Cycle 3 2015 Funding Cycle

PCORI Funding Announcement: Clinical Strategies for Managing and Reducing Long-Term Opioid Use for Chronic Pain

Published October 12, 2015

This PCORI Funding Announcement applies to the funding cycle that closes on February 16, 2016 at 5 p.m. (ET). Application guidelines, templates, and other resources are available at http://www.pcori.org/2015-Cycle-3-Opioid-Treatment.
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.”

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### Overview

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<th>Published</th>
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<tr>
<td>Letter of Intent Due</td>
<td>November 12, by 5 p.m. (ET)</td>
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Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than December 18, 2015.

<table>
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The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund studies that compare two or more alternatives for addressing the management and reduction of long-term opioid use for chronic pain.

Proposed studies must address clinical and healthcare delivery choices faced by patients, their caregivers, clinicians, or delivery systems. Proposed studies must compare two or more active interventions. They must involve patient populations that are representative of the US population, and they must 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, and/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 refer to previously documented decisional dilemmas. Successful applicants are required to work in collaboration with PCORI staff upon award of the proposed studies to establish a project Study Advisory Committee (SAC) (or other appropriate engagement body, see the [Clinical Strategies for Managing and Reducing Long-Term Opioid Use for Chronic Pain FAQs](http://www.pcori.org/2015-Cycle-3-Opioid-Treatment)) 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. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, among them scientific and methodological experts. The SAC serves to advise and assist the research team with further refinement of the study questions, outcomes, and protocol.

PCORI strongly encourages applicants to propose study designs that use randomization, either of individual participants or clusters, to avoid bias due to confounding. **Note that this funding program does not support applications that conduct cost-effectiveness analysis, systematic reviews, or development or evaluations of shared decision-making or decision-support tools.**

The proposed studies must address at least one of the two priority research questions identified in the main body of the PFA.

| Applicant Resources | See [http://www.pcori.org/2015-Cycle-3-Opioid-Treatment](http://www.pcori.org/2015-Cycle-3-Opioid-Treatment) |
### Key Dates

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<td>Online System Opens</td>
<td>October 12, 2015</td>
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<tr>
<td>Applicant Town Hall Session</td>
<td>October 28, 2015, 2 p.m. – 3:30 p.m. (ET)</td>
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<tr>
<td>Letter of Intent (LOI) Deadline</td>
<td>November 12, 2015, by 5 p.m. (ET)</td>
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<td>Screening Notification</td>
<td>December 18, 2015</td>
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<td>Application Deadline</td>
<td>February 16, 2016, by 5 p.m. (ET)</td>
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<td>Merit Review Dates:</td>
<td>May 2016</td>
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<td>Awards Announced:</td>
<td>July 2016</td>
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<tr>
<td>Earliest Project Start Date</td>
<td>September 2016</td>
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### Maximum Project Budget (Total Direct Costs)

- $10 million

### Maximum Research Project Period

- 3–5 years

### Funds Available Up to

- $40 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 unit of local, state, or federal government. All US applicant organizations must be recognized by the Internal Revenue Service. Nondomestic components of organizations based in the United States and foreign organizations may apply as long as there is demonstrable benefit to the US healthcare system and US efforts in the area of patient-centered research can be clearly shown. 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

### Contact Us

**Programmatic Inquiries:** Contact the PCORI Helpdesk via email (sciencequestions@pcori.org), phone (202-627-1884), or complete the Research Inquiry Form (http://www.pcori.org/content/research-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 prior to an LOI or application deadline.

**Administrative, Financial, or Technical Inquiries:** Contact the PCORI Helpdesk at pfa@pcori.org. PCORI will provide a response within two business days. Note that during the week of the application deadline, response times may exceed two business days. One week prior to an application deadline, applicants may also call the PCORI Helpdesk (202-627-1885). Applicants are asked to plan accordingly. It is the applicant’s responsibility to submit the application on or before the application deadline.

### Other

Deadlines are at 5 p.m. (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday.
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I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to support patient-centered comparative clinical effectiveness research (CER) that addresses important questions regarding clinical strategies for managing and reducing long-term opioid use for chronic pain. Through this PCORI funding announcement, PCORI seeks to fund studies that have a sufficient sample size to address the research questions noted below and that will generate information that is readily generalizable to the broader population.

