Patient-Centered Outcomes Research Institute

Preliminary Draft Methodology Report:
“Our Questions, Our Decisions: Standards for Patient-centered Outcomes Research”

Presented by the PCORI Methodology Committee to the PCORI Board of Governors May 10, 2012

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**Note:** Public comments will be reviewed for use in revising this draft; PCORI’s Methodology Committee will deliver a final version of the report to PCORI’s Board of Governors in November 2012.
PCORI

The Patient-Centered Outcomes Research Institute (PCORI) was established by Congress through the 2010 Patient Protection and Affordable Care Act, but is by law an independent, non-profit organization. PCORI is governed by a 21-member Board of Governors. It was created to conduct research to provide information about the best available evidence to help patients and their healthcare providers make more informed decisions. PCORI’s research is intended to give patients a better understanding of the prevention, treatment and care options available, and the science that supports those options.

(from http://www.pcori.org/about/ & http://www.pcori.org/about/establishment/)
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Forward

Americans today have more healthcare options than ever before: choices between medicine or surgery, between radiation or chemotherapy, between traditional or alternative therapies, and even between treatment or no treatment at all. But sorting out the wheat from the chaff, ensuring that the information used to make those difficult decisions is truly trustworthy can be extremely challenging. The mandate for the Methodology Committee of PCORI is to respond to that challenge by defining methodological standards and a translation table to guide healthcare stakeholders towards the best methods for patient-centered outcomes research (PCOR). Better methods will produce trusted information and lead to better healthcare decisions, and ultimately to better health. With vision, integrity, intellect, and wisdom, and with the support of dozens of scientists from around the U.S., the members of the Methodology Committee have produced the first PCORI Methodology Report. This landmark document (which will continue to be revised and improved over time) is the necessary catalyst for scientifically rigorous, patient-centered outcomes research that can inform decision-making.

Sherine Gabriel, Chair
Sharon-Lise Normand, Vice-Chair
Methodology Committee of the Patient-Centered Outcomes Research Institute
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Executive Summary

In this first report, the Methodology Committee puts forward 60 standards to guide patient-centered outcomes research (Appendix A). The initial range of topics was chosen to reflect areas in which the Committee believed that there were either substantial deficiencies or inconsistencies in how the methods were applied in practice, or for which there was specialized knowledge in how best to conduct research that had not been effectively disseminated.(1-3)

This list should be seen in terms of both its overall scope as well as the particular standards that may be most applicable to a particular research project or stage of research. Background, rationale, current practice, recommendations, and other supporting material that help to explain these standards and place them in the proper contexts are included in subsequent chapters. The number of standards within a group should not be taken as any indication of the importance of a topic area.

The report satisfies a requirement of the Patient Protection and Affordable Care Act (PPACA) of 2010, which also established the Patient-Centered Outcomes Research Institute (PCORI) and its Methodology Committee. The legislation states in part that the “purpose of the Institute is to assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed…”(Appendix E-2).

We have interpreted this legislation to mean that the PCORI Methodology Committee’s role is to advise PCORI on the best methods for prioritizing, establishing, and carrying out its research agenda by improving the conduct of patient-centered outcomes research (PCOR), supporting infrastructure for PCOR, and furthering the implementation of PCOR to help patients receive optimal outcomes. This first Methodology Committee report focuses on the patient’s perspective. Future reports will address clinicians’, healthcare purchasers’, and policy-makers’ perspectives in more detail.

The list of methodological standards for patient-centered outcomes research at the heart of this report is a milestone, but not a destination. Indeed, the legislation establishing PCORI and its Methodology Committee direct that these standards shall be periodically updated (Appendix E-5). Over time, these reports, standards, translation tables, and public engagement forums are expected
to produce better research methods, which in turn will provide information of benefit to all stakeholders—researchers planning an investigation, policy-makers weighing the value of healthcare interventions, and patients and their caregivers facing health decisions. We encourage public comments about the report, the standards, and the translation table and hope to refine the work based on this feedback.
Chapter 1. Introduction

In this first report, the Methodology Committee presents 60 standards to guide patient-centered outcomes research (Appendix A). The initial range of topics was chosen to reflect areas in which the Committee believed that there were either substantial deficiencies or inconsistencies in how available methods were applied in practice, or for which there was specialized knowledge in how best to conduct research that had not been effectively disseminated.(1-3)

The standards offer an approach to align the research agenda with questions that underlie patients’ and clinicians’ uncertainty about what works best, for whom, under what circumstances. Methodological standards aim to do this by improving the way research questions are selected, formulated and addressed, and findings reported. They can also help prevent the research agenda from employing flawed, out-of-date, or inappropriate methods to answer research questions, and may raise the bar for researchers, publishers, and industry as they try to inform decision-making. Just as standards for premarketing studies helped level the playing field by defining the requirements for decisions about regulatory approval of a new drug or device, standards for PCOR can also benefit medical innovators by providing a common set of expectations about the characteristics of high-quality research.

Patient-Centered Outcomes Research

As each of us travels the path of healthy to sick, person to patient, we are faced with a series of choices. Should we have an operation or stick with the pills for our heartburn? Should we take that screening test or skip it and hope this is not the year that we develop cancer? Is it time to bring my feverish child to the doctor or can I wait another day? Each of these decisions, and all the other decisions we make over the course of a lifetime, accounts for much of our personal experience with the healthcare system. The remainder of that experience relates to living with the consequences of the decisions and choices we make. Some of us do our own research at the library or on the internet, while others count on the advice of someone they trust. No matter how we make these decisions, we all agree on one thing: we want to rely on the best possible information.

The information we need to make decisions most often comes from clinical research. Clinical research includes investigations undertaken by scientists, who decide which questions to ask, what approaches to take, how to perform the work, how to interpret the results, and then ultimately how
to disseminate the findings through scientific journals or other means. The last 75 years of clinical research has been marked by phenomenal advances in knowledge about the causes of disease and their treatments. Our nation’s public and private research funding organizations have helped transform modern medicine, influence the daily healthcare of all of us, and have contributed to unprecedented health and well being of our country.

Yet while these successes are all around us, from the perspective of many patients facing health decisions, this research process often misses the mark. Sometimes the research is performed on people who are so different from us that we can’t interpret the results. It includes subjects of different ages, sex, race, and without the complexity of conditions that we have. It sometimes involves treatment in care settings not enough like ours—sophisticated research centers rather than places more like the communities in which we live. It sometimes focuses on choices that don’t apply enough to us—expensive treatments that we have to drive hundreds of miles to receive or that we might need to pay for out of pocket … if we have the money or time. It sometimes deals in outcomes we don’t always think are that important—whether or not our blood tests are getting better instead of whether we feel better. For a lot of us, this gap between the information we need and the information we get from research leaves us without the kind of useful information we need to make healthcare decisions. We are often left frustrated by the information we have.

The Patient Protection and Affordable Care Act (PPACA) of 2010 created the Patient-Centered Outcomes Research Institute (PCORI) to support research that can produce the type of information people and their caregivers need when they face a healthcare decision (Appendix E). The purpose of PCORI is to provide the most reliable, relevant, and useful health-related evidence for decision-makers, especially for patients and caregivers. In 2012, the Methodology Committee and the PCORI Board approved a working definition that reflects this perspective:

Patient-centered outcomes research (PCOR) helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research answers patient-centered questions such as:

1. “Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?”
2. “What are my options and what are the potential benefits and harms of those options?”

3. “What can I do to improve the outcomes that are most important to me?”

4. “How can clinicians and the care delivery systems they work in help me make the best decisions about my health and healthcare?”

To answer these questions, patient-centered outcomes research:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions (see sidebar) to inform decision-making, highlighting comparisons and outcomes that matter to people;
- Is inclusive of an individual’s preferences, autonomy, and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health-related quality of life;
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination; and
- Investigates (or may investigate) optimizing outcomes while addressing burden to individuals, availability of services, technology, and personnel, and other stakeholder perspectives.

To better connect the results of research to the needs of people and their caregivers, PCORI decided they should be involved in defining the basic questions to be asked, how studies are designed and conducted, and ultimately how research results are interpreted and communicated to the people who can use them.

By establishing the definition of and standards for PCOR, funding PCOR investigations, building infrastructure to support this approach to studying health and healthcare, and through other means, PCORI aims to promote and catalyze the
development of evidence that is relevant at the time and place that people and their caregivers make health decisions.

The legislation for PCORI established a 17-member Methodology Committee selected by the General Accounting Office “to develop and improve the science and methods of comparative clinical effectiveness research,” and to report on methodological standards for research (Appendix E-5). In order for PCORI to fulfill its mandate “to assist patients, clinicians, purchasers, and policy-makers in making informed health decisions,” critical problems related to the evidence used to support health decision-making need to be addressed (Appendix E-2). We have interpreted this legislation to mean that the PCORI Methodology Committee’s role is to advise PCORI on the best methods for promoting its agenda—in prioritizing research, establishing a specific research project agenda, reviewing research proposals, supporting infrastructure for PCOR, improving the conduct of PCOR, and furthering the implementation of PCOR to help patients receive optimal outcomes. The legislation requires the Committee to create standards and recommended actions and issue reports and a translation table to help PCORI fund high impact patient-centered research and accomplish the organization’s mission.

Problems that PCORI Hopes to Address

The founding legislation for PCORI is based on the premise that there is an opportunity for research and research funding agencies to better support decision-making by patients, caregivers, clinicians, and policy-makers. To address this opportunity we thought it best to begin by identifying the key problems in existing research from the perspectives of the patient and of these other stakeholders. This itemization highlights the effect these problems have on healthcare decision-makers and calls out the ways PCORI can address them.

