Cycle 2 2016 Funding Cycle

PCORI Funding Announcement: Pragmatic Clinical Studies To Evaluate Patient-Centered Outcomes

Published April 4, 2016

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes August 8, 2016, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at http://www.pcori.org/Cycle-2-2016-pragmatic-studies/.

About PCORI

The Patient-Centered Outcomes Research Institute (PCORI) is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI uses a variety of forums and public comment periods to obtain public input to enhance its work. PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.

PCORI was authorized by Congress in 2010 as a nonprofit, nongovernmental organization. PCORI's purpose, as defined by our authorizing legislation, is to help patients, clinicians, purchasers, and policy makers make better-informed health decisions by "advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions."

Patient-Centered Outcomes Research Institute
1828 L St., NW, Suite 900
Washington, DC 20036
Phone: 202-827-7700
Fax: 202-355-9558
Email: info@pcori.org

Follow us on Twitter: @PCORI

Overview

Published	April 4, 2016
Letter of Intent Due	May 4, 2016, by 5 p.m. (ET) Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and for fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of request to submit a full application will occur no later than June 10, 2016.
Summary	PCORI seeks to fund pragmatic clinical trials, large simple trials, or large-scale observational studies that compare two or more alternatives for addressing prevention, diagnosis, treatment, or management of a disease or symptom; improving healthcare system-level approaches to managing care; communicating or disseminating research results to patients, caregivers, or clinicians; or eliminating health or healthcare disparities. Proposed studies must address critical clinical choices faced by patients, their caregivers, clinicians, or delivery systems. They must involve broadly representative patient populations and be large enough to provide precise estimates of hypothesized effectiveness differences and to support evaluation of potential differences in treatment effectiveness in patient subgroups. For this solicitation, PCORI is not requiring that relevant national patient organizations, professional organizations, or payer or purchaser organizations be formally included as partners and active participants prior to contract award. However, applicants should document that they have consulted with patients and other stakeholders to identify the important decisional dilemmas and evidence needs that will drive development of the research questions, or reference previously documented decisional dilemmas. Successful applicants are required to collaborate with PCORI staff upon award of the studies to establish a project Study Advisory Committee (SAC)[1] that is comprised of national or regional organizations that represent, at a minimum, patients or families with lived experience, relevant clinicians, payers, and health plans. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. The SAC advises and assists the research team with refining the study questions, outcomes, and protocol. PCORI expects that most awards will be made for study designs that use randomization—either of individual participants or clusters—to avoid confounding bias. However, we recognize that exceptional opportunities may arise—by virtue of natural experiments or the existence of large registries—to address pragmatic questions using observational designs. Please note that this funding program does not support applications to conduct cost-effectiveness analyses, systematic reviews (with or without meta-analyses), or developing or evaluating shared decision-making or decision-support tools. In general, PCORI will not cover costs for interventions that are being compared in the proposed study. (See Appendix 3 in the Application Guidelines for details.) This announcement is a collaborative effort of PCORI's Comparative Clinical Effectiveness Research, Communication and Dissemination Research, Improving Healthcare Systems, and Addressing Disparities research programs.

[1] The intent of the SAC described in the PFA is to ensure that a broad spectrum of stakeholders and patients advise and assist the research team

Applicant Resources	See all templates in the PCORI Funding Center here: http://www.pcori.org/Cycle-2-2016-pragmatic-studies/.
Key Dates	Online System Opens: April 4, 2016 Applicant Town Hall Session: April 13, 2016 1:00 p.m.–2:30 p.m. (ET) LOI Deadline: May 4, 2016, by 5 p.m. (ET) LOI Screening Notification: June 10, 2016 Application Deadline: August 8, 2016, by 5 p.m. (ET) Merit Review Dates: November 2016 Awards Announced: January 2017 Earliest Project Start Date: March 2017
Maximum Project Budget (Total Direct Costs)	$10 million
Maximum Research Project Period	Five years
Funds Available Up to	$90 million
Eligibility	Applications may be submitted by any private-sector research organization, including any nonprofit or for-profit organization; any public-sector research organization, including any university or college hospital or healthcare system, laboratory, or manufacturer; or any unit of local, state, or federal government. The Internal Revenue Service must recognize all U.S. applicant organizations. Nondomestic components of organizations based in the United States and foreign organizations may apply, as long as there is demonstrable benefit to the U.S. healthcare system and U.S. efforts in the area of patient-centered research can be shown clearly. Organizations may submit multiple applications for funding. Individuals are not permitted to apply.
Review Criteria	1. Potential for the study to fill critical gaps and generate actionable evidence 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care 3. Scientific merit (research design, analysis, and outcomes) 4. Patient-centeredness 5. Patient and stakeholder engagement

with refining the study questions, outcomes, and protocols. These stakeholders and patients must include national or regional organizations that represent, at a minimum, patients or families with lived experience, relevant clinicians, payers, and health plans. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. However, PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups, and other bodies, or involving individual patient and stakeholder partners in various ways are also permissible to employ—either in addition to or instead of—the formation of the SAC. The SAC provision is not meant to require that a separate governance or advisory entity be established beyond the study governance and advisory structure the awardee has planned, if an applicant already has an approach for including the relevant and required stakeholders and patient partners. For clarification in your application materials and merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for in-person meetings at least two times per year, and appropriate budgeting.

Contact Us	**Programmatic Inquiries:** Please contact the PCORI Helpdesk via email (sciencequestions@pcori.org), phone (202-627-1884), or online (http://www.pcori.org/PFA/inquiry). PCORI will provide a response within three business days; however, we cannot guarantee that all questions will be addressed in a timely fashion when the inquiry is made three or fewer business days before an LOI or application deadline. **Administrative, Financial, or Technical Inquiries:** Please contact the PCORI Helpdesk at pfa@pcori.org. PCORI will provide a response within two business days. Applicants may also call the PCORI helpdesk at 202-627-1885. Please note that during the week of the application deadline, response times may exceed two business days. Applicants are asked to plan accordingly. It is the applicant's responsibility to submit the application on or before the application deadline.

New or Revised for the Cycle 2 2016 Funding Cycle:

- Added clarifying language about the SAC (footnote 1).
- Updated list of PCORI Priority Topics (Appendix 1).
- A new dual PI policy has been implemented.

Table of Contents

I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to expand its support of patient-centered comparative clinical effectiveness research (CER). PCORI seeks to fund large pragmatic clinical trials, large simple trials, or large-scale comparative observational studies that involve representative patient populations; have strong endorsement and study participation by relevant patient organizations, professional organizations, or payer or purchaser organizations; take place within typical clinical care and community settings; and have a sample large enough to enable precise estimates of effect sizes and to support evaluation of potential differences in treatment effectiveness in patient subgroups. Funded studies will compare the relative effectiveness[2] of two or more alternatives for improving patient-centered outcomes. Proposed studies of comparative efficacy[3] will be considered nonresponsive.