Competitive applications must address at least one of the two priority research questions described in this funding announcement.

The two priority research questions are:

- Among patients with chronic noncancer pain on moderate/high-dose long-term opioid therapy, what is the comparative effectiveness of strategies for reducing/eliminating opioid use while managing pain?
- Among patients with chronic noncancer pain on moderate/low-dose long-term opioid therapy, what are the comparative effectiveness and harms of strategies used to limit dose escalation?

Additionally, applications should:

- Focus on patient populations with chronic noncancer pain who have utilized opioids for longer than three months. All chronic pain disorders outside of cancer pain or pain at end of life are considered chronic noncancer pain
- Have strong endorsement and study participation by relevant patient organizations, professional organizations, and payer or purchaser organizations
- Take place within typical clinical care and community settings
- Have a sufficiently large study population to enable precise estimates of effect sizes and to support evaluation of potential differences in intervention effectiveness in patient subgroups such as those with comorbid mental health disorders or past/present substance abuse, and type of pain
- Compare the effectiveness\(^1\) of two or more alternatives for improving patient-centered outcomes

Background

Chronic pain, defined as pain lasting longer than three months or past the time of normal healing, is highly

\(^1\) Effectiveness is the extent to which an intervention does more good than harm in a broad mix of patients when provided under the usual circumstances of healthcare practice (modified from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1116525/).
prevalent and a leading cause of disability and decreased quality of life.\textsuperscript{2,3,4} The Institute of Medicine estimates that more than 100 million Americans—approximately one-third of the US population—suffer from chronic pain. The societal costs of pain top $560 billion per year from medical expenses, disability, and lost wages and productivity.\textsuperscript{5} Opioids are widely accepted for the treatment of cancer-related chronic pain in the palliative care setting; however, their use for other types of chronic pain remains controversial.\textsuperscript{6} Despite the stark absence of high-quality evidence to demonstrate the safety and effectiveness of long-term opioid therapy for the management of chronic pain, between five million and eight million Americans use opioids for chronic pain management.\textsuperscript{4,5} Over the last 20 years, opioid prescriptions have increased by 300 percent, with an estimated 201.5 million dispensed in 2009.\textsuperscript{7,8} Recent evidence reviews have also found that most clinical and policy decisions on the use of long-term opioid therapy for chronic pain, including US and Canadian guidelines recommendations, are based on weak or insufficient evidence and consensus opinion.\textsuperscript{6,8,9}

Although there is little evidence regarding the effectiveness of chronic opioid therapy in improving function and pain, mounting evidence suggests that opioids may be associated with important harms,
including overdose, abuse, addiction, and diversion.\textsuperscript{10,11,12,13,14,15,16} From 2001 to 2013, there was a three-fold increase in the total number of deaths from prescription opioids; in 2010, there were more than 600,000 emergency department visits due to opioid misuse and abuse.\textsuperscript{13,17} Other common adverse events from opioid therapy include sedation, impaired cognitive function, depression, constipation, and bladder dysfunction.\textsuperscript{8,18}

While findings from randomized trials do suggest that opioids may provide pain relief in the short term, most placebo-controlled randomized controlled trials (RCTs) were shorter than 16 weeks.\textsuperscript{8} No large-scale studies have assessed strategies for managing and reducing chronic opioid use in a real-world setting. Additional rigorous research is needed to inform physician and patient decision making. Results from comparative studies have the potential to be rapidly implemented, affect clinical decision making, and to guide clinician opioid-prescribing practices, resulting in a reduction in the harms and risks associated with long-term opioid therapy for the treatment of chronic pain.\textsuperscript{8,19}

Evidence Gap

A recent systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ) for the National Institutes of Health Pathways to Prevention Workshop on the effectiveness and risks of long-term opioid therapy identified large and persistent evidence gaps with regard to the use of chronic opioid therapy. Given the lack of evidence supporting the long-term use of opioids, clinical decision making is primarily guided by experience rather than evidence.