• **A relevance problem related to questions and endpoints**—Researchers often choose questions and endpoints that they consider to be of interest and importance. Sometimes these are not the questions and endpoints most relevant to the people affected. Researchers often pursue these types of endpoints because assessing them is more feasible, less expensive, and because the time required to look at the ultimate outcome may take too long to inform decision making in the short-term. For example, a researcher might study whether or not a stent placed in an artery to improve blood flow is open 30 days after placement. While that question may be reasonable to some, the question that patients want answered is whether symptoms and function, like pain and the ability to walk, are better after the stent was placed. They want to know whether a stent is the best way to achieve the benefits they
It was always hard to find time to catch up with the medical literature. The doctor had been looking forward to reading a recently released report on a randomized trial for a new rheumatoid arthritis drug. He was curious if it might be a good fit for some of his patients.

When he got to the methods section of the article, however, he was disappointed. For one, the inclusion criteria were narrow. It seemed that this study excluded participants with additional issues that could complicate their treatment, just the sort of issues faced by most of his patients, such as high blood pressure, heart problems, or liver disorders.

The outcomes reported in the trial—the number of joints affected, and how well they function—were improved for 75% of the participants. However, he knew from past trials that drugs are often more successful in a trial setting than in clinical practice. The narrow criteria for patient selection could make it more likely that each participant in the study would respond to the drug in a similar way. When used in a more diverse group of patients, the results might not be as good.

The doctor pondered the results of the study. It was true that many of his patients did not meet the study criteria, but this did not necessarily mean this drug would be useless for them; many treatments tested in randomized trials with designs like this have proven to be effective in a wide variety of people. He decided that the jury was still out on this treatment, and while he would mention it to patients who were not doing well on other treatments, he would wait for future studies to test this treatment on a wider segment of the population with outcomes that could be applied directly in clinical practice and more information on side effects before he would tell all his patients about it.

Sources: (4, 5)

are hoping for. Measuring whether the stent is open at 30 days may be easier than measuring walking and quality of life at a year, but just because it’s easier to assess doesn’t mean studying that endpoint will help patients decide if a stent is right for them.

Research can also lack relevance when the big questions patients ask are divided up into pieces that researchers are more able to tackle. While researchers hope that eventually all the pieces get addressed, failing to connect research programs to clinical decisions means that too often not all the pieces are addressed, leaving decision-makers with an incomplete, frustrating patchwork of information.

• A “patients like me” problem—Research sometimes focuses on patients with a narrow set of characteristics and conditions. Often there are practical purposes for this—it takes a much larger study to account for differences between patients, and the bigger the study, the greater the cost. Sometimes there are scientific purposes—narrowing the number of variables in a trial of a new drug makes it more likely that any effects are due to the drug and not something else. Sometimes researchers want to include patients with broader characteristics but struggle to accomplish that goal. They often have trouble recruiting study participants who represent the full spectrum of patients. Many people are reluctant to participate in research because they lack trust in researchers, don’t have the time, or are even scared by the concept of being involved in research. For whatever reason, if research doesn’t account for “our” characteristics, then the results aren’t as likely to be relevant to us. What people want is information that takes into account all their unique characteristics and conditions.

Personalizing research results is becoming ever more challenging as we learn more about the genetic variation that makes each of us different from the “average” patient.

• A trust problem—There are serious concerns that research being proposed, reviewed, funded, and performed is not independent enough of those with a financial or professional interest in the results. Distrust is also the result when the aims of researchers and the people they want to study are not aligned. Typically, decisions about whom to include in a study, how to deliver treatments, how long the study should continue, and what outcomes to
measure are most often made by funders and researchers, whose intellectual or financial bias can influences these and other aspects of a study’s design. For example, a specialist who has developed a new procedure and is the main researcher of that procedure may be more interested in the positive outcomes of treatment but less interested in the risks. A pharmaceutical company that conducts studies of its own products will normally choose whom to study, what to compare, and what outcomes to measure so as to support an application for regulatory approval and ultimately success in the marketplace. As a result, the apparent efficacy or safety of a medical treatment may depend on who is studying it and what they have to gain or lose by the results. Sometimes, rather than performing a comparison to the best alternative treatment to see which is better, investigators may choose, and sometimes regulatory agencies encourage, a comparison to a placebo, or an inferior alternative. Sometimes investigators are less inclined to publish results when the study shows no difference. Failure to fully publish the results of research also undermines trust and can create a false impression of the effectiveness and safety of treatments. (6)

* A quality problem—The phenomenal volume of research obscures high-quality studies (that employ the right methods in the right way) in a clutter of reports that fail to provide results useful to those making health decisions. Not infrequently, comprehensive reviews of research about a clinical problem find that many studies re-address questions that have already been answered, fail to address questions that are widely known to be important, or use study designs that render the results useless for decision-makers. (12)

* A user-friendliness problem—The public wants and needs research results clearly connected to their health decisions. Many patients and most of their caregivers also want information presented so that they can understand the strengths and limitations of a given research design. We are barraged with healthcare information: conversations about a friend or family member’s healthcare experience; claims made by promoters of a certain procedure, medicine, or approach; and media accounts of purported medical breakthroughs. Certain segments of the public want to engage in PCOR, but believe the methods being used are
not responsive to their needs. Some want to be involved in debates about methodological alternatives and tradeoffs in traditional study design so that they can shape the way healthcare questions are addressed. The public and those interested in being part of the research process need a way to understand how different methods for conducting, evaluating, and implementing healthcare research are likely to produce useful information.

- **A priority problem**—When it comes to health and healthcare interventions, there are so many important questions, and with limited research dollars we need to prioritize. We need a set of methods to guide which questions the system should tackle first and a way to keep patients central in that prioritization process. Too often this ranking has been done out of public view through a process subject to political and economic forces that lacks a coherent strategy. Applying methodological standards to set priorities will produce “winners and losers”—some topics will receive more funding support sooner than others. Like any funding agency, PCORI cannot be all things to all people. If it places the highest priority on research questions that will offer the greatest good for the greatest number of people, then it might be thought to signal a focus on common conditions or majority populations to the dismay of advocates for those with rare but serious diseases or minority populations. Conversely, focusing on less common conditions or smaller populations with the loudest advocates could drain research funding without producing adequate progress against widespread health threats. PCORI’s Methodology Committee promotes a thoughtful and reasoned approach to prioritization using a suite of techniques that includes value of information analysis and incorporates all the domains of relevance when deciding what to fund.

- **An implementation problem**—It takes too long to disseminate research results to providers, patients, and other stakeholders so that discoveries can be applied to health decisions and support the most effective healthcare practice. PCORI hopes to develop and apply optimal methods for encouraging the adoption of what we know into what we do.

- **A record-keeping problem**—While millions of American doctor and hospital and other health visits are now recorded in electronic medical records (EMR), the vast majority of those electronic data cannot be used for research. This enormous potential of EMR to answer significant PCOR questions remains largely untapped. PCORI is just beginning to explore how to leverage its investment in this arena to achieve substantive improvements in these systems to permit their use as a research tool, answering questions of meaning to patients.

Addressing these problems is the purpose of these and future Methodology Committee standards, recommendations to the PCORI Board of Governors, reports, and translation tables.
An Evolving Document

PCORI aims to incorporate the standards and recommendations discussed in this report into the funding process and will encourage their adoption by the broader scientific community. The next three years of Methodology Committee work will be a continual process of reconsidering, refining, and widening the scope of the standards to include the full spectrum of PCOR questions and approaches. Similarly, the translation table within this report will be expanded over time to include more examples, methodological issues, and approaches.

The list of methodological standards for patient-centered outcomes research at the heart of this report is a milestone, but not a destination. Indeed, the legislation establishing PCORI and its Methodology Committee directs that these standards shall be periodically updated (Appendix E-5). Over time, these reports, standards, translation tables, and public engagement forums are expected to produce better research methods, which in turn will provide information of benefit to all stakeholders—researchers planning an investigation, policy-makers weighing the value of healthcare interventions, and patients and their caregivers facing health decisions. We encourage public comments about the report, the standards, and the translation table and hope to refine the work based on this feedback.

The legislation establishing PCORI conveys a sense of urgency related to setting methodological standards and establishing national priorities. Federal funding also helped support related activities related to setting priorities including; 1) an Institute of Medicine study to develop standards for conducting systematic reviews of comparative clinical effectiveness,(13) a crucial tool for setting priorities; 2) a report on Initial National Priorities for Comparative Effectiveness, conducted by an Institute of Medicine panel(14) that included patient and consumer representatives and that applied criteria for prioritization similar to those specified in the Affordable Care Act; and 3) funding for an initial program of comparative clinical effectiveness research through the Agency for Healthcare Research and Quality (AHRQ) and the National Institutes of Health (NIH). The standards proposed in this report can help PCORI use this previous work effectively and efficiently to prioritize and establish a specific research project agenda.
Contents of this Report

Chapter 2 of this report focuses on how the Committee approached this core task of developing methodological standards, and Chapter 3 provides an overview of the standards and actions we recommend to make them effective. We then describe the rationale for standards for patient-centeredness (Chapter 4); prioritizing topics for research (Chapter 5); choosing a study design (Chapter 6); and for designing, conducting, and reporting research (Chapter 7-8). These chapters also highlight gaps in the evidence that should be addressed by PCORI’s program of methodological research. Finally, we describe priority areas for the Methodology Committee over the next 2-3 years (Chapter 9).
Chapter 2. How the Methodology Committee Developed the Recommended Standards

The Methodology Committee’s Approach to the Authorizing Legislation

The Methodology Committee began its work by defining terms and considering the various approaches that might be taken in responding to requirements in the authorizing legislation. Three specific activities were named: the creation of a “translation table,” the proposal of methodological standards for research, and the proposal of activities for enforcing the methodological standards.