Background

Although traditional randomized controlled trials (RCTs) are widely accepted for assessing the efficacy of medical interventions, RCTs are expensive and time-consuming. Furthermore, findings from these trials may have limited generalizability for evaluating the comparative effectiveness of interventions already in use because of the following well-documented factors: (1) the comparisons in the trial often fail to reflect the choices faced by patients and clinicians; (2) the chosen study population tends to be homogeneous, highly motivated, and relatively free of many comorbid conditions; (3) research tends to take place in specialized research settings; (4) research protocols are often rigid and not representative of typical clinical practice; and (5) the trial may use a placebo, rather than an active comparator, as the comparison.

To meet these concerns, trials can be designed to address practical comparative questions faced by patients and clinicians—to include broader and more diverse populations—and to be conducted in real-world clinical and diverse health-system settings. Such trials are often referred to as "pragmatic clinical trials" because they are intended to provide information that healthcare providers can adopt directly. They tend to be conducted in routine clinical care settings and, in many cases, they must be relatively large because expected differences in comparative effectiveness may be small yet important. The large size of these trials will also permit the evaluation of effectiveness in different patient subgroups. In some cases, these trials may be much simpler than traditional RCTs, and such trials would be considered large simple trials.

The protocols for these trials are typically less complex and less intrusive to routine clinical practice than are efficacy studies. For more extensive discussion on pragmatic versus traditional explanatory trials, see

[2] "Effectiveness" is the extent to which an intervention does more good than harm across a broad mix of patients when provided under the usual circumstances of healthcare practice (modified from http://www.europarl.europa.eu/RegData/etudes/workshop/join/2013/518741/IPOL-ENVI_AT%282013%29518741_EN.pdf).

[3] "Efficacy" is the extent to which an intervention does more good than harm in ideal patients under ideal circumstances (modified from http://www.europarl.europa.eu/RegData/etudes/workshop/join/2013/518741/IPOL-ENVI_AT%282013%29518741_EN.pdf).

Patsopoulos,[4] Thorpe et al.,[5] and Loudon et al.[6]

For those trials that target populations at risk for experiencing disparities (e.g., racial or ethnic minorities and low-income groups), it may be necessary to tailor interventions that take place in real-world settings to address the population's specific needs. These trials may require complex, multicomponent, multilevel interventions (e.g., targeting the patient, provider, and system), as evidenced by the literature on disparities. It may be necessary to gather more than a minimal level of outcome data to assess the impact of the intervention adequately.

Examples of Successful Pragmatic Clinical Trials

- Choudhry and colleagues[7] enrolled 5,855 patients to test whether the elimination of out-of-pocket expenses for medications prescribed after a myocardial infarction would increase the percentage of patients adhering to medication regimens and improve clinical outcomes.
- In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 33,357 participants 55 years or older with hypertension and at least one other coronary heart disease risk factor, drawn from 623 North American centers, were randomized to chlorthalidone, amlodipine, or lisinopril.[8]
- A randomized, real-world, open-label comparative clinical effectiveness trial enrolled patients diagnosed as depressed by primary-care practitioners. Patients were randomly assigned to a serotonin reuptake inhibitor or one of two tricyclic antidepressants and followed (passively) for two years to evaluate depression symptoms, health-related quality of life, healthcare utilization patterns, and costs.[9]

Features of Patient-Centered Outcomes Research

PCORI funds patient-centered outcomes research (PCOR), which helps patients and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, and palliative health information communication or dissemination strategies, or health delivery-system features to inform decision making, highlighting the choices that matter to people
- Is inclusive of an individual's preferences, autonomy and needs, focusing on outcomes that

[4] Patsopoulos, N.A. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci.* 2011; 13:217–24; http://ncbi.nlm.nih.gov/pmc/articles/PMC3181997/.
[5] Thorpe, K.E., et al. A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. *CMAJ*. 2009; 180:E47–E57; http://cmaj.ca/content/180/10/E47.full.pdf/.
[6] Loudon, K., et al. The PRECIS-2 tool: Designing trials that are fit for purpose. *Research Methods & Reporting*. 2015; 350:h2147; http://www.bmj.com/content/350/bmj.h2147. (Note that this article describes an updated process to assess how closely the proposed study design elements [e.g., delivery of intervention and population of interest] mirror those encountered in usual care, a proxy for pragmatic. The term "usual care," as used in this article, differs from how PCORI interprets and uses the term in the context of CER funding announcements—a control comparator.)
[7] Choudhry, N.K., et al. Full coverage for preventive medications after myocardial infarction. *N Engl J Med.* 2011; 365(22): 2088–97; http://www.nejm.org/doi/full/10.1056/NEJMsa1107913/.
[8] ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. *JAMA.* 2002; 288:2981–97; http://www.ncbi.nlm.nih.gov/pubmed/12479763/.
[9] Simon, G.E., et al. Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs. tricyclic antidepressants. *JAMA*. 1996; 275(24): 1897–902; http://www.ncbi.nlm.nih.gov/pubmed/8648870/.

people notice and care about (including survival, functioning, 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
- Directly compares clinical and delivery-system interventions that are currently available or used in the settings in which people access health care
- Obtains stakeholder perspectives to address the burdens to individuals, care access, care quality, and technology and personnel requirements

Research Characteristics and Objectives

PCORI seeks to support new research that addresses critical clinical and health-related questions faced by patients, their caregivers, and their providers. PCORI seeks to fund investigator-initiated research displaying the following characteristics:

- The research studies the benefits and harms of different interventions and strategies that are currently delivered in typical clinical and community settings.
- The research compares at least two alternative clinical approaches. Because PCORI's mission is to develop evidence to inform difficult decisions, PCORI strongly prefers applications that propose to compare well-defined interventions that are already being used in the condition and the population of interest.
- The research examines such interventions as specific drugs, devices, procedures, assistive technologies, behavioral change, communication or dissemination, or complementary treatments. Studies may also address complex interventions occurring at, or pertaining to, care delivery systems. Please note that "usual care" is not an appropriate comparator for CER studies submitted to PCORI for funding consideration. Usual care is too often ill-defined, difficult to quantify, and subject to considerable geographic and temporal variations, which limits interpretability, applicability, and reproducibility. If the applicant proposes usual care as a rational and important comparator in the proposed study, then it must be described in detail, coherent as a clinical alternative, and properly justified as a legitimate comparator (e.g., usual care is guidelines-based). It must also be accompanied by an explanation of how the care given in the usual care group will be measured in each patient, to the extent possible, and how appropriate inferences will be drawn from its inclusion.
- The research compares health outcomes that are meaningful to the study's patient population (e.g., morbidity, mortality, symptoms, functional status, quality of life, and absenteeism from work or school). Such outcomes should be measured using validated methods. In select instances, surrogate physiological measurements may be sufficiently linked to final health outcomes to be of interest, but they might not be the sole study outcome.

