as the availability of suitable data and the likelihood that the analysis could inform clinical decision making. Ultimately, authors should make this subjective judgment in consultation with the entire SR team, including both clinical and methodological perspectives. If appropriate, the meta-analysis can provide reproducible summaries of the individual study results and offer valuable insights into the patterns in the study results. A strong meta-analysis features and clearly describes its subjective components, scrutinizes the individual studies for sources of heterogeneity, and tests the sensitivity of the findings to changes in the assumptions, the set of included studies, the outcome metrics, and the statistical models.

The Final Report

Authors of all publicly sponsored SRs should produce a detailed final report. The committee recommends three standards for producing the SR final report: (1) including standards for documenting the SR process; (2) responding to input from peer reviewers, users, and stakeholders; and (3) making the final report publicly available (Box S-5). The committee's standards for documenting the SR process drew heavily on the PRISMA checklist. The committee recommends adding items to the PRISMA checklist to ensure that the report of an SR describes all of the steps and judgments required by the committee's standards (Boxes S-2, S-3, and S-4).

RECOMMENDATIONS

The evidence base supporting many elements of SRs is incomplete and, for some steps, nonexistent. Research organizations such as the AHRQ Effective Health Care Program, CRD, and the Cochrane Collaboration have published standards, but none of these are universally accepted and consistently applied during planning, conducting, reporting, and peer review of SRs. Furthermore, the SR enterprise in the United States lacks both adequate funding and

coordination; many organizations conduct SRs, but do not typically work together. Thus, the committee concludes that improving the quality of SRs will require improving not only the science supporting the steps in the SR process (Boxes S-2, S-3, and S-4), but also providing a more supportive environment for the conduct of SRs. The committee proposes a framework for improving the quality of the science underpinning SRs and supporting the environment for SRs. The framework has several broad categories: strategies for involving the right people, methods for conducting reviews, methods for synthesizing and evaluating evidence, and methods for communicating and using results.

The standards and elements form the core of the committee's conclusions, but the standards themselves do not indicate how the standards should be implemented, nor do the standards address issues of improving the science for SRs or for improving the environment that supports the development and use of an SR enterprise. In consequence, the committee makes the following two recommendations:

Recommendation 1: Sponsors of SRs of CER should adopt appropriate standards for the design, conduct, and reporting of SRs and require adherence to the standards as a condition for funding.

SRs of CER in the United States are now commissioned and conducted by a vast array of private and public entities, some supported generously with adequate funding to meet the most exacting standards, others supported less generously so that the authors must make compromises at every step of the review. The committee recognizes that its standards and elements are at the "exacting" end of the continuum, some of which are within the control of the review team whereas others are contingent on the SR sponsor's compliance. However, high-quality reviews require adequate time and resources to reach reliable conclusions. The recommended standards are an appropriate starting point for publicly funded reviews in the United States (including PCORI, federal, state, and local funders) because of the heightened attention and potential clinical impact of major reviews sponsored by public agencies. The committee also recognizes that authors of SRs supported by public funds derived from nonfederal sources (e.g., state public health agencies) will see these standards as an aspirational goal rather than as a minimum requirement. SRs that significantly deviate from the standards should clearly explain and justify the use of different methods.

BOX S-5
Recommended Standards for
Reporting Systematic Reviews

Standard 5.1 Prepare final report using a structured format

Required elements:

- 5.1.1 Include a report title*
- 5.1.2 Include an abstract*
- 5.1.3 Include an executive summary
- 5.1.4 Include a summary written for the lay public
- 5.1.5 Include an introduction (rationale and objectives)*
- 5.1.6 Include a methods section. Describe the following:
 - Research protocol*
 - Eligibility criteria (criteria for including and excluding studies in the systematic review)*
 - Analytic framework and key questions
 - Databases and other information sources used to identify relevant studies*
 - Search strategy*
 - Study selection process*
 - Data extraction process*
 - Methods for handling missing information*
 - Information to be extracted from included studies*
 - Methods to appraise the quality of individual studies*
 - Summary measures of effect size (e.g., risk ratio, difference in means)*
 - Rationale for pooling (or not pooling) results of included studies
 - Methods of synthesizing the evidence (qualitative and meta-analysis*)
 - Additional analyses, if done, indicating which were prespecified*