Translation table. The legislation specifies that the Methodology Committee must develop or devise “a translation table that is designed to provide guidance and act as a reference for the Board to determine research methods that are most likely to address each specific research question” (Appendix E-5). In Chapter 6, the Committee proposes a general framework for the translation table, with several of the research domains presented as examples of what a final product might look like. It is expected that the translation table will eventually include versions appropriate for use by different stakeholder groups, and that the Committee will also define ways to further develop the concept and evaluate its usefulness.

Methodological standards for research. The language of the legislation around the establishment of methodological standards has several salient features that outline the Congressional expectations for the committee and its work. First, the legislation defines expectations with regard to the process by which the committee should proceed, stipulating that the establishment of methodological standards should build on existing work, and that the process should be ongoing, scientifically based, and inclusive. Second, the legislation specifies both specific and general content areas that the proposed standards should address, including internal validity, generalizability, feasibility, and timeliness of research. Third, the committee is to provide specific criteria for health outcome measures, risk adjustment, and other relevant aspects of research and assessment with respect to design of research. Fourth, standards must be recommended by which patient subpopulations can be accounted for and evaluated. Finally the scope of the committee’s work is to include “each of the major categories of comparative clinical effectiveness research methods” (Appendix E-5), which are listed as:
• “Systematic reviews and assessments of existing and future research and evidence including original research conducted subsequent to the date of the enactment of this section.
• Primary research, such as randomized clinical trials, molecularly informed trials, and observational studies.
• Any other methodologies recommended by the methodology committee established under paragraph (6) that are adopted by the Board under paragraph (9)” (Appendix E-3).

**Recommended actions to comply with methodological standards.** The enabling legislation instructs the Committee not only to propose methodological standards but also to recommend actions necessary to comply with them:

“The methodology committee shall submit reports to the Board…Reports shall contain recommendations for the Institute to adopt methodological standards…as well as other actions deemed necessary to comply with such methodological standards” (Appendix E-6).

The Methodology Committee and PCORI Board and staff are developing a coordinated approach to promote the uptake of PCORI methods standards. This includes engaging all stakeholders who might use the standards, creating reporting and surveillance opportunities, and developing enforcement functions over time.

### Defining Methodological Standards

A comprehensive resource specifying standards for research in all relevant aspects of comparative effectiveness research (CER) with a patient-centered focus would be a vast undertaking, and the Committee’s initial work in this space was defined more narrowly. The Committee presents here a first installment of what will be an ongoing task, both in completing the inventory of recommended standards and in periodically reviewing and updating them. The Committee identified general areas for its initial focus that would allow PCORI to address its first round of funding announcements and priority development. Small working groups were formed which explored patient-centeredness, research prioritization, and research methods. A fourth group coordinated communication and prepared draft report components. The goal was to propose methodological standards in important research domains that are representative of research issues in CER and that will eventually be covered more comprehensively.
Building on the work of the Institute of Medicine,(13) the Committee defined a standard as follows:

- A process, action, or procedure for performing PCOR that is deemed essential to producing scientifically valid, transparent, and reproducible results. A standard may be supported by scientific evidence, reasonable expectation that the standard helps achieve the anticipated level of quality in PCOR, or by broad acceptance of the practice in PCOR.
- The recommendation is actionable, feasible, and implementable.
- Proposed standards are intended for use by the PCORI Board, in PCORI policies and procedures, and by PCORI researchers.

**Select and Assess Proposed Standards**

Committee working groups developed provisional lists of major research methods questions and chose 129 for focused review for this first methods report, based on considerations presented in Box 2.1, below. Contractors were secured to assist the Committee in developing materials for each topic (see Appendix G). (Full reports are available at [http://www.pcori.org/what-we-do/methodology/](http://www.pcori.org/what-we-do/methodology/). Citations were not carried forward into this report to increase readability, but are fully documented in the contractor reports posted on the PCORI Web site.) In addition to full reports, contractors summarized key information regarding each proposed standard in a template format to assist Committee members in making direct comparisons between proposed standards (see Table 2.1) based broadly on criteria derived from AGREE, an international project developing guidelines for the appraisal of research and evaluation (Box 2.1). Four criteria were deemed especially important: contribution to patient-centeredness, contribution to transparency, contribution to scientific rigor, and empirical evidence/theoretical basis. The workgroups of the Committee held workshops at which contractors presented their findings and recommendations for discussion with Committee members and invited experts, including patient representatives. In addition to reports from contractors, the Committee relied on its members to bring their experience, knowledge, and additional publications and documents to the table. Committee workgroups reduced the original list of 129 methods questions to 88 potential standards by eliminating those clearly not yet ready to be considered standards and by removing those that were out of scope or redundant.

Materials were then developed around the 88 proposed standards that Committee members reviewed in depth. A preliminary poll was taken that informed a meeting attended in person or by
teleconference by all Committee members at which standards were discussed. Formal votes were taken, requiring approval by a minimum of two-thirds of members (12 of 17) for a standard to be recommended. In the final voting, Committee members were asked to consider each standard as a minimum requirement for PCORI. Thus some proposed standards, while perhaps finding agreement that they may be good practice, were not recommended as standards. The Committee agreed that there would be no formal “minority” statements for those standards not approved or for approved standards where approval was not unanimous, although some of the complexities in the decisions are presented in the detailed discussions that follow presentation of the standards in the chapters that follow.

**Box 2.1. Modified AGREE Criteria**

- The purpose of the work is to define methodological standards for CER.
- The people to whom the standards apply are described.
- The application of the standards to CER is clear.
- The standards were developed by a relevant professional group.
- Patient’s views and preferences were sought.
- Stakeholders were involved in the development of the standards.
- A systematic process was used to generate recommendations.
- Details of the systematic process used to generate recommendations are provided.
- There is an explicit link between the rational for the standard and the recommended standard itself.
- The standards were externally reviewed before publication.
- The recommendations are specific and unambiguous.
- Key recommendations are clear.
- The standards are editorially independent from the funding body.
- Conflicts of interest have been recorded.

Modified from AGREE Instrument Available at: [http://www.agreetrust.org/](http://www.agreetrust.org/)
Table 2.1. Committee Criteria for Adopting Proposed Standards

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contribution to patient-centeredness</td>
<td>The degree to which the proposed standard contributes to respect for and responsiveness to individual patient preferences, needs, and values; whether the proposed standard would help ensure that patient values and circumstances guide clinical decisions.</td>
</tr>
<tr>
<td>Contribution to scientific rigor</td>
<td>The degree to which the proposed standard contributes to objectivity, minimizes bias, improves reproducibility, and leads to more complete reporting.</td>
</tr>
<tr>
<td>Contribution to transparency</td>
<td>The degree to which the proposed standard contributes to explicit methods, consistent application, and the opportunity for public review so that users can link judgments, decisions, or actions to the data on which they are based. Allows users to assess the strengths and weaknesses of the study to which the standard is applied.</td>
</tr>
<tr>
<td>Empirical evidence and theoretical basis</td>
<td>Description of the information upon which a proposed standard is based, emphasizing empirical evidence about the proposed standard and theoretical support.</td>
</tr>
<tr>
<td>Degree of controversy about use of standard</td>
<td>Description of controversy or alternative views of the proposed standard, particularly with respect to criteria above (e.g. patient-centeredness, scientific rigor, transparency) in the context of comparative effectiveness research.</td>
</tr>
<tr>
<td>Other considerations</td>
<td>Description of other considerations that might influence adoption of the proposed standard, such as practicality, feasibility, barriers to implementation, and cost.</td>
</tr>
</tbody>
</table>

Finally, in addition to the recommended standards, the Committee reached a number of consensus conclusions regarding recommended actions, directed to the PCORI Board of Governors. These statements appear throughout the report and are collected in Appendix B.

As the basis for developing a translation table and framework, Committee staff searched MEDLINE, Scopus, and the AHRQ Scientific Resource Center Methods Database (http://www.citeulike.org/user/SRCMethodsLibrary) for articles that use the term “translation table.” The results were reviewed by Committee members. A Request for Information was also used to gather stakeholder input regarding the translation table (see Appendix D-1 and Appendix D-2).
Chapter 3. Overview of the Standards

Background

There are few more important aims of medical research than to conduct studies that provide accurate estimates of benefit or harm. But no estimate can be perfectly accurate; there is always some uncertainty around it. Getting that uncertainty correct is as important as the estimate itself. This is particularly important for PCOR, which is specifically designed to inform decision-making. For example, if a study estimates a two-fold increase in a serious side effect due to a drug interaction, decisions based on that information could be very different if the confidence interval around that 2-fold estimate were 0.5 to 4, indicating considerable doubt about the existence of the effect, as opposed to 1.9 to 2.1, indicating that the 2-fold estimate was right on the mark.

However, understanding all the contributors to uncertainty often takes years of development and application of a method, just as it does for any applied technology. Such experience leads to an appreciation of the potential pitfalls in practice and in theory, and the ways to avoid them. In this way, methods evolve and improve over time. But there are no formal mechanisms to guarantee that best practices are adopted. One of the more effective ways is for the sponsors of research to articulate standards for the conduct of research they fund. This was recognized in the PCORI authorizing legislation, which tasked the Methodology Committee with developing and promulgating such standards (Appendix E-5).