This solicitation has two objectives. First and most important, PCORI seeks to commit adequate funding to address critical clinical and health-related questions faced by patients, their caregivers, and their clinicians. Second, when randomized studies are proposed, PCORI is interested in testing novel and

efficient methodological approaches, such as cluster randomization or Bayesian adaptive designs. PCORI has particular interest in funding studies that:

- Use validated measures of patient-reported outcomes (PROs)
- Can be completed quickly because the primary outcomes focus on symptoms or other patient-reported measures
- Examine interventions and outcomes that cut across specific diagnoses (e.g., studies with primary outcomes focused on symptoms, such as pain)
- Employ strategies to enhance study efficiency, such as Bayesian adaptive designs in which trial characteristics (e.g., sample size, randomization proportions, treatment arms, and eligibility criteria) evolve during the trial in response to interim trial data (see PCORI's Standards for the Design, Conduct, and Evaluation of Adaptive Randomized Clinical Trials[10])

Such studies will help determine not only how these approaches might be employed within real-world settings, but also how such approaches might be integrated within a dynamic and rapidly learning environment.

Topic Selection

PCORI's multi-stakeholder advisory panels have identified high-priority topics and research questions (see Appendix). During PCORI's award selection process, PCORI Board of Governors (Board) members on the Selection Committee, merit reviewers, and program staff pay attention to applications that address PCORI-identified priority topics and research questions. Although other prioritized lists of CER questions are also of interest (e.g., the Institute of Medicine [IOM] Priorities for CER[11] and the Agency for Healthcare Research and Quality [AHRQ] Future Research Needs Projects[12]), PCORI will give first consideration to applications that directly address one or more of the 18 PCORI-identified priority topics (see Appendix). Note that PCORI is open to receiving and reviewing LOIs for studies on investigator-initiated CER questions. In such cases, applicants must explain why the proposed research question should be considered a high priority. Regardless of the research questions, applicants are expected to adhere to PCORI Methodology Standard RQ1,[13] which states that "gap analysis and systematic reviews should be used to support the need for a proposed study."

Since August 2015 PCORI has made funding decisions on applications submitted for three Pragmatic Studies Funding Cycles. PCORI may entertain additional studies within a given research topic if the proposed study is deemed complementary to the funded (or to-be-funded) studies. Applicants should therefore be aware that the application topic could be a factor in PCORI's decision to invite a full application. *(Note: PCORI does not provide information about pending awards.)*

In all cases, PCORI expects researchers preparing applications to have consulted with patients and other

[10] Available at http://pcori.org/assets/Standards-for-the-Design-Conduct-and-Evaluation-of-Adaptive-Randomized-Clinical-Trials.pdf/.
[11] Available at http://iom.edu/~/media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx/.
[12] Available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=521.
[13] Available at http://pcori.org/assets/2013/11/PCORI-Methodology-Report.pdf/.

stakeholders to identify the important decisional dilemmas and evidence needs that will drive research question development or to reference previously documented decisional dilemmas.

To describe the decisional dilemma, state the specific clinical decision(s) or treatment choice(s) confronted by the decision makers and how the findings from the proposed research will inform those decisions. State why this decision—such as choosing a specific medication, surgical approach, intervention, or care delivery strategy to treat a condition or manage a specific population—is important to patients and their caregivers. Document the uncertainty patients, clinicians, and other decision makers face in making this decision. Identify the stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continuing to engage them actively in the conduct of the study.

Successful applicants will be required to collaborate with PCORI staff upon award of the proposed studies to establish a project Study Advisory Committee (SAC), or other appropriate engagement body, that is comprised of national or regional organizations that represent, at a minimum, patients or families with lived experience, relevant clinicians, payers, and health plans. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. The SAC advises and assists the research team by refining the study questions, outcomes, and protocol. It is expected that the SAC will meet regularly in-person at least two times per year and may use virtual communications at other times. These should be budgeted activities represented in the project milestones.

PCORI expects that project budgets and duration will vary substantially depending on the topic and approach selected, the recruitment or primary data collection needs, the length of follow-up, and the analytic complexity. PCORI seeks efficient studies, such as those taking advantage of large populations already under observation and the supportive involvement of delivery systems or health plans to enhance recruitment and data collection. A prolonged recruitment period is not an acceptable rationale for longer studies, except possibly in the case of a rare disease. Funding requests to develop or build on initial collaboration between researchers and patient/stakeholder groups are also not appropriate.

In-kind contributions to a proposed study are welcome, as are opportunities for co-funding between PCORI and another research sponsor. Each of these factors is taken as further evidence of the research question's importance.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet the following requirements:

- Focus on a comparative effectiveness question that is important to patients and other decision makers.
- Address an evidence gap in deciding among available options; this gap should have been substantiated by an existing (recent or updated) rigorously conducted systematic review or emphasized by an official professional society's clinical practice guideline.

- Demonstrate consultation with patients and other stakeholders or their representative groups, or reference previously documented decisional dilemmas to determine whether the study is answering a critical question—one that, if adequately answered, would substantially improve decision making.
- Propose a sample size that is sufficiently large to allow for precise estimation of hypothesized effect sizes or for clear demonstration of non-inferiority. The sample size must also support testing of a priori hypotheses related to potential differences in effectiveness in relevant patient subgroups (Heterogeneity of Treatment Effect, or HTE).
- Examine diverse populations receiving care in real-world settings.
- For studies aiming to reduce or eliminate health or healthcare disparities, specify one or more of the Addressing Disparities Program target populations (i.e., racial or ethnic minorities; low-income groups; residents of rural areas; individuals with special healthcare needs [including individuals with disabilities]; individuals with low health literacy or numeracy and/or limited English proficiency; and lesbian, gay, bisexual, and transgender [LGBT] persons) that will be the focus of the study. Studies should test the ability of interventions to improve outcomes (including patient-centered, clinical, and structural outcomes) and reduce disparities for at-risk populations.
- Have strong interest from and support of host delivery systems and clinical care settings.
- Specify broad and simple eligibility criteria that will allow wide generalization of results while attending appropriately to ethical concerns of excess risk in some patient subgroups.
- Compare interventions that are known to be efficacious, effective, or commonly used and that can be implemented in real-world settings.
- Feature near-term outcomes and PROs as primary outcomes, when appropriate.
- Plan to collect patient-centered outcomes data efficiently periodically during follow-up.
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions, if applicable. PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and should present evidence that the study will not encounter significant barriers to recruitment or participation. The relevant IRBs make the final determination of the adequacy of informed consent procedures and participant protections.
- Adhere to all applicable PCORI Methodology Standards.[14]
- In the case of randomized trials, also adhere to current best practices (standardized inclusion or exclusion criteria; proper randomization; techniques to minimize potential for missing data; and

[14] Available at http://www.pcori.org/research-results/research-methodology.

appropriate safety monitoring, including establishing a data and safety monitoring plan that gives a rationale for whether or not a data and safety monitoring board [DSMB] is required).