Recommendation 2: The Patient-Centered Outcomes Research Institute and the Department of Health and Human Services (HHS) agencies (directed by the secretary of HHS) should collaborate to improve the science and environment for SRs of CER. Primary goals of this collaboration should include

- **Developing training programs for researchers, users, consumers, and other stakeholders to encourage more effective and inclusive contributions to SRs of CER;**
- **Systematically supporting research that advances the methods for designing and conducting SRs of CER;**

- 5.1.7 Include a results section; organize the presentation of results around key questions; describe the following (repeat for each key question):
 - Study selection process*
 - List of excluded studies and reasons for their exclusion*
 - Appraisal of individual studies' quality*
 - Qualitative synthesis
 - Meta-analysis of results, if performed (explain rationale for doing one)*
 - Additional analyses, if done, indicating which were prespecified*
 - Tables and figures
- 5.1.8 Include a discussion section. Include the following:
 - Summary of the evidence*
 - Strengths and limitations of the systematic review*
 - Conclusions for each key question*
 - Gaps in evidence
 - Future research needs
- 5.1.9 Include a section describing funding sources* and COI

Standard 5.2 Peer review the draft report

Required elements:

- 5.2.1 Use a third party to manage the peer review process
- 5.2.2 Provide a public comment period for the report and publicly report on disposition of comments

Standard 5.3 Publish the final report in a manner that ensures free public access

* Indicates items from the PRISMA checklist. (The committee endorses all of the PRISMA checklist items.)

- **Supporting research to improve the communication and use of SRs of CER in clinical decision making;**
- **Developing effective coordination and collaboration between U.S. and international partners;**
- **Developing a process to ensure that standards for SRs of CER are regularly updated to reflect current best practice; and**
- **Using SRs to inform priorities and methods for primary CER.**

This recommendation conveys the committee's view of how best to implement its recommendations to improve the science and sup-

port the environment for SRs of comparative effectiveness research, which is clearly in the public's interest. PCORI is specifically named because of its statutory mandate to establish and carry out a CER research agenda. As noted above, it is charged with creating a methodology committee that will work to develop and improve the science and methods of SRs of CER and to regularly update such standards. PCORI is also required to assist the Comptroller General in reviewing and reporting on compliance with its research standards, the methods used to disseminate research findings, the types of training conducted and supported in CER, and the extent to which CER research findings are used by healthcare decision makers. The HHS agencies are specifically named because AHRQ, NIH, CDC, and other sections of HHS are major funders and producers of SRs. In particular, the AHRQ EPC program has been actively engaged in coordinating high-quality SRs and in developing SR methodology. The committee assigns these groups with responsibility and accountability for coordinating and moving the agenda ahead.

The committee found compelling evidence that having high-quality SRs based on rigorous standards is a topic of international concern, and that individual colleagues, professional organizations, and publicly funded agencies in other countries make up a large proportion of the world's expertise on the topic. Nonetheless, the committee followed the U.S. law that brought this report into being, which suggests a management approach appropriate to the U.S. environment. A successful implementation of the final recommendation should result in an enterprise in the United States that participates fully and harmonizes with the international development of SRs, serving in some cases in a primary role, in others as a facilitator, and in yet others as a participant. The new enterprise should recognize that this cannot be entirely scripted and managed in advance—structures and processes must allow for innovation to arise naturally from those individuals and organizations in the United States already fully engaged in the topic.

FINDING WHAT WORKS IN HEALTH CARE

STANDARDS FOR SYSTEMATIC REVIEWS

Committee on Standards for Systematic
Reviews of Comparative Effectiveness Research

Board on Health Care Services

Jill Eden, Laura Levit, Alfred Berg, and Sally Morton, *Editors*

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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*“Knowing is not enough; we must apply.
Willing is not enough; we must do.”*

—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **ENRIQUETA C. BOND** of the Burroughs Wellcome Fund, and **MARK R. CULLEN** of Stanford University. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

Knowing what works in health care is of highest importance for patients, healthcare providers, and other decision makers. The most reliable way to identify benefits and harms associated with various treatment options is a systematic review of comparative effectiveness research. Increasingly recognized for their importance, systematic reviews are now being sponsored and conducted by a number of organizations across the United States. When conducted well, a systematic review identifies, appraises, and synthesizes the available body of evidence for a specific clinical question. However, not all of these reviews meet the appropriate standards of quality and methodology. At the request of the U.S. Congress, the Institute of Medicine (IOM) undertook this study to develop a set of standards for conducting systematic reviews of comparative effectiveness research.