The pursuit of medical knowledge has evolved from predominately case studies to clinical trials and observational studies that use increasingly complex designs and analytic methods. Over the past four decades, explicit, formal standards for planning, conducting, and reporting clinical trials were developed for the subset of research studies that were conducted to obtain regulatory approval from the U.S. Food and Drug Administration. These standards, articulated in formal “guidance documents,” helped to create a level playing field for regulatory decision-makers and for the companies designing such studies (http://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm). The wider range of research studies used to inform clinical decisions has been governed by less formal approaches, such as peer review of research proposals and of reports submitted to scientific journals. Many specialty societies or ad hoc groups of experts have taken it upon themselves to issue methodological
A Thought Experiment

Consider two treatments for rheumatoid arthritis. We’ll call them Alpha and Beta. Alpha requires infusions given in a clinic. Beta is a pill taken each morning and evening. Previous studies have shown that each is effective. What researchers want to do now is compare them in a setting as close as possible to typical clinical use. Special outreach to patients in low-income neighborhoods and rural areas, as well as the use of materials and practices suited to people with limited education and those who don’t speak or read English well, produce a study population that resembles the broad spectrum of people being treated from rheumatoid arthritis in routine clinical practice.

After randomizing study participants to start on Alpha or Beta, the researchers step back, allowing the patients, their doctors and nurses to make their own healthcare choices, including switching treatments, just as in routine practice. And just as in actual practice, the patients’ care is covered by their existing insurance, rather than a special grant.

When the data is analyzed, it appears that Beta, the twice-a-day pill, appears to be more effective than Alpha, the clinic-administered infusion, at relieving pain, improving daily function and other outcomes important to patients.

But before writing up their results, the researchers look for explanations. It wasn’t side effects or other biomedical parameters that made the difference. Two themes emerged from patient reports. Some stopped using Alpha because it cost them more out of pocket. Others said that even if they could afford the copays, they couldn’t take time off work to get infusions or they had trouble finding transportation to the clinic.

In this example, then, the results do not tell us much about what can work better, because out-of-pocket costs, access to care, insurance, and perhaps even more remote factors (such as the frequency of bus service to the medical center or from there to work) influenced the result.

Balancing the Aims of PCOR—A Critical Methodological Challenge

The standards presented in this report attempt to balance several aims of PCORI. One aim is to counter overgeneralization from studies in narrow populations or in highly controlled research settings to the broader range of people and settings in “real life.” (17, 18) But another aim, undoubtedly, is to learn more about how well the different treatment choices can work, and for whom they work best and are safest. Designing studies so we can be confident that the treatment is producing the results is particularly difficult in clinical effectiveness research. (19) (See the box entitled “A Thought Experiment” for an illustration of this point.) The Committee will return to the issue of balancing these aims in the near future.
future.

The Phases of Research on Patient-centered Outcomes

The standards address selected topics in four broad phases or categories of activities (Table 3.1):

- “What should we study?”
- “What study designs should we use?”
- “How do we carry out and govern the study?”
- “How do we enable people to apply the study results?”

The table lists key activities within each phase and provides selected details for each activity. The specific phases and activities involved in any given study may vary, depending, for example, on whether a study compares different treatments for individual patients or delivery interventions in health systems.

Table 3.1. Phases of PCOR

<table>
<thead>
<tr>
<th>Phase of PCOR</th>
<th>Details of phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What should we study?</td>
<td></td>
</tr>
</tbody>
</table>
| Identify and define important research questions   | • Identify topics, decisions, and questions that are important to patients, caregivers, and other stakeholders  
  • Specify the research questions in a manner highlighting patient-centered outcomes and information needs                                                                                                 |
| Prioritize research questions                      | • Decide on the importance and priority of topics and questions, taking into account evidence gaps and the value of information                                                                                 |
| Refine and specify details of research questions   | • Specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) to accurately capture each research question                                                                              |
| Develop funding announcements                      | • Develop and release funding announcements for high-priority questions  
  • Incorporate guidance and standards to ensure alignment with the resulting projects                                                                                                                           |
<p>| Conduct peer review and funding decisions          | • Incorporate guidance to reviewers to facilitate assessment of investigator responsiveness to patient-centeredness aspects of studies                                                                              |
| 2. What study designs should we use?               |                                                                                                                                                                                                                  |
| Create conceptual framework                        | • Specify hypothesized mechanisms of effect, influences on outcomes, and clinical context of affected care processes to guide data collection and analysis plans                                                                 |</p>
<table>
<thead>
<tr>
<th>Phase of PCOR</th>
<th>Details of phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select research approach and study design</td>
<td>• Select study designs and research approaches (quantitative and/or qualitative) that suit the question, taking into account tradeoffs in the internal validity, generalizability, feasibility, and timeliness of each approach (see Translation Table)</td>
</tr>
</tbody>
</table>
| Design data collection and analysis plans | • Select data sources and specify data collection methods most likely to produce valid, useful data  
• Design analysis plan to optimally answer the research questions |
| Develop dissemination and related follow-up plans | • Assess the likely value and relevance of projected study findings for each potential stakeholder group (including policy, practice, patient, research) and identify appropriate use of findings  
• Develop broad outline of dissemination plans and plans for follow-up for each affected stakeholder group and projected use of findings |

3. How do we carry out and govern the study?

| Employ strategies to reduce dropouts and maximize validity of data | • Work with representatives of study population to achieve ongoing engagement and support for accurate, complete data |
| Employ strategies to maximize validity of analysis and interpretation of results | • Work with representatives of study population and affected stakeholder groups to review and discuss study findings and consider alternative explanations |

4. How do we enable people to apply the study results?

| Report the results | • Convey the findings of research in a comprehensible manner that is useful to patients and providers in making healthcare decisions  
• Fully convey findings and discuss considerations specific to certain subpopulations, risk factors, and comorbidities, as appropriate  
• Discuss limitations of the research  
• Do not include any data which would violate the privacy of research participants or any confidentiality agreements (Appendix E-7) |
| Assess study implications | • Assess implications and appropriate “next steps” (follow-up) to study results (e.g., incorporation in systematic reviews; progression to larger, more definitive study; dissemination to policy/practice audiences) |
| Disseminate | • Disseminate study findings to appropriate audiences based on their identified implications for research, policy, and practice  
• Provide necessary interpretation and explanation to facilitate stakeholder understanding and appropriate interpretation of findings and implications |
| Implement | • Plan and conduct activities to facilitate implementation of study results if they are relevant to policy or practice |

The phases and activities listed in the table correspond with the scope of work of PCORI. The legislation sets instructions for PCORI to prioritize, establish, and carry out a research agenda, making reference to methodological standards (Appendix E-3). The standards concern aspects relevant to these duties, with a particular focus on the design of research studies (Appendix E-5).
In this first report, we focused most of our attention on the earlier phases, those needed to support PCORI’s first specific agenda for comparative clinical effectiveness research. Many of these standards specify what to include in research protocols and reports. Getting the questions right (‘‘what should we study?’’) is the starting point. This chapter (Standards 3.1.1-3.1.5) and chapters 4 and 5 propose standards for making the patient’s voice the central focus of defining research questions.
Standards for Formulating Research Questions

3.1.1  **Develop a Formal Study Protocol**

The study protocol should include all the elements specified in the standards.

3.1.2  **Identify Specific Populations and Health Decision(s) Affected by the Research**

To produce information that is meaningful and useful to people when making specific health decisions, research proposals and protocols should describe: 1) the specific health decision the research is intended to inform; 2) the specific population for whom the health decision is pertinent; and 3) how study results will inform the health decision.

3.1.3  **Identify and Assess Participant Subgroups**

In designing studies, researchers should identify participant subgroups of interest and, where feasible, design the study with adequate precision and power to reach conclusions specific to these subgroups. In addition, subgroup information should be reported for later systematic reviews.

3.1.4  **Select Appropriate Interventions and Comparators**

When evaluating an intervention, the comparator treatment(s) must be chosen to enable accurate evaluation of effectiveness or safety compared to other viable options for similar patients. Researchers should make explicit what the comparators are and how they were selected, focusing on clearly describing how the chosen comparator(s) define the causal question, reduce the potential for biases, and allow direct comparisons. Generally, non-use (or no specific treatment) comparator groups should be avoided unless no specific treatment is a likely option in standard care.

3.1.5  **Measure Outcomes that People in the Population of Interest Notice and Care About**

Identify and select outcomes the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform an identified health decision. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria. Provide information that supports the selection of outcomes as meeting the criteria of “clinically meaningful,” “patient-centered,” and “relevant to decision-makers,” such as patient and decision-maker input from meetings or surveys or published literature relevant to the question of interest. Select outcomes based on input directly elicited from patient informants, persons representative of the population of interest, either in previous studies or in the proposed research.

The first set of standards does not cover all of the possible combinations of types of studies and interventions set out in the legislation. Most notably, although systematic reviews of effectiveness play a central role in PCOR, we did not develop standards for them because the Institute of Medicine has recently done so. The Committee plans to review and will consider endorsing some or
all of them. Some topics we consider to be high-priority, such as cluster randomized trials, additional aspects of the evaluation of diagnostic tests, systematic reviews of system interventions, and modeling, will be addressed in future reports.

The potential range of methods for which standards could be developed is substantially larger than what is presented herein and will be the subject of further standards development in future PCORI Methodology Committee work. We do not present standards for every aspect of conducting research. Rather, the standards focus on a few methodologies and issues that the Methodology Committee identified as likely to contribute to rapid improvement in the quality and value of PCOR.