- Include a plan for sharing de-identified data.

To carry out pragmatic studies, readily adopt the findings in a real-world setting, and maximize the efficient use of resources, applicants must take care to prevent these trials from becoming more complex and onerous than necessary. The applicant is encouraged to be creative and consider the following innovative strategies, as appropriate and feasible:

- Consult with patients and other stakeholders on their decisional dilemma and evidence needs, or reference previously documented decisional dilemmas in preparation for the submission of LOIs and full applications.
- Carefully describe the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers and families, and other stakeholders, including clinicians and policy makers. Similarly, applicants should document why project outcomes are especially relevant to patients and meaningful endpoints for patients and their families. Minimize disruption to participants' daily routines (e.g., minimize participant visits intended for study-assessment purposes; capture PROs during office visits, electronically, or by phone).
- Design the study so that the conduct can integrate with routine clinic or office operations as seamlessly as possible.
- Use efficient methods to obtain participant consent while still meeting ethical and legal requirements.
- Capitalize on the existing electronic health records and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information. PCORI specifically encourages applications that use the National Patient-Centered Clinical Research Network (PCORNet) infrastructure.
- If data standardization and interoperability across study sites have not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different electronic health record systems.

Nonresponsiveness

Applications will be considered nonresponsive to this PFA if the proposed research:

- Tests efficacy or comparative efficacy of interventions that are novel or with limited evidence of efficacy
- Involves studies conducted within tightly controlled research environments instead of in clinical settings reflective of real-world healthcare delivery
- Conducts a formal cost-effectiveness analysis
- Measures the relative costs of care of two or more alternative approaches as the primary

criteria for choosing the preferred alternative

- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or biological mechanisms
- Evaluates validity or efficacy of (rather than comparative effectiveness of) new or existing decision-support tools; this includes the development and efficacy evaluation of decision-support or shared-decision tools or systems for patients, clinicians, or both
- Develops clinical prediction or prognostication tools
- Establishes efficacy for a new clinical strategy
- Pilots studies intended to inform larger efforts
- Compares patient characteristics rather than clinical strategy options
- Compares interventions for which the primary focus or the sole intervention is examining the role of compensated or volunteer community health workers, including patient navigators

Applications that include studies of these issues may measure and report use of any or all health services, but may not employ direct measurements of care costs. For further information, please reference our cost-effectiveness analysis FAQs.

PCORI does have an interest, however, in studies addressing questions about conditions that lead to high costs to the individual or to society. This is included in our review criterion on the potential for research to fill a critical gap in knowledge or practice. As a result, PCORI is interested in studies that:

- Examine the effect of costs on patients, such as patients' out-of-pocket costs, hardship or lost opportunity, or costs as a determinant of or barrier to access to care
- Address cost-related issues, such as the resources needed to replicate or disseminate a successful intervention
- Evaluate interventions to reduce health-system waste or increase health-system efficiency

Addressing this issue specifically, our funding announcements say that "applications that include studies of these issues without utilizing a formal cost-effectiveness analysis or directly measuring and comparing costs of care alternatives will be considered responsive and will be reviewed."

Leveraging Existing Resources

Investigators are encouraged to propose studies that leverage existing resources, such as adding PCOR to an existing large clinical trial or analyzing existing large databases that contain valuable, relevant information that may be used to answer important CER questions.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures and to include preliminary data that support the use of the proposed measures in the study population. Investigators are encouraged to consider those measures described in the Patient-Reported

Outcomes Measurement Information System (PROMIS).[15]

Studies in Rare Diseases

PCORI is interested in investigating strategies that address care for patients with rare conditions. Rare diseases are life-threatening or chronically debilitating diseases that are of such low prevalence in populations that special efforts, such as combining data across large populations, may be needed to address them. The term "low prevalence" is defined as conditions that affect fewer than 200,000 individuals in the United States or have a prevalence of less than one in 1,500 persons.

Methodological Considerations

Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards.[16] These include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These five categories are:

- Standards for Formulating Research Questions
- Standards Associated with Patient-Centeredness
- Standards on Data Integrity and Rigorous Analyses
- Standards for Preventing and Handling Missing Data
- Standards for Heterogeneity of Treatment Effect

Six other standards categories will be applicable to particular study designs and methods. The standards in each of these categories should be used for guidance when they are relevant to a particular study. These categories are:

- Standards for Data Registries
- Standards for Data Networks as Research-Facilitating Infrastructures
- Standards for Causal Inference Methods
- Standards for Adaptive and Bayesian Trial Designs
- Standards for Studies of Diagnostic Tests
- Standards for Systematic Reviews

Most of these standards should be considered minimal. Additional best practices, including relevant guidelines for conducting clinical trials developed by other organizations, should be addressed in the application for PCORI funding. To help reviewers quickly identify adherence to a particular standard, applicants must cite each relevant PCORI Methodology Standard within their application as the standard is being addressed. For example, when applicants describe the need for their proposed study within the Background section, they should indicate the particular standard to identify gaps in evidence in parentheses, such as "(RQ-1)." Please refer to the PCORI Methodology Standards Checklist for guidance.

[15] Available at http://www.nihpromis.org/.
[16] Available at http://www.pcori.org/research-results/research-methodology/pcori-methodology-report/.

Program staff members use the checklist to evaluate applications.

Applicants should specifically discuss their capacity to measure such factors as differential adherence to chosen treatments (or participation in intervention programs) that could create or explain apparent differences in the effectiveness of the alternative interventions being compared in clinical populations.

Clinical Trial Design Guidance and Consultation

PCORI realizes that some applicants may not have extensive experience conducting large, real-world, comparative, pragmatic, and patient-centered trial designs, nor in nontraditional designs such as adaptive designs. Applicants selected for funding may expect PCORI to seek and provide external expert statistical and trial design consultation in collaboration with the applicants at PCORI's expense. The trial design consultation is a new initiative under development, with the expectation that PCORI will put into place a capacity for trial design consultation in the coming year. This capacity includes experience and expertise in techniques such as trial design simulation and adaptive designs and will enhance the scientific rigor and efficiency of large pragmatic trials funded by PCORI.

Patient and Stakeholder Engagement

PCORI strongly supports active engagement of patients and other stakeholders, and is committed to their meaningful participation in PCORI-funded research. All PCORI funding applicants are expected to consult with patients and other stakeholders on their decisional dilemma and evidence needs or to reference previously documented decisional dilemmas in preparation for the submission of LOIs and applications. Applicants should describe carefully the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers and families, and other stakeholders, including clinicians and policy makers. Similarly, applicants should document why project outcomes are especially relevant to patients and can be meaningful endpoints for patients and their families.

PCORI has developed the Engagement Rubric[17] to guide the integration of patients and other stakeholders in the development, oversight, management, and implementation of research studies. Studies are also expected to adhere to PCORI Methodology Standards associated with patient-centeredness and to the PCOR Engagement Principles found within the rubric. PCORI also has a compensation framework[18] for guidance on compensating individual patient partners on the research team. These and additional resources are available in the PCORI Funding Center.