The report will have direct implications for implementation of the *Patient Protection and Affordable Care Act of 2010*. This law established the first nonprofit, public-private Patient-Centered Outcomes Research Institute (PCORI). PCORI will be responsible for setting methodological standards for clinical effectiveness research, including systematic reviews of research findings. I hope this study will support PCORI's development of standards to ensure that systematic reviews meet a minimum level of objectivity, transparency, and scientific rigor. The IOM study should also help to inform other

public sponsors of systematic reviews of comparative effectiveness research.

To conduct this study, the Institute of Medicine convened a highly qualified committee with diverse backgrounds, ably led by Alfred Berg, chair, and Sally Morton, vice chair. The committee was assisted by dedicated IOM staff led by Jill Eden. This report draws on available evidence, review of expert guidance, and careful consideration of alternative standards according to specified criteria. While this report presents an initial list of standards for improving the quality of publicly funded systematic reviews, it also calls for continued investment in methodological research to identify better practices for future reviews. A companion report establishes standards for developing clinical practice guidelines. I hope these documents will help guide a robust systematic review enterprise for health in the United States.

Harvey V. Fineberg, M.D., Ph.D.
President, Institute of Medicine
February 2011

Preface

Page through any volume of a medical journal from the 1970s and read a clinical review. The authors are likely to be recognized as experts in the field, and the introduction will often open with “we reviewed the world’s medical literature,” moving on to reach clinical conclusions based as much on the experience and opinions of the authors as on the published evidence. Systematic literature searches, critical appraisal, quantitative meta-analysis, and documented pathways linking the evidence to reaching clinical conclusions were virtually unknown. Today’s explicit, scientifically rigorous, transparent, and publicly accountable systematic reviews (SRs) and clinical practice guidelines (CPGs) are the barely recognizable heirs to that earlier convention for giving clinical advice.

Enormous progress has been made by a large and growing international community of clinicians, methodologists, statisticians, and other stakeholders in developing SRs and CPGs, yet problems remain. There are many competing systems for evaluating and synthesizing evidence, and there are no internationally agreed-upon standards for how to conduct an SR or create a CPG. In the United States, the decades-old interest in SRs and CPGs among public and private agencies is receiving a boost from the highlighting of the importance of both in debates about healthcare reform; a specific provision in the *Medicare Improvements for Patients and Providers Act of 2008* brought two Institute of Medicine (IOM) committees into being, aimed at setting standards for SRs and CPGs. Furthermore, in the United States there is enormous interest in and high expecta-

tions for the newly created Patient-Centered Outcomes Research Institute, whose authorizing legislation specifically names SRs and CPGs as important components in developing a national program of comparative effectiveness research.

As both SR and CPG reports indicate, the term “standard” is problematic. Our two committees found a sparse evidence base that directly evaluates alternative approaches to SRs and CPGs. The SR committee thus relied on available literature, expert guidance from organizations engaged in SRs, and its own criteria and internal discussions to propose a set of standards, recognizing that any such recommendations must be considered provisional pending further development of the evidence. Collectively the standards set a high bar that will be difficult to achieve for many SRs, yet the evidence and experience are not reassuring that it is safe to cut corners if resources are limited. The standards will be especially valuable for SRs of high-stakes clinical questions with broad population impact, where the use of public funds to get the right answer justifies careful attention to the rigor with which the SR is conducted. The best practices collected in this report should be thoughtfully considered by anyone conducting an SR. In the end the most important standard is to be transparent in reporting what was done and why. Importantly, the committee concludes with recommendations that the United States invest in a program to improve both the science of SRs (with attention to both scientific rigor and feasibility/cost) and the environment that supports them, including a process to update standards as the evidence improves.

Finally, one of the most professionally satisfying benefits of leading an IOM committee is the opportunity to work with committee members with an amazing breadth and depth of experience, and IOM staff whose anticipation and completion of the next steps always appears effortless. We are deeply grateful that this committee and staff have again demonstrated the process at its best.

In conclusion, the committee believes we are at an important juncture in the development of SRs and CPGs, and that timely investment in both will produce an excellent return in improving health care and patient outcomes. We hope our recommended standards will serve as a useful milestone as the United States joins international partners to advance the science and improve the environment for SRs and CPGs.

Alfred O. Berg, *Chair*
Sally C. Morton, *Vice Chair*
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