We do not intend our articulation of standards to inhibit methodological innovation, and, in fact, hope to promote such innovation. For this reason, in the areas of research methodology addressed in Chapters 7 and 8, the Committee chose to present “minimal” standards, those practices that few would dispute are necessary for sound science and that should not inhibit further evolution of the methods. All of the standards presented have scientific justification, either from empirical studies or from theoretical considerations, which typically apply to mathematical methods. Quite a few promote transparency: how to properly communicate, both in study protocols and in published reports, exactly what was planned and what was done.

In other areas, particularly in methods to engage patients in prioritizing and refining research topics, it is not possible to identify evidence-based standards. We believe that standards for engaging patients in each phase of the research process are essential, but lack the evidence to specify which methods for doing so are best. Several of these patient engagement standards call for researchers to describe the methods they propose or employ. Such information will allow for evaluation of the performance of different research methods. As more PCOR is conducted and as more evaluation of patient engagement occurs, more specific standards, including those addressing engagement of stakeholders beyond patients, will be developed.

Transparency in Research: The Context for Implementing the Standards

How PCORI and other funding agencies apply the Committee’s standards will help determine whether the perceived problems with research are addressed in an effective, equitable, and transparent fashion. Basic good research practices are a required foundation for the standards for PCOR. Departures from basic good research practices are partially responsible for the mismatch
between the quality and relevance of the information research provides and the information patients need to make informed clinical decisions.

One of the most important components of this foundation is a commitment to transparency in research. Transparency is needed to enable researchers to verify research findings. Many of the standards promote transparency by requiring detailed protocols for proposed research and compliance with guidelines for study registration and reporting results. Not only can these requirements help PCORI judge the quality and relevance of proposed research plans, but they also may help protect against practices, such as selective reporting, that can distort or misrepresent research results.

The Methodology Committee recommends that, in the near future, PCORI develop and implement additional policies to encourage research that is transparent and reproducible (see Recommended Actions for Transparency, page 22). Specifically, the Methodology Committee recommends that PCORI develop policies to encourage public registration of all PCORI studies and the sharing of study protocols, statistical code, and data. A standing committee within PCORI should be formed to assess appropriate methods for data sharing and to ensure that proper scientific credit is given to those sharing protocols, code, and data (see Recommended Actions for Transparency).

PCORI has a stake in transparency and reproducibility not only in the research it undertakes, but also in research conducted by other entities. For example, systematic reviews, which are a key type of research for PCORI and which underlie judgments about future research needs, are highly dependent on the degree to which evidence is reported fully and in an unbiased manner. Credible standards for conducting systematic reviews specific to clinical effectiveness recognize that “reporting biases, particularly publication bias and selective reporting of trial outcomes and analyses, present the greatest obstacle to obtaining a complete collection of relevant information on the effectiveness of health care interventions.”(16) An important next step for PCORI is to develop policies that can remove or overcome this obstacle, not only in its own research, but throughout the broader clinical research community.

Preparing and publishing a detailed research protocol and asking a well-formulated research question are critical for transparency. Many of the 60 standards specify what should be included in a research
protocol. The first requirements are components of a well-formulated research question, often abbreviated “PICOTS”:

- Population of patients/research participants and relevant subgroups of patients
- Intervention(s) relevant to patients in target population
- Comparator(s) relevant to patients in target population
- Outcomes that are meaningful to patients in the target population, including the Timing of outcomes and length of follow-up
- Healthcare Settings and providers.

These standards are part of a larger group of general standards that apply across all research on patient-centered outcomes. We return to them throughout this report.

**Recommended Actions for Transparency**

- The Methodology Committee recommends that PCORI develop policies to encourage public registration of all PCORI studies and the sharing of study protocols, statistical code, and data.
- Form a standing committee within PCORI to recommend appropriate methods for data sharing and to ensure that proper scientific credit is given to those sharing protocols, code, and data.
- To speed implementation of standards in funding announcements, peer review, and other internal processes, PCORI staff should develop or have developed templates for the preparation and review of proposals that incorporate the key elements of the standards. Because some standards apply only to certain types of studies, a portfolio of templates applicable to various study designs should be developed.
Chapter 4. Methodological Standards for Patient-Centeredness of Research Proposals and Protocols

Introduction

Patient-centered outcomes research helps people to make informed healthcare decisions by directing research toward questions that are important to patients, measuring outcomes that are noticeable and meaningful to them, and producing results that help them weigh the value of health-care options given their personal circumstances, conditions, and preferences (see Chapter 1). While patient is defined here as any individual with or at risk for a specific health condition, this discussion applies also to caregivers and patient surrogates where appropriate. We take special notice of patients who may be hard to reach because of socioeconomic, geographic, racial, or ethnic barriers or due to physical or cognitive impairments, and we are especially aware of the efforts needed to ensure that researchers engage the full spectrum of individuals and communities.

Many other individuals are involved in health decisions, including clinicians, healthcare system administrators, payers, regulators, and policy makers. In this report we focus on patients rather than on other health decision stakeholders, who will be the focus of future standards.

Patient-Centeredness Standards

PCOR starts from the vantage point of individuals facing health decisions. Every step of the design, conduct, analysis, and dissemination of PCOR should be directed towards informing health decisions that affect outcomes that are meaningful to a specific group of patients. From the earliest phases of defining a research topic and formulating a study question; then identifying a study population and choosing interventions, comparators, and outcomes to measure; through the conduct of a study and analysis of results; and ultimately to the dissemination of research findings into clinical practice, researchers should ensure PCOR results accurately and effectively inform
health decisions important to patients. This requires patient engagement throughout the research process.

**Standards for Patient-Centeredness and Engagement**

3.1.2 **Identify Specific Populations and Health Decision(s) Affected by the Research.**

To produce information that is meaningful and useful to people when making specific health decisions, research proposals and protocols should describe: 1) the specific health decision the research is intended to inform; 2) the specific population for whom the health decision is pertinent; and 3) how study results will inform the health decision.

3.1.5 **Measure Outcomes that People in the Population of Interest Notice and Care About**

Identify and select outcomes the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform an identified health decision. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria. Provide information that supports the selection of outcomes as meeting the criteria of “clinically meaningful,” “patient-centered,” and “relevant to decision-makers,” such as patient and decision-maker input from meetings or surveys or published literature relevant to the question of interest. Select outcomes based on input directly elicited from patient informants, persons representative of the population of interest, either in previous studies or in the proposed research.

4.1.1 **Engage Patient Informants, Persons Representative of the Population of Interest, in All Phases of PCOR**

Research proposals should 1) describe how patient informants will be: identified, recruited, and retained; involved in determining the study design and monitoring of its conduct; and involved in dissemination of research results, and 2) state how the research process will follow PCOR principles of trust, transparency, co-learning, respect, and partnership. Patient informants include individuals who have the condition or who are at risk of the condition, and, as relevant, their surrogates or caregivers. At a minimum, patient informants should be engaged in formulating research questions; defining essential characteristics of study participants, comparators, and outcomes; monitoring study conduct and progress; and disseminating results.
Standards for Patient-Centeredness and Engagement (continued)

4.1.2 Identify, Select, Recruit, and Retain Study Participants Representative of the Spectrum of the Population of Interest Facing the Health Decision of Interest and Ensure that Data Are Collected Thoroughly and Systematically from All Study Participants.

Research proposals and subsequent study reports should describe: 1) the plan to ensure representativeness of participants; 2) how participants are identified, selected, recruited, enrolled, and retained in the study to reduce or address the potential impact of selection bias; 3) efforts employed to maximize adherence to agreed-on enrollment practices; and 4) methods used to ensure unbiased and systematic data collection from all participants.

If the population of interest includes people who are more difficult to identify, recruit, and/or retain than other study populations (for example, individuals historically underrepresented in health care research such as those with multiple disease conditions, low literacy, low socioeconomic status, or poor health care access, as well as racial and ethnic minority groups and people living in rural areas), then specify plans to address population-unique issues for participant identification, recruitment, and retention.

4.1.3 Use Patient-Reported Outcomes When Patients or People at Risk of a Condition Are the Best Source of Information.

When patients or people at risk of a condition are the best source of information regarding outcomes of interest, then the study should employ patient-reported outcome (PRO) measures in lieu of, or in addition to, measures derived from other sources. Proposals should describe: 1) the concept(s) underlying each PRO measure (e.g., symptom or impairment) and how it is meaningful to, and noticed by, patients in the population of interest; 2) how the concept relates to the health decisions the study is designed to inform; 3) how the PRO measure was developed, including how patients were involved in the development; and 4) evidence of measurement properties including content validity, construct validity, reliability, responsiveness to change over time, and score interpretability, including meaningfulness of score changes in the population of interest with consideration of important subgroups. If these measurement properties are not known, a plan for establishing the properties must be provided.

4.1.4 Develop and Implement a Dissemination Assessment to Achieve Broad Awareness of Study Results.

PCOR research proposals and protocols must include an assessment that describes how the project and the composition of the research team supports dissemination and the anticipated facilitators, barriers, and potential strategies for dissemination to key stakeholder groups, including patients and individuals at risk of a condition, clinicians and other health care system staff, and policy leaders. Effective dissemination includes the reporting of results in a manner understandable to each target audience, information regarding the relevance of the results for decision-making (recognizing that research findings from a single study alone should not necessarily affect decision-making or practice), along with attention to how the results can be incorporated into health decision-making if applicable. The plan must specify how the dissemination strategy is expected to affect the identified health decisions and how dissemination engages the study participants or the population of interest. Requiring research dissemination, as well as engagement of patients and other stakeholders at this stage of research, represents a cultural shift for many institutions and researchers.
Rationale for the Standards

PCORI must ensure that research proposals and protocols clearly identify the relevant patient populations and those health decisions that will be affected by the research.