PCORI understands that applicants may not have the resources to establish formal partnerships prior to contract award, but expects applicants to discuss in their applications their plan to work with PCORI to create partnerships with national and regional patient and other stakeholder groups that will contribute to refining research questions, outcomes, protocols, and study conduct and dissemination.

Successful applicants are required to collaborate with PCORI staff upon award of the studies to establish a project SAC, or other appropriate engagement body, that is comprised of national or regional organizations that represent, at a minimum, patients and families with lived experience, relevant clinicians, payers, and health plans. Additional representation may be recommended in collaboration

[17] Available at http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf.
[18] Available at http://www.pcori.org/sites/default/files/PCORI-Compensation-Framework-for-Engaged-Research-Partners.pdf.

with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. The SAC advises and assists the research team with refining the study questions, outcomes, and protocol. It is expected that the SAC will meet regularly in-person at least two times per year and may use virtual communications at other times. These should be budgeted activities represented in the project milestones.

Populations Studied

PCORI seeks to fund research that includes populations that are diverse with respect to age, gender, race, ethnicity, geography, and clinical status. PCORI recognizes that some proposed studies may represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant in such cases to justify the study's importance in the absence of diversity.

Alternatively, PCORI is interested in the inclusion of previously understudied populations for whom effectiveness information is particularly needed, such as hard-to-reach populations or patients with multiple conditions. As a result, comparisons should examine the impact of strategies in various subpopulations, with attention to the possibility that the effects might differ across subgroups. Populations of interest include those that are less frequently studied. PCORI has developed the following list of populations of interest to guide our research and engagement efforts:

- Racial and ethnic minority groups
- Low-income groups
- Women
- Children (age 0–17 years)
- Older adults (age 65 years and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Individuals with low health literacy or numeracy and/or limited English proficiency
- LGBT persons
- Veterans and members of the Armed Forces and their families

Budget and Duration of Project

Applicants may request up to $10 million in total direct costs for a research project period not to exceed five years (not including peer review). Obligated funding is available for the duration of the project period. The maximum budget includes all research and peer-review-related costs. (Please refer to the Application Guidelines for further details.) PCORI will not cover costs for interventions that are being

compared in the proposed study. (See Appendix 3 in the Application Guidelines for details.) Applicants should submit a realistic budget and timeline reflective of the proposed study's scope and requirements. In some rare circumstances, the estimated budget may exceed $10 million total direct costs, depending on the nature of the research question, the design and analytical requirements of the proposed study, the expected size of the patient enrollment, or the complexity and frequency of the outcomes assessment. PCORI expects these to be selective cases, which include high-priority topics that are of greatest interest to PCORI. Applicants who intend to propose such studies must provide evidence of prior approval by PCORI scientific staff to exceed the budgetary limit and succinct justifications in their LOI, documenting the budget requirements with respect to the scope of the proposed research and the data collection and analysis efforts. Please note that this justification counts toward the LOI five-page limit. Any request for a project period longer than five years will be denied.

The funding mechanism for this program is a contract. A milestones and deliverables schedule, as well as specified recruitment targets, should be directly linked to and included in the proposed budget, which will be subject to negotiation at the time of award. Some of the other activities that will be considered during negotiations include:

- Developing a study protocol and manual of procedures for the intervention
- Assigning roles and responsibilities to members of the study team for implementing the project
- Forming a SAC, or other appropriate engagement body, with relevant patient and stakeholder organization representation
- Providing a detailed task-based budget with level of effort for project staff specified by task
- Obtaining clearances from all institutional and community partners, including IRB approvals
- Considering your submitted data and safety monitoring plan (DSMP) and its rationale for including or excluding a data and safety monitoring board (DSMB)
- Executing all subcontractor agreements
- Agreeing on eligible patient populations for study recruitment
- Identifying barriers to patient recruitment in the study and addressing these barriers effectively
- Structuring a feasibility phase to demonstrate the potential for successful recruitment

Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Awardees will be expected to provide corroborating evidence to receive continual funding support. Specifically, at the conclusion of the Year One performance period, PCORI will conduct a formal programmatic assessment of the study's progress and specified recruitment targets to determine the study's viability and sustainability. Only studies that are deemed satisfactory in this assessment will receive continual funding support.

Refer to the Application Guidelines[19] for a list of additional project milestones specific to the PFA.

[19] Available at http://www.pcori.org/sites/default/files/PCORI-PFA-2015-Cycle-3-Pragmatic-Studies-Application-Guidelines.pdf/.

Collaboration

PCORI is particularly interested in applications that plan to involve community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We encourage applications that will include novel collaborations with accreditation organizations, credentialing bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

Protection of Human Subjects

This component is included in the Research Plan Template and should not exceed five pages. Describe the protection of human subjects involved in your research. PCORI follows the Federal Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information please see Section 5, which is titled "Human Subjects Research Policy," from the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports,[20] which is issued by the U.S. Department of Health and Human Services. PCORI does not require that applicants comply with sections of this policy referring to requirements for federal-wide assurance or referring to standards for including women, minorities, and children. All PCORI applications involving interventions with human subjects should include a data and safety monitoring plan. Depending on the anticipated level of risk associated with the proposed study intervention(s), different approaches and options, including a full external DSMB, may be required. Applicants should provide justification of the proposed option in accordance with the expected risk to human subject research participants. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to using human subjects in research.

PCORI merit reviewers will examine plans for the protection of human subjects in all applications and may provide comments regarding the plans (see How to Evaluate Human Subjects Protections[21]). Reviewers' comments on human subjects research are not reflected in the overall application score, but may be used by PCORI staff during any potential funding negotiations. Final determinations about adequacy of human subjects protections rest with the IRB or IRBs that have jurisdiction for the study.

The awardee institution or organization, whether domestic or foreign, bears ultimate responsibility for safeguarding the rights and welfare of human subjects in PCORI-supported activities.

Required Education of Key Personnel on the Protection of Human Research Participants

PCORI requires that all applicants adhere to the National Institutes of Health (NIH) policy on education in the protection of human research participants in the conduct of research. This applies to all individuals listed in the application as key personnel. The policy and FAQs are available on the NIH website.[22]

Replication and Reproducibility of Research and Data-Sharing Plan

PCORI is committed to maximizing the utility and usability of data collected in our funded projects. This is essential to building confidence in the accuracy of these findings. PCORI supports policies to promote sharing study documentation (e.g., study protocol, programming code, and data definitions) so that

[20] Available at http://grants.nih.gov/grants/funding/424/supplementalinstructions.docx/.
[21] Available at http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/.
[22] Available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html.

other researchers can replicate the findings in other populations. Please propose a method and budget for sharing data and appropriate documentation upon request.