Specifically, the review found that no studies of opioid or non-opioid alternative therapies (e.g., physical therapy, behavioral therapy, or proven complementary and alternative medicine approaches) have

evaluated outcomes related to pain, function, or quality of life for longer than one year. Likewise, no studies examined the comparative effectiveness of opioids plus non-opioid interventions versus opioids or non-opioid interventions alone for the patient-centered outcomes (i.e., pain, function, quality of life).

Per the AHRQ Evidence Review, there is also limited evidence on the effectiveness of different opioid dosing strategies. Of the few studies in this area, there was only one small study of 10 participants on decreasing doses or tapering off versus continuation, but results from the crossover trial cannot be applied to the general population. Two studies focused on different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal, and likelihood of opioid cessation, but were classified as poor-quality, nonrandomized prospective observational studies. Neither study evaluated effects of discontinuing opioids on pain, function, quality of life, or withdrawal symptoms. All studies had methodological shortcomings and showed no clear differences on outcomes related to pain and function. Additionally, there were no studies on the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal for patients on long-term opioid therapy. Finally, no studies have examined how treatment effectiveness may vary based on cause of pain, patient demographics, or comorbidities.

The systematic review concluded that there were insufficient data on the long-term effectiveness of chronic opioid therapy. However, increasing evidence does support the increased risk for harm associated with the use of chronic opioid therapy. A number of studies have noted an association between higher opioid doses and risk of an opioid use disorder and overdose. The likelihood for developing an opioid use disorder increased 122-fold for patients on chronic high-dose opioids (>120 mg/day morphine equivalent dose [MED]), compared to patients who were not prescribed opioids. Overdose risk increased by almost 1.5 at doses between 20 to 49 mg/day MED and increased almost 9-fold for doses greater than 100 mg/day MED. These studies also identified that, for patients on doses between 50–100 mg/day...
MED, the risk of overdose was 2.2 to 4.6 times higher than it was at lower doses. Research also suggests an association between patients on higher-dose opioids and mental health disorders, substance use disorder, and opioid misuse.\textsuperscript{24,29}

Based on the findings from the systematic review, additional research is needed to understand the long-term patient outcomes, the risks of opioid abuse, and the effects of different opioid prescription methods and risk mitigation strategies. Importantly, the review also identified key questions regarding the effectiveness of treatment options for patients with comorbid disorders, including mental health disorders and past/current substance use disorders and different causes of pain.

Research Topic Prioritization

PCORI relies on input from multiple stakeholders to set its research priorities. Members of its advisory panels include patients, clinicians, researchers, purchasers, payers, industry, and other healthcare stakeholders. Staff identified the use of long-term opioids for chronic pain as an important topic, which PCORI’s Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options then ranked as a high priority when it met on April 9, 2015. PCORI then convened a large multi-stakeholder workshop on June 9, 2015, to provide further input on whether specific opioid CER questions could be addressed by PCORI-funded research. Approximately 47 invited stakeholders attended in person. The meeting was open to the public via teleconference and webinar.

Questions for discussion were submitted by workshop participants prior to the meeting and refined by PCORI staff to yield a total of 24 comparative effectiveness questions that were reviewed by two opioid panels. Panel 1 focused on pharmacologic treatment options and dosing strategies, while Panel 2 focused on studies that include multimodal therapy, risk mitigation strategies, and opioid dependency.

Questions were discussed, revised, and ranked by the participants during breakout sessions at the workshop. PCORI staff used the results of this ranking to help inform its selection of two high-priority research questions. Staff further refined and modified the draft questions in consultation with the Scientific Oversight Committee members. These questions were reviewed and approved by PCORI’s Board of Governors (Board) as the basis for this targeted funding announcement.

Based on the key gaps noted above, input from our large multi-stakeholder workshop, and the Scientific Oversight Committee, PCORI is interested in applications that respond to the following comparative effectiveness questions:

The two priority research questions are:

- Among patients with chronic noncancer pain on moderate/high-dose long-term opioid therapy, what is the comparative effectiveness of strategies for reducing/eliminating opioid use while managing pain?
- Among patients with chronic noncancer pain on moderate/low-dose long-term opioid therapy,
what are the comparative effectiveness and harms of strategies used to limit dose escalation?