A focus on patient-centered outcomes is a defining characteristic of PCORI and one that sets it apart from other research funding organizations. Inclusion of patient-centered outcomes is therefore a necessary component of PCORI-funded research. As suggested by Guyatt et al., a patient-centered outcome must meet the following test: “Were it to be the only thing that changed, patients would be willing to undergo a treatment with associated risk, cost, or inconvenience.” (20, 21)

Many (though not all) meaningful and important patient-centered outcomes, such as symptoms, are best reported by patients themselves. Pain and some other outcomes cannot reliably or accurately be assessed by any means other than direct patient report. If informants from the study population identify outcomes that can only be ascertained by self-report, then inclusion of patient-reported outcomes is essential to patient-centeredness. Even when other sources can provide meaningful outcomes data, patient reports represent the patient perspective and so add value.

Researchers must also incorporate the patient perspective when selecting the type and timing of interventions or exposures to test and the comparisons to make in a study. The selection of appropriate research designs is discussed in more detail in Chapter 6, and specific research method issues are presented in Chapter 7.

To complete the research continuum from the patient-centeredness perspective, an a priori dissemination strategy for integrating study results with related work is necessary to optimally affect identified health decisions and outcomes.
While this is the first step to achieving patient-centeredness and relevance in a study, there is a paucity of evidence regarding best practices for patient engagement. The proposed standards in this area thus require investigators to describe in detail in their research proposals and in their publications the ways in which they approached engagement, while avoiding prescribing a particular approach. It is expected that this will focus attention on the importance of this engagement and facilitate evaluation, thus helping to create evidence regarding the effectiveness of different approaches.

To be patient-centered, PCORI and researchers must also engage “informants” in the design, conduct, and dissemination phases of research. Informants are people who are representative of a specific population but are not necessarily study participants. For some populations—for example, children or cognitively impaired persons—informants also include surrogates and caregivers. Although not the focus of this standard, informants representative of other stakeholder groups may also be engaged in the research process.

Further, researchers must ensure that study participants are representative of the spectrum of the population facing the health decision of interest. Work performed for PCORI as background for this standard has identified specific strategies for involving people who have been historically underrepresented in research or who are considered to be hard to reach (See the report Integrating Patients’ Voices in Study Design Elements with a Focus on Hard-to-Reach Populations). Although there are a number of guideline and recommendation documents regarding patient engagement in research,(23, 24) the quality and quantity of empirical evidence regarding patient engagement in research are insufficient to make a full assessment.(24, 25) The first set of patient-centeredness standards for PCOR thus directs researchers to rigorously formulate and describe their methods of patient engagement, without prescribing a specific approach. Detailed and consistent descriptions of the strategies employed in funded studies will facilitate efforts to evaluate the effectiveness of alternative strategies for engaging patients and other stakeholders. Appendix C presents a brief narrative review of the Committee’s current approach to patient engagement and patient-centered outcomes.
Research Gaps and Future Work

Evidence in a number of areas relevant to the proposed standards is limited, and the standards will evolve over time as additional information becomes available. The Committee intends to focus on three important gaps in knowledge:

- First, what are the consequences of patient engagement in research on health decisions and clinical outcomes?
- Second, what are the specific consequences of patient engagement on the research process?
- Third, which patient engagement methods are most effective, and for which populations?

The PCORI Methodology Committee is interested in advancing the science of patient-centered study design, informant engagement, dissemination, and implementation. Particular areas of interest include understanding optimal approaches to engaging patients and other informants throughout the research continuum; understanding how such engagement affects study design and outcomes; improving strategies for recruiting and retaining informants and patients, especially those who are historically underrepresented or hard to reach; and defining approaches to minimize missing patient-reported data.

While this set of standards focused on patients (and their surrogates and caregivers), research is needed to clarify which other stakeholder groups should be engaged in which research activities and how to do so. We also need to learn how to balance and reconcile the inputs from the various stakeholder groups in the design, conduct, and dissemination of PCOR.
Recommended Actions

The following actions are recommended for PCORI to adopt in order to better enable patient engagement in its activities:

• Support training in patient engagement methods for investigators and patient informants.
• Improve the patient-reported outcomes (PRO) evidence base by supporting research on methods for assessing measurement properties (based on qualitative and quantitative evaluations), score interpretability, meaningfulness of score changes, and strategies for minimizing and interpreting missing PRO data in PCOR.
• Evaluate patient dissemination activities, and require incorporation in future research of relevant learnings from this evaluation.

Research Recommendations

• Create an infrastructure to support research on patient engagement. To facilitate this, PCORI should:
• Develop a sample patient engagement plan to demonstrate the key elements required for patient engagement in the research process. The sample plan should illustrate engagement of both patient informants and study participants.
• Systematically collect information about patient engagement methods from PCORI-sponsored studies.
• Evaluate the effectiveness of patient informant engagement.
• Synthesize results across studies.
• Disseminate findings to improve patient engagement in PCOR.
Chapter 5. Methods for Prioritizing Patient-Centered Outcomes Research and for Peer Review

Establishing a specific research agenda is a core duty of PCORI. Unless the mismatch between current research priorities and the information needs of patients and clinicians is addressed, our methodological standards will have little effect. PCORI research must be directed toward providing the answers patients need in order to make health decisions. Peer review of research proposals is a key component of effectively implementing research priorities.

The PCORI Board of Governors is charged with developing, refining, informing priorities for, and selecting among, research investments. In this chapter, the Committee provides guidance to the Board regarding how the methodological tools for research prioritization might be of use in these processes, including guidance on peer review. The Committee provides a framework and narrative overview of topics related to research prioritization and peer review and proposes three standards with supporting recommendations. The Committee also presents five general recommended actions and five recommendations regarding research in research prioritization and peer review.

Elements of the prioritization framework have already been used by the Agency for Healthcare Research and Quality (AHRQ) and the Institute of Medicine to identify gaps in the evidence and topics that PCORI should consider.(14, 26) PCORI should work closely with the Methodology Committee to build on previous work and implement the framework efficiently.

Background

The 2010 Patient Protection and Affordable Care Act (PPACA) lists factors that should be taken into account in identifying priorities (Box 5.1) (Appendix E-3). In addition, research funded by PCORI should seek to take into account differences across individuals and groups of individuals (Appendix E-4).
Box 5.1. Research Prioritization Factors

- Disease incidence, prevalence, and burden (with emphasis on chronic conditions)
- Gaps in evidence in terms of clinical outcomes, practice variation, and health disparities
- Potential for new evidence to improve health, well-being, and the quality of care
- Effect on national expenditures associated with a healthcare treatment, strategy, or health conditions
- Patient needs, outcomes, and preferences
- Relevance to patients and clinicians in making informed health decisions
- Priorities in the National Strategy for Quality Care

While this list includes the effect of the proposed research on national healthcare expenditures as a consideration, elsewhere the legislation restricts consideration of cost. The Committee’s view is that in the context of PCOR, cost, like other aspects of the healthcare delivery system, can be a factor in the effectiveness of care if it influences choices made by patients and clinicians. Cost can be an incentive for delivering inappropriate care, not just a barrier to appropriate care. Providers may have incentive to favor more costly treatments under the common belief that “more is better” in healthcare.

The PPACA makes clear that PCORI must spend its resources effectively and efficiently (see Box 5.1). When there is more than one acceptable research approach available, the potential added cost of the methods should be balanced against the potential value, including the timeliness, of the research results they are likely to produce. Techniques such as Value of Information (VOI) analysis—a statistical method for estimating the average improvement in outcomes that may be expected by obtaining additional information (27)—may be useful in clarifying tradeoffs between study cost and the degree of certainty that is expected from study results.
Framework for Establishing Research Priorities

The focus of the framework is to inform the selection of PCOR research proposals for funding that attempt to answer specific diagnostic, therapeutic, or health system questions. There are four key components to this framework:

1. **Topic Generation.** The purpose is to ensure that a sufficient number and range of topics are considered before topics for research funding are selected. Engagement of multiple stakeholders, especially patients, is critical at this stage. (See the report *Methods for Involving Patients in Topic Generation for Patient-Centered Comparative Effectiveness Research — An International Perspective.* )

2. **Systematic Review and Gap Analysis.** By involving patients and other stakeholders in developing questions for a systematic review, researchers can compare what people want and need to know with what is and is not known. As a result, systematic reviews can identify gaps in knowledge that underlie uncertainty among patients and clinicians. Sometimes, systematic reviews can generate new questions. For example, a pooled analysis of several studies can reveal an important finding that was not evident in the individual studies. (See the report *Prioritizing Future Research through Examination of Research Gaps in Systematic Reviews.* )

3. **Value of Information Analysis.** Value of information analysis may be used to identify questions that have the greatest potential to improve population health by considering uncertainty in the health benefits and risks associated with alternative treatment choices, the ability of research findings to alter that uncertainty, and the resulting care decisions. (See the reports *Value of Information and Research Prioritization* and *Value-of-Information Analysis for Patient-Centered Outcomes Research Prioritization.* )

4. **Peer and Stakeholder Review.** Peer and stakeholder review is the final stage in selecting research proposals for funding. The review process identifies those proposals most likely to fulfill PCORI’s objectives and agenda. (See the report *Peer Review — A Research Priority.* )
The Committee adopted standards for only two of the four components listed above: gap analysis and peer review. We acknowledge that the evidence on methods for prioritizing PCOR is incomplete. Therefore, the Committee proposes that PCORI support empirical research to assess and improve research prioritization methods (see Recommendations for Research). Although Figure 5.1 depicts the research prioritization components as linear, in practice the process is iterative so that, for example, results of value of information analysis might influence topic generation.
Including patients in topic generation is unconventional. Chapter 4 of this report, Standard 4.1.1 emphasizes the Committee’s commitment to the principle that patients should be engaged in all phases of patient centered outcomes research. While at this time, the Committee proposes neither standards nor recommended actions specific to topic generation, recommendations in Chapter 4 include training in patient engagement methods as core principles for both patients and researchers. Topic selection is usually done by researchers or sponsors, and while they may believe they know what patients want, their choices may be influenced by their training and by their professional or commercial interests. Without adequate input from patients, research priorities may not fully reflect patient perspectives on potential benefits or risks, ultimately impeding the uptake of research discoveries.