Recruitment

Applications should include information about the size of the potential recruitment pool of patients and the means by which this size estimate was determined (e.g., electronic medical records, claims records, clinic logs, or other administrative systems). Likewise, applications should provide evidence-based estimates of how many participants are ultimately expected in the study, based on expected recruitment; application of the study's inclusion and exclusion criteria; anticipated acceptance (or refusal) rates; and other factors, such as loss to follow-up. Such estimates must be discussed in the applications, must be specified in the milestones, will be reviewed by Merit Review Officers (MROs) and PCORI staff, and will be monitored by PCORI in the funded research.

III. How To Submit an Application

Letter of Intent

Applicants should download the Cycle 2 2016 Pragmatic Studies LOI template from the PCORI Funding Center. They must complete the document and convert it to a PDF with a five-page limit. All references should be included as in-text citations using American Medical Association (AMA) citation style. LOIs that exceed the page limit will not be reviewed. Do not upload additional documents, such as letters of endorsement or support, as part of your LOI because they are not requested at this stage. Their inclusion will result in LOI rejection without review. Please visit the PCORI Funding Center for additional applicant resources, including FAQs and required templates.

Please answer all of the questions in the LOI template. This includes the question on brief justification for the proposed cost of the study. Providing the answer, "costs not to exceed $10 million" is not sufficient. Upload your document as a PDF into PCORI Online. The deadline for LOI submission is May 4, 2016, by 5 p.m. (ET).

Letter of Intent Review

LOIs are evaluated based on the following criteria:

- Whether the topics are related to those on PCORI's own priority list (see Appendix), versus the IOM/AHRQ lists, versus other topics initiated by investigators
- Importance to current clinical decision making, as evidenced by critical gaps identified by clinical guidelines developers or recent relevant systematic reviews
- A size or scope sufficient to have a significant impact on patient outcomes or healthcare practices
- Clarity and credibility of applicants' responses to the LOI questions, as well as their justification of the need for a large pragmatic study, including the rationale for the estimated sample size, citing published estimates, including effect sizes and standard deviations and the need for rigorous comparative analysis of important subgroups

- Prior relevant experience
- Programmatic fit and balance, considering whether the application significantly overlaps with concurrent applications or previously funded studies or, conversely, whether the application fills a gap in PCORI's portfolio, considering such characteristics as disease category, topics, priority population, and methodologies
- Adherence to the administrative and formatting requirements listed in the Application Guidelines, especially the five-page limit for the LOI

LOIs are reviewed qualitatively; they are not scored. Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. LOIs are reviewed by at least two PCORI staff and are not scored during review. Notification of denial or approval to submit a full application will occur no later than June 10, 2016. Please refer to the Application Guidelines in the PCORI Funding Center for due dates and information on how to submit your LOI in PCORI Online.

All applicants, including those resubmitting from previous Pragmatic Studies PFA cycles, are required to submit a competitive LOI for PCORI staff to review. This allows PCORI to determine whether proposed revisions and changes made to specific aims or methodological approaches from the original applications align with PCORI's evolving strategic priorities.

If you are invited to submit an application, do not make significant changes to your proposed project without consulting a program officer. For example, you should not revise your major aims and study design. Any significant changes are grounds for removal from the review process.

Note: A Principal Investigator (PI) can only submit one LOI per PFA. However, an individual listed as a PI on one LOI may be listed as and serve in another role (e.g., co-investigator or consultant) on other LOIs within the same PFA during the same cycle. A PI may submit multiple LOIs to different program PFAs in a cycle, but the PI must ensure that the research topics and projects are not similar. If a PI submits an LOI to multiple program PFAs, LOIs that exhibit scientific overlap or that appear to be duplicate submissions will be disqualified. PCORI will contact the PI and provide him or her with an opportunity to choose which PFA he or she would like to apply to. This applies to single and dual-PI submissions.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the Overview in this PFA and in the PCORI Funding Center.[23]

PCORI Online System

To submit an application, you must register in PCORI Online[24] and submit both an LOI and an application for each cycle to which you are applying.

Applicant Resources

PCORI Funding Center	http://www.pcori.org/Cycle-2-2016-pragmatic-studies/

[23] Available at http://www.pcori.org/funding-opportunities.

[24] Available at https://pcori.fluxx.io/.

PCORI Online System	pcori.fluxx.io
PCORI Funding Awards	pcori.org/pfaawards

IV. Merit Review

PCORI's merit review process is designed to support the following goals:

- To identify applications that have the strongest potential to help patients, caregivers, clinicians, and other stakeholders make informed decisions to improve patient outcomes
- To implement a transparent, fair, objective, and consistent process to identify these applications
- To elicit high-quality feedback that reflects a diversity of perspectives to ensure that the research funded by PCORI reflects the interests and views of patients and those who care for them and that it meets the criteria for scientific rigor
- To fund projects that fill important evidence gaps and have strong implementation potential
- To regularly evaluate and continually improve the merit review process and policies in support of PCORI's mission

PCORI merit review is a multiphase process that includes PFA development; staff evaluation of LOIs; preliminary review of full applications by review panels; in-person panel discussion of a subset of full applications (identified by PCORI's Research Priority Area Program staff, based on the preliminary review and program priorities); Selection Committee recommendation of applications for funding; and finally, Board award approval.

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Note that applications may be eliminated from the review process for administrative or scientific reasons (e.g., nonresponsiveness). An application may be administratively withdrawn if it is incomplete, is submitted past the stated due date and time, or does not meet the formatting criteria outlined in the Application Guidelines, in the PCORI templates, and in PCORI Online. An application may be scientifically withdrawn if it is not responsive to the guidelines as described in this PFA, describes research that is not comparative, includes cost-effectiveness analysis, or otherwise does not meet PCORI programmatic requirements.

PCORI Merit Review Officers (MROs) recruit each panel based on the number and topic areas represented by invited LOIs. MROs recruit the panel chair, scientist reviewers who are subject matter experts, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that all understand the programmatic and organizational goals of review.

Below are PCORI's merit review criteria. PCORI's merit review panels use these criteria during the preliminary and in-person review phases to evaluate and score all submitted applications:

Criterion 1. Potential for the study to fill critical gaps and generate actionable evidence
The proposal should address the following questions:

- Does the application convincingly describe clinical burden?
- Does the application identify a critical gap in current knowledge as noted in systematic reviews, clinical practice guidelines, or previous research prioritizations?
- Does the study identify variations in practice patterns that suggest clinical uncertainty?
- Does the application describe the decisional dilemmas experienced by patients and other stakeholders that this study would address?
- Does the study/application have the potential to fill these evidence gaps and inform decision making for key stakeholders (provide example)?

Criterion 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care
The application should describe how evidence that is generated from this study could be adopted into clinical practice and delivery of care by others. The application should address the following:

- Does the application identify potential end-users of study findings, such as local and national stakeholders, and does it incorporate strategies to engage these end-users in dissemination of outcomes? Does the application provide information that supports a demand for this kind of a study from end-users?
- How likely is it that positive findings could be reproduced by others, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder adoption of the intervention by others, including generalizability to other health systems or treatment settings, or complexity of the intervention, as applicable.
- Does the application describe a plan for how study findings will be disseminated beyond publication in peer review journals and national conferences?
- Can the study be readily adopted in other settings with minimal adaptations or complexities?