Priority Research Questions

Applications should propose pragmatic clinical trials or well-designed observational studies that address one or more of the following two priority research questions. Pragmatic trials are designed to maximize applicability of the study’s results in routine clinical practice. They are conducted in routine clinical care settings, and in many cases, they must be relatively large, in part to be able to demonstrate differences in comparative effectiveness between different patient subgroups. They should impose fewer constraints on usual practice than traditional RCTs. PCORI strongly encourages randomized controlled trials for this targeted funding announcement.

Among patients with chronic noncancer pain on moderate/high-dose long-term opioid therapy, what is the comparative effectiveness of strategies for reducing/eliminating opioid use while managing pain?

PCORI is interested in receiving applications that propose to compare distinctly different clinical strategies, which could include structured dose reduction protocols and nonopioid therapies (pharmacological or nonpharmacological options) among patients on moderate/high-dose long-term opioid therapy. Given that the definition of moderate to high-dose opioid therapy has varied in previous guidance (e.g. 90mg MED, 100mg MED, to 120 mg MED), applicants should provide a strong rationale along with supporting evidence for the selection of a particular threshold definition. Studies that integrate pharmacological options may include nonsteroidal anti-inflammatory drugs (NSAIDS), antidepressants, mood stabilizers, and others. Nonpharmacological options may include physical therapy, behavioral therapy, commonly used complementary and alternative medicine approaches, and others. As appropriate and necessary, studies should include risk mitigation strategies across all treatment comparators. Applicants may propose alternative nonopioid interventions not noted above.

Applicants should provide a convincing explanation for the relevance of the treatment options being compared in the proposed study, citing evidence gaps that are justified on the basis of systematic reviews. PCORI is interested in studies that include important comorbidities such as mental health disorders and past or current substance use disorders. Other key patient subgroups include groupings based on the source or type of pain. Applications should include information about the efficacy of the interventions compared and provide clear justification that the interventions represent a realistic choice faced by patients and clinicians. In the absence of strong efficacy data, pilot data should be provided.

Among patients on moderate/low-dose long-term opioid therapy, what are the comparative effectiveness and harms of strategies used to limit dose escalation?

PCORI is interested in studies that compare alternative strategies for limiting dose escalation among patients on moderate/low-dose chronic opioid therapy. We encourage comparisons that may include combinations of: nonopioid interventions, opioid rotation, dosing strategies, or risk mitigation strategies. Applicants should provide a convincing explanation for the relevance of the clinical options being compared, including efficacy data. Pilot data should be provided when strong efficacy data are not available. Subgroup analyses should include important comorbidities such as mental health disorders, past or current substance use disorders, and type of pain.
Outcomes

For both of the priority questions, applicants should consider a broad range of outcomes that are important to patients. In addition to measures of opioid dose, studies must include measures of pain control and function. Other key outcomes include pain control at 6 and 12 months, opioid dose at 6 and 12 months, functional status, health-related quality of life, opioid misuse, safety, mortality, medical side effects of treatment, depression score, and health services use. Applicants should consider a minimum one-year follow-up for main outcome measures.

Funds Available

PCORI seeks to fund studies that address each of the two priority questions but does not commit to such. PCORI will consider the merit of each submitted application and its responsiveness to each priority question as well as programmatic requirements and portfolio balance when making final funding recommendations.

PCORI has devoted up to $40 million in total costs under this PCORI PFA to fund high-impact studies related to the management of long-term opioid therapy for chronic pain. The proposed budget for individual studies may range up to $10 million in total direct costs as appropriate, depending on the specific priority research question or questions the study proposes to address. The maximum project period is five years.

Given the significant treatment costs associated with many opioid and nonopioid therapies (including nonpharmacological options), the applications must specifically address, in the context of the proposed studies, the support from payers, health plans, industry sponsors, or others in covering the study interventions and non-study protocol-related clinical costs and services rendered in the care processes. Because high levels of out-of-pocket costs would be likely to drive down the use of particular nonpharmacologic therapies, investigators must also explain how this would be handled. Of particular concern would be different levels of co-payment between two arms in a comparative study. Ideally, cost-sharing barriers will be eliminated or equalized in the study arms. If the study design does not allow for either option, the applicant should describe why and should also discuss how differences in co-payment costs will be accounted for in the study analysis. Please refer to Appendix 2 in the Application Guidelines for details on costs that PCORI will cover.