Some empirical research, mostly conducted outside the United States, has shown that patient involvement can produce more relevant research questions and results that are more useful for making decisions.\(^{28, 29}\) The Committee commissioned a review that examined some of these approaches in detail (Methods for Involving Patients in Topic Generation for Patient-Centered Comparative Effectiveness Research – An International Perspective). The Committee believes that PCORI should test and develop existing alternative approaches and novel methods to obtaining patient input in research topic generation in order to determine which approaches work best for specific patient

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**Standards for Prioritizing Research and for Peer Review**

5.1.1 **Use Systematic Reviews to Identify Gaps in Evidence**

Gap analysis of systematic reviews should be used as part of the process of identifying and prioritizing research gaps to establish funding priorities by PCORI.

5.1.2 **Protect Independence in Peer Review of Research Funding Proposals**

Methods of peer review should be adopted to safeguard independence between reviewers and those being reviewed.

5.1.3 **Ensure Adequate Representation of Minorities and Disadvantaged Segments of the Population in Peer Review of Research Funding Proposals**

Approaches to topic generation in PCOR should involve both consultative and collaborative functions.
populations (see Recommended Actions). As noted in Chapter 4, specific strategies are needed for engaging patients who have been underrepresented in research.

**Systematic Review and Gap Analysis**

Gap analysis of systematic reviews should be used as part of the process of identifying and prioritizing research gaps to establish funding priorities by PCORI.

**Rationale for Standards**

Using a systematic approach to identify gaps in the existing literature and deficiencies in completed studies should reduce investments in research that are unlikely to help answer important questions, consistent with PCORI’s obligation to efficiently use resources. Ethics also require that researchers avoid recruiting patients into unneeded studies. No study is without risk, and patients should not be exposed to needless risk. Using gap analysis of systematic reviews also fosters transparency and accountability in funding prioritization. However, it is critical to rely only on systematic reviews that are credible; the Institute of Medicine recently issued standards for systematic reviews.(16)

While the Committee does not formally endorse a specific approach, it notes that AHRQ has advanced the field in the United States significantly with its Future Research Needs (FRN) Approach. In 2009 AHRQ selected eight Evidence-based Practice Centers (EPCs) to conduct comparative effectiveness reviews and complementary FRN (Figure 5.2).(30) Other national and international organizations have used similar approaches.
Figure 5.2. Adapted Example of a Future Research Needs Process

1. Systematic review is published with systematic review-determined research gaps
2. Orientation of stakeholders to CER question, FRN process, and prioritization criteria
3. Elaboration and consolidation of research gaps through iterative process with stakeholders
4. Priority ranking of the research gaps
5. Transformation of research gaps into research needs
6. Refinement and re-ranking of priorities by stakeholders
7. Addition of study design considerations

This figure was adapted from a draft AHRQ FRN methods paper (31). May include identification of additional research gaps. Reduction through topic consolidation, preliminary prioritization, and consideration of ongoing research (duplication criteria). Research gaps that address specific methods issues would not use PICOTS framework. May require iterative steps.

Value of Information Analysis

The Committee proposes no standards for but recommends two actions regarding VOI analysis. VOI analysis takes into account the research prioritization factors listed in the PPACA by integrating them into a single measure – the expected (average) increase in population health that might be expected from a research project. VOI analysis is the idea, rooted in statistical decision and economic theory, that the value of information can be defined by the average improvement in outcomes expected by obtaining additional information (32, 33). Background papers commissioned by the Committee for this report provide an overview of this approach and highlight specific issues that must be addressed in its potential application by PCORI. Value of information analysis is a tool that decision makers can use to compare research options, but does not dictate a threshold of accepting or rejecting a research proposal.

Peer Review

The Committee proposes two standards regarding peer review. Despite its central role in scientific discourse and decision-making, peer review has had little attention as the subject of research.
Rigorous experiments testing alternative approaches to peer review are rare; most peer-review practices are maintained by convention.

PCORI has particular advantages and responsibilities in developing its approach to peer review. For example, incorporating patient stakeholders presents both a new opportunity and a challenge for peer review. A paper commissioned by the Committee presents the limitations of current methods of peer review for research proposals and the ways patients or their advocates have been involved (Peer Review – A Research Priority). Review practices vary substantially, and in the absence of evidence it is not possible to recommend one mode over another, or even to recommend when peer review of proposals is the best possible way to allocate funding and other resources. Nevertheless, effective peer review is indispensable to the conduct of PCOR, and independence between those being reviewed and those reviewing proposals must be safeguarded.

Rationale for the Standards

Lack of independence is likely to create circles of insiders, propagate inbreeding of ideas, and to decrease innovation and quality in scientific research. Most research funding agencies try to exclude scientists who have perceived conflicts of interest from reviewing applications, although definitions of conflicts vary. In a densely connected world of scientific research, links between investigators can be complex, subtle, and difficult to identify, and it is often difficult to determine whether a given relationship is or is not likely to affect the review process. There is great variability in processes used to protect the integrity and independence of the review process.

Including patients or their representatives in the peer review process will introduce new conflicts of interest due to potential links of these stakeholders to particular investigators, advocacy groups, and other patients with the condition. Methodological research is needed to understand the potential threats to independence that could arise from conflicts of interest when patients and related stakeholders are involved in the peer review process.

In addition, the adequate and appropriate representation of minorities is routinely considered as a standard in NIH funding opportunities and many other funding agencies. Differences in disease burden may suggest different research priorities. There is empirical evidence that minorities and disadvantaged segments of the population are underrepresented in many areas of clinical research. Whether or not the peer review process is responsible, it may help remedy the imbalance.
In conclusion, the dearth of strong scientific evidence on the most effective methods for peer review with respect to independence and representativeness of reviewers and the efficiency of the process, along with special considerations relating to minority populations, points to the need for additional research.

**Recommended Actions**

To begin a program of patient-centered research prioritization, PCORI should take a number of actions, including the following.

- Work closely with the Methodology Committee to build on previous work and implement the framework efficiently.
- Base all PCORI targeted funding opportunity announcements on evidence gap analysis.
- Require that applicants demonstrate how their proposed research fills a research gap for non-targeted funding opportunity announcements.
- Support education and training activities to broaden the base of individuals prepared to apply and evaluate VOI.
- Maintain peer review processes that avoid interference of participants and stakeholders with potential conflicts of interest. Peer review should incorporate patient perspectives.
Research Recommendations

- Encourage intra- and extramural research in the development and practical application of VOI methods for PCOR, including through studies that examine the contribution of VOI methods to research prioritization when used in conjunction with other approaches to research prioritization.
- Support empirical research to assess and improve research prioritization methods for use by PCORI.
- Support extra- and/or intramural research to establish a best practice approach to consultative and collaborative patient engagement in topic generation that is suitable for the heterogeneity of the US patient population.
- Study the employment of research gap analysis to continue to develop the empirical evidence on its use.
- Encourage studies, ideally with experimental designs, that assess different methods for engaging patients with diverse views and preferences and funneling their input into the peer review process in a consultative manner.
Chapter 6. Choosing Data Sources, Research Design, and Analysis Plan: Translation Framework and Development of a Translation Table

The choice of a study design is one of the most critical factors in PCOR. The legislation expected the Methodology Committee to address this question, calling on it to develop “a translation table that is designed to provide guidance and act as a reference for the Board to determine research methods that are most likely to address each specific comparative clinical effectiveness research question” (Appendix E-5). The choice of study designs has practical implications for the timeliness, validity, and relevance of PCORI’s specific research project agenda.

The translation table serves to guide the design of new comparative clinical effectiveness research studies for specific research questions. Clearer guidance regarding the selection of appropriate research designs for specific research questions could avoid studies that are inappropriate for the research question and could direct researchers to designs that reach the “right” answers sooner, thus improving the efficiency of research. When research designs clearly match the questions patients and their healthcare advisers consider important, research results should be more readily accepted and implemented. A translation table could help build a comprehensive research program recognizing and balancing the inherent tradeoffs of each study design and analytical methodology.

Research funding agencies, including PCORI, could require that a translation table be used for developing research proposals and for evaluating the quality of such proposals. The legislation names the PCORI Board as the primary audience for the translation table, but other entities that generate or interpret comparative effectiveness research/patient-centered outcomes research are likely to be guided by such an instrument. These include applied researchers, regulatory and funding agencies, and payer and provider organizations.

Very few published articles mention the concept of a “translation table,” and stakeholders have varying opinions about what it should include (see Appendices 6-1, 6-2, and 6-4). The lack of expert consensus required the Committee to pursue its own approach to developing a translation table, using information from the public to inform our decisions about the scope and form a translation table could have. We developed a set of principles and a translation framework, which we refined by applying case studies contributed by Committee members and members of the public (see Appendices 6-3, 6-5).
**Scope**

The Methodology Committee decided that the translation table should address two main tasks:

1. Choosing a basic study design. By basic design, we mean whether the study is experimental or observational. Other study designs, such as systematic reviews and decision models, are also within the scope of PCORI but are not addressed in this version of the translation table.