Criterion 3. Scientific merit (research design, analysis, and outcomes)
The application should show sufficient technical merit in the research design to ensure that the study goals will be met.

- Does the proposal describe a clear conceptual framework to anchor the background literature and inform the design, key variables, and relationship between interventions and outcomes being tested?
- Does the application provide justification that the outcome measures are validated and appropriate for the population?
- Does the research plan describe rigorous methods that demonstrate adherence to PCORI's Methodology Standards?
- Are each of the comparators (e.g., active intervention arm and comparator arm) clearly

described and well justified? If usual care is one of the arms, is it sufficiently justified and will it be sufficiently measured?

- Are the sample sizes and power estimates based on careful evaluations of the anticipated effect size? Is the effect size adequately justified in relation to the size or dose of the intervention and the research design (e.g., cluster randomized design)?
- Is the study plan feasible?
    - Is the project timeline realistic, including specific scientific and engagement milestones?
    - Are planned start-up times realistic, including training of personnel? Have the investigators considered and addressed the potential barriers to study initiation within the targeted clinical setting?
    - Is the strategy for recruiting participants feasible?
    - Are assumptions about participant attrition realistic and are plans to address patient or site attrition adequate?

Criterion 4. Patient-centeredness

The application should demonstrate that the study focuses on improving patient-centered outcomes and employs a patient-centered research design (i.e., design is informed or endorsed by patients). *(Note: a study can be patient-centered even if the end-user is not the patient, as long as patients will benefit from its information.)* The proposal should address the following:

- Does the application include a thorough description about which outcomes (both benefits and harms) are important to patients? Are those outcomes included in the study plan?
- Are the interventions being compared in the study available to patients now and are they the best options for comparison (including whether they would be chosen by patients and their healthcare providers for managing the condition being studied)?

Criterion 5. Patient and stakeholder engagement

The proposal describes plans for the engagement of and collaboration with relevant stakeholders (e.g., patients, caregivers, clinicians, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, policy makers, and training institutions) in the conduct of the study. PCORI understands that applicants may not have the resources to establish formal partnerships prior to contract award, but expects applicants to discuss in their application their plans to work with PCORI to create the types of partnerships with national and regional patient and other stakeholder groups that will contribute to refinement of research questions, outcomes, protocols, and study conduct and dissemination.

Successful applicants shall plan to work in collaboration with PCORI staff upon award of the proposed studies to establish a project SAC, or other appropriate engagement body, that is comprised of national or regional organizations that represent, at a minimum, patients and families with lived experience, relevant clinicians, payers, and health plans. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant

stakeholders, including scientific and methodological experts. The SAC serves to advise and assist the research team with further refinement of the study questions, outcomes, and protocol. It is expected that the SAC will meet regularly in person at least two times per year and may use virtual communications at other times. These are to be budgeted activities and are to be represented in the project milestones. The proposal should address the following:

- Does the application provide a well-justified and comprehensive description of plans to build an interdisciplinary study team that includes appropriate patient and stakeholder representation?
- Are the plans for a strong partnership among scientists, patients, and others throughout the entire research process (e.g., finalizing questions, identifying outcomes, monitoring study, dissemination, and implementation) appropriate and tailored to the study?
- Are the scope, form, and frequency of patient and stakeholder involvement planned throughout entire research process sufficient to support the study goals?
- Are the roles and the decision-making authority of all study partners clearly described?
    - (Dual-PI option only) Does the leadership plan adequately describe and justify roles/areas of responsibility of the PIs?
- Are the organizational structure and resources appropriate to carry out the project?

In-Person Review

During preliminary review, all administratively and scientifically compliant applications are evaluated and scored based on PCORI's merit review criteria, including evaluation of adherence to PCORI's Methodology Standards. During the in-person review, merit reviewers meet to discuss the applications, further clarify the merits of the proposed research, and identify areas for improvement. Each application is assigned a score based on the content of that discussion. The chair and a PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review according to the standards outlined in the PFA.

In-Person Applicant Presentation

Based on the results of the merit review and PCORI's programmatic priorities, a selective subset of applicants whose proposed studies are deemed to be highly meritorious or aligned with PCORI's strategic priorities will be invited to the second phase of project presentation and follow-up discussions with PCORI on study methodological and execution issues. Applicants are also expected to address concerns and critiques identified in the merit review in this presentation. The selected applicants will be notified of the logistics, including travel arrangements, for this presentation in separate communications.

Post-Panel Review

After the in-person meeting, PCORI program staff evaluate final merit review panel scores and comments, identify duplication or synergy among funded projects, and consider the fit of applications within the programmatic vision. Program staff members then recommend projects to a Selection Committee, which is comprised of members of PCORI's Board of Governors. The Committee considers

recommendations and works with staff to identify a slate of applications for possible funding based on merit review scores, programmatic balance and fit, and PCORI's strategic priorities. This slate is then proposed to PCORI's Board for its consideration and approval.

Summary Statements and Funding Recommendations

Summary statements are provided to applicants approximately two weeks before funding decisions are announced. The applicant will receive a summary statement inclusive of:

- In-person panel discussion notes
- Final average overall score
- Preliminary reviewer critiques
- Application quartile, which provides information for applicants to understand how they did relative to other discussed applications.

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to PCORI's Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to PCORI's Board for approval. Applicants to this current cycle's PFA will receive summary statements in early January 2017 and notification of the funding status of their application no later than January 2017.

Board of Governors Approval

The PCORI Board will consider the selected applications, factoring in the total available funds allotted for this announcement and programmatic needs. PCORI will inform applicants of the Board's decision no later than January 2017.

Appendix: Research Topics of Interest to PCORI

PCORI Priority Topics

Please note that these topics are not listed in rank order.