It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, recruitment needs, length of follow-up, and analytic complexity. PCORI seeks efficient studies and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of treatment-related costs. A prolonged recruitment period is not an acceptable rationale for longer studies.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet all of the following requirements:
• Address a research gap that has been substantiated by an existing (recent or updated) rigorously conducted systematic review or specifically emphasized by an official professional society’s clinical practice guideline(s)

• Demonstrate consultation with patients and other stakeholders, or their representative groups, or reference previously documented decisional dilemmas, in order to determine whether the study is answering a critical question—one that, if adequately answered, would substantially improve decision making

• Receive endorsement by relevant patient organizations, clinician organizations, payer/purchaser consortia, or life sciences industry representatives as potentially 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; in addition, the sample size must support testing of a priori hypotheses related to potential differences in effectiveness in relevant patient subgroups (heterogeneity of treatment effect [HTE])

• Examine diverse populations receiving care in real-world settings

• Have strong interest from and support by host delivery systems and clinical care settings

• Specify broad and simple eligibility criteria that will allow wide generalization of results while attending appropriately to any ethical concerns of excess risk in some patient subgroups

• Compare interventions that are known to be efficacious, effective, or commonly in use, and can be implemented in real-world settings

• Include patient-reported outcomes (PROs) as outcome measures, when appropriate

• 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. 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

• Adhere to all applicable PCORI Methodology Standards\(^{30}\)

• Adhere to current best practices (standardized inclusion and exclusion criteria; proper randomization; techniques to minimize potential for missing data; appropriate safety monitoring, including establishment of a data and safety monitoring board [DSMB] or indication of why such a board is unnecessary)

• Include a plan for sharing de-identified data

\(^{30}\) Available at http://www.pcori.org/research-results/research-methodology.
To carry out pragmatic studies, readily adopt the findings in a real-world setting, and maximize the efficient use of resources, care must be taken to prevent these trials from becoming more complex and onerous than necessary. The applicant is encouraged to be creative and consider innovative strategies such as the following, 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 the full applications
- Carefully describe the pertinent evidence gaps and explain 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 solely for study-assessment purposes; capture PROs during office visits, electronically, or via phone)
- Design the study so that the conduct can be integrated, as seamlessly as possible, with routine clinic or office operations
- 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. Specifically, PCORI encourages proposals that utilize the infrastructure of the National Patient-Centered Clinical Research Network (PCORNet).
- 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) within a tightly-protocol-controlled research setting (as opposed to more real-world, pragmatic CER)
- Conducts a formal cost-effectiveness analysis
- Directly compares the costs of care between two or more alternative approaches to providing care
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or study of biological mechanisms
- Evaluates new or existing decision support tools; this includes the development and evaluation of a decision support or shared decision tool or system for patients, clinicians, or both patients and clinicians
- Develops clinical prediction or prognostication tools
Proposals that include studies of these issues may measure and report utilization of any or all health services, but may not employ direct measurements of costs of care. For further information, please reference our cost-effectiveness analysis FAQs.

PCORI does have an interest, however, in studies that address questions about conditions that lead to high costs to the individual or to society. This is included in our review criterion on impact of the condition on the health of individuals and populations. Thus, 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 “proposals 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.”

Furthermore, PCORI discourages proposals in the following categories and is likely to deem them nonresponsive:

- Study of the natural history of disease
- Instrument development
- Pharmacodynamics
- Fundamental science or study of biological mechanisms
- Establishing efficacy for a new clinical strategy
- Pilot studies intended to inform larger efforts
- Comparisons of patient characteristics rather than clinical strategy options

Features of Patient-Centered Outcomes Research (PCOR)

PCOR 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, or palliative care 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 people notice and care about, such as 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 interventions that are generally available in clinical settings
• Obtains the perspectives of stakeholders to address the burdens to individuals, availability of services, and requirements for technology and personnel