2. Determining additional design details. Once a decision is made to conduct an observational or experimental study, a number of options about study design need to be considered and weighed. In the last section of this chapter, we provide a detailed example of choosing additional design features for a randomized trial.

Table 6.1 shows two basic design types—the randomized clinical trial design and the nonrandomized study—used to assess the effectiveness of therapies. Within each basic design, three examples of more specific designs are described. A translation table would be used to decide first between a randomized or nonrandomized design; once that decision was made, it could then be used to choose additional, more specific design features.
Table 6.1. Selected Study Designs for Assessing the Effectiveness of Therapeutic Interventions

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trial</td>
<td>A study in which randomization is used to assign study subjects to interventions and which can range in the amount of control exercised by the investigators. Randomized controlled trials determine whether a clinical intervention is effective under optimal circumstances. This is achieved by using rigorous inclusion and exclusion criteria and a highly controlled research environment. Pragmatic randomized studies determine the harms, benefits, and costs of an intervention as it would occur in routine clinical practice. This is achieved by including a combination of a broader range of subjects, study sites, and outcomes.</td>
</tr>
<tr>
<td>Cluster randomized clinical trial</td>
<td>A randomized clinical trial that groups subjects according to “clusters,” such as clinic site or community. Randomization is used to assign entire clusters to interventions. This design is useful when evaluating health policies or when randomization at the subject level is not possible.</td>
</tr>
<tr>
<td>Crossover trial</td>
<td>A trial in which the subject acts as his/her own control. This is accomplished by having each subject receive a sequence of interventions over periods of time, crossing over to an alternative intervention as part of the sequence. The order of intervention is assigned randomly. The N-of-1 trial is a special case of a crossover trial that compares two or more interventions for a single patient.</td>
</tr>
<tr>
<td>Delayed start trial</td>
<td>A form of crossover trial conducted in two phases, sometimes used to evaluate whether an intervention acts by reducing symptoms (Phase I) or by modifying disease (Phase II). In Phase I, subjects are randomized to receive either the intervention or comparator; in Phase II, all subjects receive the intervention.</td>
</tr>
<tr>
<td>Nonrandomized study</td>
<td>A study that does not use randomization to assign participants to intervention arms.</td>
</tr>
<tr>
<td>Cohort study</td>
<td>A nonrandomized study of subjects with a common feature or condition. Subjects are observed to receive specific interventions. Data may be collected and evaluated prospectively or retrospectively. Efficient sampling designs are available for cohort studies, including case-control studies, case-cohort studies, and 2-stage sampling designs.</td>
</tr>
<tr>
<td>Self-controlled designs</td>
<td>A nonrandomized study in which subjects act as their own controls by observing a sequence of treatments over periods of time crossing over to an alternative intervention as part of the sequence.</td>
</tr>
<tr>
<td>Controlled time-trend analysis design</td>
<td>A nonrandomized study in which sudden changes or shocks in the healthcare settings are exploited to compare outcomes before the change with outcomes observed after the change. When subjects who have not been exposed to the shock over the same time period are available, this design is referred to as a difference-in-difference or quasi-experimental design.</td>
</tr>
</tbody>
</table>

Emerging Principles

The Committee recommends the following principles in the translation framework.

1. Keep the research question and the methodology separate: In order for the translation table to function in the way envisioned by the legislation, the Committee believes that it is important to separate the development of the research questions from the task of finding the best methodology to answer the question.
The Committee views the research methodology as the means to answer a research question as well as possible, not as a factor that should influence the choice of research question. Problems occur when the choice of study design or research question is driven by data availability. Defining the question should not be limited by concerns about eventual methodological constraints. In PCOR, identifying decisions and defining a patient-centered research question should come first.

2. **Focus on clarifying tradeoffs:** After a research question is defined, choices have to be made about the type and level of evidence needed to inform the decisions that it was intended to address. This will direct the choice of research design and analytic strategy. Preference should be declared on a series of factors including (in no specific order) the timeliness of findings, their representativeness, their validity, the ability to identify subgroup effects, and others. Such *study characteristics* (see Box 6.1) need to be defined with stakeholder input as they will substantially influence the utility of the results for decision-making. Clearly articulating the tradeoffs between these choices will bolster the transparency of the analytical approach.

**Box 6.1. Examples of Study Characteristics**

<table>
<thead>
<tr>
<th>Intrinsic study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Internal validity (the extent to which effects are caused by the intervention or exposure).</td>
</tr>
<tr>
<td>• External validity (generalizability or applicability to non-study settings and populations).</td>
</tr>
<tr>
<td>• Precision (having small random error of estimation).</td>
</tr>
<tr>
<td>• Heterogeneity in risk or benefit (risks or benefits vary by subgroup).</td>
</tr>
<tr>
<td>• Ethical dimensions of the study (including considerations of risk-benefit balance and study burden for study participants).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extrinsic study characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Timeliness (rapidly changing technology, policy, or public health needs).</td>
</tr>
<tr>
<td>• Logistical constraints (feasibility of collecting information from participants, number of participants available, study complexity).</td>
</tr>
<tr>
<td>• Data availability, quality, and completeness.</td>
</tr>
</tbody>
</table>
3. Expect that several versions of a translation table might be needed for different decision-makers and different research categories (see Box 6.2): Different decision-makers may have different evidentiary needs. The play of study characteristics as well as the preferences of decision-makers may depend on whether the topic is about a choice of diagnostic approaches, an attempt to estimate risk or predict future complications, a choice of surgical versus nonsurgical treatment, or a choice of ways to change the way care is delivered. Eventually each kind of researchable question will require its own translation table that can provide meaningful advice on its specific methodological requirements.

4. Place individual research studies in the context of a research program: The legislation asked for a translation table that helps match the best methodology to a specific research question. This implies a one-to-one relationship. It is widely accepted that most research questions can be answered in several ways. A research program may, for example, include an effectiveness study based on secondary healthcare data, a detailed interview study, and a randomized trial to balance population representativeness, timeliness, depth, and validity for informed decision-making. The translation table should help identify the tradeoffs between different approaches to answering a question. For example, suppose a new surgical procedure to repair heart valves that is less invasive than the standard surgery has been developed but requires specialized surgical training and skill and the participation of cardiac surgery team. A randomized trial may be required to establish the benefits or harms of the new procedure compared to the standard procedure under these ideal conditions. Regulators are likely to be very interested in the outcome of this type of design. An observational study may also be needed to determine the safety and effectiveness of the new procedure compared to the standard approaches when the procedure becomes more widely available. Patients and professional societies may be interested in the outcome of this study—patients to determine if the new procedure is a good choice for “people like me” and professional societies to determine if and how best to adopt the new procedure.

5. The choice of study design must take into account the state of the art of research methodology: Over the past 20 years, the choice of study design has been debated intensely in scientific and, more recently, political circles. These discussions often reiterate commonly held beliefs about randomized controlled trials (RCTs) and observational studies. One asserts that RCTs are less relevant to decision-makers than observational studies. Another is that
observational studies nearly always suffer from serious flaws that render them invalid and even irrelevant. In fact, many RCTs have proven to have long-lasting value in clinical decision-making. In many fields, critical evidence comes from RCTs, many of them conducted in patient populations and circumstances that are broadly applicable. Observational studies have been extremely valuable as a complement to RCTs, helping to determine under what circumstances and to what patients the findings of RCTs are applicable. Serious errors in clinical practice can be due to overreliance on narrowly focused RCTs or on flawed observational studies, but widely cited examples do not represent the potential of these basic designs to contribute to PCOR.

The familiar overgeneralizations do not take into account developments in research methodology that can make randomized studies more relevant, timely, and flexible, and can improve the validity of observational studies. In particular, the use of observational studies to make causal inference is potentially much stronger than it has been in the past. Many of the standards that we developed address ways to improve the value of observational studies as a substitute for RCTs for questions about comparative clinical effectiveness. Decisions about study design need to take into account these standards, described in Chapters 7 and 8, below, and the advances in methodology they reflect.

Translation Framework

A single translation table would not work for all types of research questions. We developed a conceptual model of the translation task based on three concepts, defined below (Box 6.2).
**Box 6.2. Terms for Describing the Translation Table**

**Research Category:** Breaking research into categories will make each translation table more informative and less complex. For example, original research on the effectiveness of therapeutics will require a different approach than will research on the effectiveness of diagnostic tests or imaging. Research categories and their relationship to each other are not yet defined and will develop as the translation framework develops.

**Translation Framework:** The translation framework provides the theoretical underpinning and organizing structure for the translation table that will help PCORI identify the range of appropriate research designs and analytic approaches to answer specific patient-centered research questions. It includes a set of study characteristics that can be used to guide the user in making choices in study design and analytic methods based on current scientific knowledge, research categories, and the corresponding translation tables.

**Translation Tool:** Although the legislative mandate is to create a translation table, the usefulness of a literal “table” format may be limited. As the combination of study characteristics, research categories, and translation tables may be complex, a translation tool, rather than a table, would make the translation framework more accessible to users.

The Committee envisions the translation tool as a dynamic implementation of the translation framework to help users apply it to specific research questions. Such a tool might take the form of weighting or optimization algorithms that are made accessible to users in electronic formats. The tool would point to one or more recommended designs and to other designs that not acceptable.

The basic structure and function of the proposed translation framework (Figure 6.1) can be summarized in four phases, corresponding with the phases described in Chapter 3, Table 3.1.