1. **Compare the effectiveness and safety of alternative antibiotic regimens in the empiric outpatient treatment of adults with community-acquired pneumonia. Comparisons of interest include fluoroquinolone-based antibiotics versus other antibiotic regimens and varying durations of antibiotics. Studies should address effectiveness in distinct subpopulations (e.g., patients with chronic conditions, patients with immunosuppression, and the elderly).**
2. **Compare the effectiveness and safety of Screening, Brief Intervention, and Referral to Treatment (SBIRT) for adolescent alcohol abuse in different settings (school-based versus primary-care-based), using different delivery modes (in-person, remote, computer-based) or providers (physician, mental health specialist, nurse, staff worker, peer).**
3. **Surgical options for hip fracture in the elderly**
    - Compare the effectiveness of different surgical treatments in elderly patients with hip fractures in terms of functionality and other patient-centered outcomes.
4. **Pelvic floor mesh implants**
    - Compare the effectiveness of the use versus non-use of currently Food and Drug Administration (FDA)-approved surgical mesh in reparing pelvic floor dysfunction in terms of infections, urinary or fecal incontinence, bowel injury, pain, sexual function, and other patient-centered outcomes.
    - Compare the effectiveness of different types of currently FDA-approved mesh using different surgical techniques in terms of the outcomes mentioned above.
5. **Treatment strategies for patients with autism spectrum disorder**
    - Perform a large-scale, multicenter, randomized control trial or well-designed observational study with long-term follow-up comparing the effectiveness of applied behavioral analysis (in children 2–5 years old) with other accepted treatments for alleviating externalizing and internalizing behavior and improving social skills, parent-child interactions, family well-being, and other patient-relevant outcomes (e.g., changes in core and associated symptoms). Studies should be sufficiently large to permit rigorous analysis of HTE related to provider, parent, family, child, intervention, and other characteristics.
6. **Benefits and harms of continuous ambulatory peritoneal dialysis compared with hemodialysis (daily or intermittent home, or conventional in-center) in patients with end-stage renal disease and in important patient subgroups (e.g., by age, race, ethnicity, cardiovascular risk, or other comorbidities)**
7. **Multicomponent interventions to reduce initiation of tobacco use and promote cessation of tobacco use among high-risk populations with known disparities**
    - Compare the effectiveness of clinical interventions to reduce initiation of tobacco use and promote tobacco cessation among populations with known tobacco disparities, including high-risk and vulnerable populations.
8. **Teledelivery of evidence-based interventions for anxiety and depression**

- Compare the effectiveness of different delivery approaches to evidence-based, non-pharmacological, Internet-based treatments for mild to moderate depression and anxiety conditions.
- PCORI is particularly interested in research that compares the effectiveness of different levels of intensity of monitoring, guidance or feedback, and of different types of professionals (e.g., technicians, clinicians, and mental health clinicians) providing such monitoring, guidance or feedback for Internet-based non-pharmacological treatment.
- Specific subgroups of interest include patients with differing severities of the target condition(s), as well as patients at risk of reduced access to care (e.g., rural populations, low-income individuals, and racial and ethnic minorities).

9. **Integration of mental and behavioral health services into the primary care of persons at risk for disparities in health care and outcomes**
    - Compare the effectiveness of care models that integrate mental and behavioral health care—including substance abuse treatment—into the primary care provided by community health centers and other relevant settings, with the goal of reducing disparities in care (i.e., access to mental and behavioral health services and the diagnosis and treatment of mental and behavioral health conditions) and improving health outcomes among underserved populations, including racial and ethnic minorities, low-income individuals, and rural populations.
10. **Treatment strategies for adult patients with migraine headache**
    - Compare pharmacologic and non-pharmacologic strategies to prevent the transition from episodic to chronic migraine.
    - Compare pharmacologic and non-pharmacologic strategies for treating individual headache episodes on the incidence of medication-overuse headache in patients with high-frequency episodic or chronic migraine.
11. **Treatment strategies for symptomatic osteoarthritis (OA), including joint replacement**
    - Compare methods for deciding when to have surgery for OA; use outcomes such as patient satisfaction, functional status, clinical status, and quality of life.
    - Compare the effectiveness of strategies for engaging early-stage OA patients to adopt behaviors that can prevent OA progression and disability.
    - Compare different nonsurgical therapies (e.g., pharmacotherapy, injections, physical therapy or exercise, weight loss alone and in combination with other therapies, and complementary medicine alternatives) to prevent OA progression and disability. The studies should seek to identify heterogeneity of treatment response among important subgroups of patients.
12. **Improving outcomes in mothers and babies at risk for disparities by comparing evidence-based models of perinatal care**
    - Compare the effectiveness of multicomponent systems interventions, such as evidence-based models of perinatal care, aimed at improving outcomes like pre-term birth and low birth weight, for mothers and babies at risk for health disparities.

13. **Clinical interventions to reduce nontraumatic lower-extremity amputations in racial or ethnic minorities and low-income populations with diabetes: Does expert, protocol-driven, team-based care reduce the risk of nontraumatic lower-extremity amputations compared with existing and established guideline-based care for racial or ethnic minorities and low-income populations with diabetes?**
    - Team-based care could include, for example, acute-care teams with patient teams; staff working as a team (triage staff, etc.); use of standing orders, electronic medical records (EMRs), or hardcopy templates and reminders; knowledge and use of community resources; EMR registry functionality; empanelment; group visits; and novel outpatient-based interventions with rapid response from the outpatient setting.
14. **Compare the effectiveness of diverse models of comprehensive support services (e.g., incorporation of wrap-around services, alternative providers, and technology) for infants and their families or caregivers after discharge from the neonatal intensive care unit.**
    - PCORI is particularly interested in studies that would help bridge the gap between acute and post-acute care.
    - Proposed research should plan, justify, and adequately power the study to address prespecified patient subgroups (e.g., urban, rural, and socioeconomically challenged).
15. **Compare the effectiveness of multidisciplinary rehabilitation programs (e.g., community-integrated rehabilitation: neurobehavioral, residential community, comprehensive holistic, and home-based services) for moderate to severe traumatic brain injury in nonmilitary or veteran adults.**
    - PCORI is particularly interested in studies that would help bridge the gap between acute and post-acute care, and examine the impact on a patient's functional status.
    - Proposed research should plan, justify, and adequately power the study to address prespecified patient and clinical subgroups (e.g., severity, injury type, impairment level, and social support).
16. **Compare the effectiveness of pharmacist- or nurse-led interventions or health information technology-based interventions to enhance primary-care physician management of patients suffering from chronic, noncancer pain.**
    - Outcomes of primary interest include the impact of such evidence-based strategies on improving patient functioning, patient quality of life, and reducing opioid dependence.
17. **Compare the effectiveness of alternative delivery models (e.g., primary care, schools, and mobile vans) versus the dentist's office in preventing dental caries in children in medically underserved areas.**
18. **Compare the effectiveness of strategies aimed at integrating pharmacists or pharmacy services into patient care (e.g., primary/acute care and pharmacy integration, pharmacist-provided preventive care, pharmacist-provided medication management or reconciliation services, and other pharmacy-specific collaborative care models) on patient-centered outcomes (e.g., reduction in inappropriate medication use and polypharmacy, access to preventive vaccines, reduction in adverse events and hospital readmissions, and improved disease- or condition-specific outcomes).**

19. **Compare the effectiveness of evidence-based screening and primary prevention approaches, including different modes and settings (e.g., universal screening versus targeting at-risk individuals, virtual versus face-to-face screening, and within primary-care setting versus school-based) at minimizing suicidality among adolescents and improving other patient-centered outcomes.**

Institute of Medicine 100 Initial Priority Topics for Comparative Effectiveness Research[25]

AHRQ Future Needs Projects[26]

[25] Available at http://iom.edu/~/media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx/.
[26] Available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=521.