Leveraging Existing Resources

Investigators are encouraged to propose studies that leverage existing resources as appropriate for the proposed study, such as adding PCOR to an existing large clinical trial.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures and 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).\textsuperscript{31}

Methodological Considerations

Regardless of study design, proposals must adhere to all relevant PCORI Methodology Standards.\textsuperscript{32} These include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and are 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 HTE

Six other categories of standards 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” standards. Additional best practices, including relevant guidelines for the conduct of clinical trials developed by other organizations, should be addressed

\textsuperscript{31} Available at http://nihpromis.org/.
\textsuperscript{32} Available at pcori.org/research-we-support/the-pcori-methodology-report/.
in the application for PCORI funding. To help reviewers quickly identify adherence to a particular standard, applicants must cite to each methodology standard within their proposals 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 for Identify Gaps in Evidence in parentheses, such as “(RQ-1).”

All applicants should discuss specifically 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 currently 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 serve to enhance the scientific rigor and efficiency of large pragmatic trials funded by PCORI.

**Patient and Stakeholder Engagement**

PCORI strongly supports active engagement of patient 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 reference previously documented decisional dilemmas in preparation for the submission of LOIs and applications. To describe the decisional dilemma, state the specific clinical decision(s) and/or treatment choice(s) confronted by the decision makers, and explain how the findings from the proposed research will inform those decisions. State why this decision, such as choosing between specific treatment strategies, is important to patients and their caregivers. Document the uncertainty faced by patients, clinicians, and other decision makers 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. Similarly, applicants should document why project outcomes are especially relevant to patients and should be meaningful endpoints for patients and their families.

PCORI has developed the Engagement Rubric\(^33\) to guide the integration of patients and other stakeholders in the development, oversight, management, and implementation of research studies. Additionally, studies are expected to adhere to PCORI’s Methodology Standards associated with patient-centeredness and to the PCOR Engagement Principles found within the rubric. PCORI also has a compensation framework\(^34\) for guidance on compensating individual patient partners on the research team. These and

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additional resources are available in PCORI’s 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 application their plan 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 are required to work in collaboration with PCORI staff upon award of the proposed studies to establish a project SAC (or other appropriate engagement body, see the Clinical Strategies for Managing and Reducing Long-Term Opioid Use for Chronic Pain FAQs) 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. 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 represented in the project milestones.

Populations Studied

PCORI seeks to fund research that includes diverse populations with respect to age, gender, race, ethnicity, geography, or clinical status, so that possible differences in CER may be examined, otherwise known as HTE. 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 importance of the study in the absence of diversity and to discuss which subgroups are most important and how they will be analyzed, including whether the study will be powered to examine the question of effectiveness in subgroups. PCORI is particularly interested in the inclusion of previously understudied populations for whom effectiveness information is especially needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of the strategies in various subpopulations with attention to the possibilities that the effects of the strategy might differ across subpopulations. PCORI has developed a list of priority populations to guide our efforts in research and engagement, which includes:

- 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
• Patients with low health literacy or numeracy or limited English proficiency
• Lesbian, gay, bisexual, and transgender (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). The maximum budget includes all research and peer review related costs (please refer to the Application Guidelines for further details). Note that PCORI will not cover costs for interventions that are being compared in the proposed study (see Appendix 2 in the Application Guidelines for details). Applicants should submit realistic budgets and timelines. For those rare circumstances in which the estimated total direct costs exceed $10 million, provide in your LOI a detailed justification that ties the extra expense to the success of the project. Not all requests for additional funds will be approved. Any request for a research project period longer than five years will be denied. For further information regarding PCORI’s policies about allowable and unallowable costs, refer to Appendix 2 of the Application Guidelines.

The funding mechanism for this program is a contract. Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Milestones and targets, as well as possible pilot phases for the sole purpose of assessing feasibility of recruitment, should be included in the budget and will be negotiated at the time of the award. Awardees will be expected to provide corroborating evidence to receive continual funding support. Some of the activities that will be considered during negotiations and subsequently include:

• Developing a study protocol and manual of procedures for the intervention
• Assigning roles and responsibilities of members of the study team for implementing the project
• Obtaining clearances from all institutional and community partners, including IRB approvals
• Establishing a DSMB, or providing a clear description of why a DSMB is not considered necessary
• Executing all subcontractor agreements
• Agreeing on eligible patient populations for study recruitment
• Identifying barriers to patient recruitment into the study and addressing these barriers effectively
• Demonstrating successful recruitment during a pilot phase (if indicated)

Refer to the Application Guidelines for a list of additional PFA-specific project milestones.

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 (up to five pages) is included in the Research Plan Template. 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, see Section 5 “Human Subjects Research Policy” from the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports, issued by the US Department of Health and Human Services (HHS). PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal-wide assurance (FWA), or that refer to standards for inclusion of women, minorities, and children. PCORI requires applicants proposing clinical trials to consider including a data- and safety-monitoring plan. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI merit reviewers will examine plans for protection of human subjects in all applications and may provide comments regarding the plans (see How to Evaluate Human Subjects Protections). 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 Subject Participants

PCORI requires all applicants to adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all personnel listed as Key Personnel in the application. The policy and FAQs are available from the NIH website.

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 of study documentation (e.g., study protocol, programming code, and data definitions) so that other researchers may replicate the findings in other populations. Propose a method for sharing data and appropriate documentation upon request.

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Peer Review and Release of Research Findings

PCORI has a legislative mandate to ensure the scientific integrity of the primary research it supports and to make study findings widely available and useful to patients, clinicians, and the general public within a specific timeframe. The PCORI Board of Governors adopted the following process for peer review and public release of the results of all funded studies.

Awardee Institutions are required to submit to PCORI for peer review a draft final research report that provides the methodological details, describes the main study results, and interprets properly the findings in clinical or other decisional contexts. Subject matter experts, individuals with expertise on research methodology or biostatistics, and patients, caregivers, and other healthcare stakeholders will review the draft final research report. After awardees have responded to reviewers’ comments to PCORI’s satisfaction, the report will be accepted and considered final. PCORI will then prepare a 500-word abstract summarizing the study results for patients and the general public, which the Awardee Institution will review and approve.

PCORI will post the following materials on its website no later than 90 days after the draft final research report is accepted: a 500-word abstract for medical professionals, a standardized summary of the study’s results for patients and the general public, and a link to the study record on ClinicalTrials.gov (as applicable). The final research report, along with anonymized reviewer comments, will be made publicly available on the PCORI website no later than 12 months after its acceptance, except by prior mutual agreement with the Awardee Institution.

III. How To Submit an Application

Letter of Intent

Applicants should download the LOI template for the Opioids PFA specifically for the Cycle 3 2015 Funding Cycle from the PCORI Funding Center. They must complete the document and convert it to a PDF with a four-page limit (not including references, which should be listed at the end). LOIs that exceed the page limit will not be reviewed. Do not upload additional documents as part of your LOI, such as letters of endorsements or support, as they are not requested at this stage. Their inclusion will result in LOI rejection without review. Visit the PCORI Funding Center for additional applicant resources, including the PFA and required templates.

Answer all of the questions in the LOI template. This includes the question on brief justification for the proposed cost of the study; providing an answer “the cost not to exceed $10 million” is not sufficient. Then upload your document to the PCORI Online System. The deadline for LOI submission is November 12, 2015, by 5 p.m. (ET).

Letter of Intent Review

LOIs are evaluated on the following criteria:

- Whether the proposed topic addresses one of the high-priority research questions identified in this funding announcement
• Importance of the specific research question (comparison), as evidenced by critical gaps identified by clinical guidelines developers and/or recent relevant systematic reviews

• A sufficient size or scope that the proposed topic will have a significant impact on patient outcomes and/or healthcare practices

• Clarity and credibility of applicants’ responses to the LOI questions, as well as their justification of the proposed size of the study citing published estimates, including effect sizes, standard deviations, and need for rigorous comparative analysis of important subgroups

• Prior relevant experience

• Programmatic fit and balance, taking into consideration whether the research study question and study design are compliant with requirements in this funding announcement

• Adherence to the administrative and formatting requirements listed in the Application Guidelines, specifically the four-page limit for the LOI (not including references)

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. LOIs are reviewed by a minimum of two PCORI staff and are not scored during review. Notification of denial or approval to submit an application will occur no later than December 18, 2015. Please refer to the Application Guidelines for information on how to submit your LOI via PCORI Online.

You are invited to submit an application based on the information provided in the LOI. Any changes to the following require PCORI’s approval:

• Research question(s)
• Specific aims
• Study design
• Comparators
• Principal Investigator (PI)
• Institution

If you need to change any of this information or have any questions, email pfa@pcori.org.

Note: A PI may submit only one LOI for this PFA. An individual listed as a PI on one LOI may be listed and serve in another role (e.g., co-investigator, co-PI) on other LOIs.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the overview of this PFA and in the PCORI Funding Center.  

39 Available at http://www.pcori.org/funding-opportunities/.
IV. Merit Review

PCORI merit review is a multiphase process that includes:

- Evaluation of LOIs
- Inviting a subset of LOIs to submit full applications
- Administrative and programmatic review of full applications
- Preliminary review by review panels for full applications that meet administrative and programmatic requirements
- In-person review panel discussion of full applications
- Post in-person or webinar presentation (at PCORI’s discretion), Selection Committee deliberation, and recommendation of applications for funding
- Board award approval (no later than July 2016)

Application Review Criteria

PCORI’s review panels use the following five criteria during the preliminary and in-person phases to evaluate all submitted applications. Each application should address the listed questions.

**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, guideline development efforts, 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 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?
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: study can be patient-centered even if the end-user is not the patient, as long as patients will benefit from 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 and explain that those outcomes are 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 plan 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.

At a minimum, 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, see the Clinical Strategies for Managing and Reducing Long-Term Opioid Use for Chronic Pain FAQs) that is comprised of national or regional organizations that represent, at a minimum, patients and/or 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, among them 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 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?
- Are the organizational structure and resources appropriate to carry out the project?

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Applications may be eliminated from the review process for administrative or programmatic reasons (i.e., nonresponsiveness). An application may be eliminated if it is incomplete or submitted past the stated due date and time, or if it does not meet the administrative or formatting criteria outlined in the Application Guidelines, in the PCORI templates, and in PCORI Online. It may also be withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes cost-effectiveness analysis, or otherwise fails to meet PCORI programmatic requirements. Per our authorizing legislation, if two proposed research plans overlap, funding preference must be given to applications submitted on behalf of NIH and the AHRQ.

One or more specially convened merit review panels will review responsive applications. PCORI Merit Review Officers (MROs) recruit each panel. MROs identify the chair, scientist reviewers who are clinical experts familiar with the clinical content of submitted applications, methodological and statistical experts familiar with PCTs and large database analyses, patient representatives trained in review of scientific proposals, and representatives of other stakeholder groups.

In-Person Review

After the preliminary review is completed, PCORI program staff members evaluate panel scores and critiques to identify a subset of applications to be discussed at the in-person review meeting. Not all submitted applications move forward to in-person review, but all applications are evaluated and scored based on PCORI’s merit review criteria, which include evaluation of adherence to PCORI’s Methodology Standards.

During the in-person review, panels meet to discuss applications and to clarify further the merits of the proposed research, as well as to identify areas for improvement. Additionally, each application is re-scored based on the content of discussion. The chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review informed by the standards outlined in the PFA.

In-Person Applicant Presentation

Based on the results of merit review and PCORI’s programmatic priorities, a selective subset of applicants whose proposed studies are deemed to be highly meritorious and/or aligned with PCORI’s strategic

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41 Available at https://pcori.fluxx.io.
priorities may 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 panel review, PCORI program staff evaluate merit review 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 includes members of PCORI’s Board. 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. If an application progresses to in-person discussion, the applicant will receive a summary statement inclusive of the panel discussion notes, the final average overall score, preliminary reviewer critiques, and a quartile, which provides information for applicants to understand how they did relative to other discussed applications. Quartile 1 includes applications that score in the top 24 percent of discussed applications; quartile 4 includes applications that score in the bottom 25 percent of discussed applications.

Summary statements for applications that do not progress to in-person discussion include only the preliminary reviewer critiques.

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 late June 2016 and notification of the funding status of their application no later than July 2016.