Fall 2014 Funding Cycle

PCORI Funding Announcement:
Large Pragmatic Studies to Evaluate Patient-Centered Outcomes

This PCORI Funding Announcement applies to the funding cycle that closes November 4, 2014, at 5:00 p.m. (ET). Application guidelines, templates, and other resources are available at pcori.org/PFA/large-pragmatic-studies-fall/.
About PCORI

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 the Patient Protection and Affordable Care Act of 2010 as a nonprofit, nongovernmental organization. PCORI’s purpose, as defined by the law, 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) 202-355-9558
Email: info@pcori.org

Follow us on Twitter: @PCORI
## Overview

### Published
May 19, 2014

### Letter of Intent Due
June 27, 2014, by 5:00 p.m. (ET)

Letters of Intent will be screened for responsiveness to this PFA and 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 July 31, 2014.

### Summary
Patient-Centered Outcomes Research Institute (PCORI) seeks to fund pragmatic clinical trials (PCTs), large simple trials (LSTs), or large-scale observational studies that compare two or more alternatives for addressing prevention, diagnosis, treatment, or management of a disease or symptom; improving health care system–level approaches to managing care; or eliminating health or healthcare disparities.

Proposed studies must address critical clinical choices faced by patients, their caregivers, clinicians, and/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 requiring that relevant patient organizations, professional organizations, and/or payer or purchaser organizations be included as partners and actively participate in the study. 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 and/or the existence of large registries, to address pragmatic questions using observational designs. **This PCORI program does not support applications to conduct cost-effectiveness analysis, evidence synthesis, or study decision-support tools.**

### Applicant Resources
See all templates in our Funding Center here [pcori.org/PFA/large-pragmatic-studies-fall/](http://pcori.org/PFA/large-pragmatic-studies-fall/)

### Key Dates
- **Online System Opens:** May 19, 2014
- **Applicant Town Hall Session:** June 4, 2014, 3:00–4:00 p.m. (ET)
- **Letter of Intent (LOI) Deadline:** June 27, 2014, by 5:00 p.m. (ET)
- **LOI Screening Notification:** July 31, 2014
- **Application Deadline:** November 4, 2014, by 5:00 p.m. (ET)
- **Merit Review Dates:** February 2015 (Date pending)
- **Awards Announced:** Spring 2014 (Date pending)
- **Earliest Project Start Date:** 2015 (Date pending)

### Maximum Project Budget (Total Direct Costs)
$10 million
<table>
<thead>
<tr>
<th>Maximum Project Period</th>
<th>Five years</th>
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<tbody>
<tr>
<td>Funds Available Up To</td>
<td>$90 million</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Applications may be submitted by any private sector research organization, including any nonprofit or for-profit organization, and 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.</td>
</tr>
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| Review Criteria         | 1. Impact of the condition on the health of individuals and populations  
|                         | 2. Potential for the study to improve health care and outcomes  
|                         | 3. Technical merit  
|                         | 4. Patient-centeredness  
|                         | 5. Patient and stakeholder engagement |
| Contact Us              | Programmatic Inquires: Please contact the PCORI Helpdesk via email (pfa@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 three business days prior to a Letter of Intent 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. Please 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. |
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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 (PCTs), large simple trials (LSTs), or large-scale observational studies that involve representative patient populations; have strong endorsement and study participation by relevant patient organizations, professional organizations, and/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 support evaluation of potential differences in treatment effectiveness in patient subgroups. Funded studies will compare the relative effectiveness\(^1\) of two or more alternatives for improving patient-centered outcomes. Proposed studies of comparative efficacy\(^2\) will be considered non-responsive.

Background
While traditional randomized controlled trials (RCTs) are widely accepted for assessing the efficacy of medical interventions, RCTs are generally 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 well-documented factors: 1) the comparisons in the trial often fail to reflect the choices faced by patients and clinicians; 2) the population selected for study 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 as the comparison rather than an active comparator.

To meet these concerns, trials can be designed to address practical comparative questions faced by patients and clinicians; include broader and more diverse populations; and be conducted in real-world clinical and diverse health-system settings. Such trials are often referred to as PCTs because they are intended to provide information that can be directly adopted by healthcare providers. They tend to be conducted in routine clinical care settings, and in many cases, they must be relatively large, in part because expected differences in comparative effectiveness may be small, yet important, or diverse trials may be able to address effectiveness in different patient subgroups. They often must be much

\(^1\) 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 ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf).

\(^2\) Efficacy is the extent to which an intervention does more good than harm in ideal patients under ideal circumstances(modified from ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf).
simpler than traditional RCTs. For these and other reasons, such trials have also been called LSTs. The protocols for these trials are typically less complex and less intrusive to routine clinical practice than efficacy studies. For more extensive discussion on pragmatic versus traditional explanatory trials, see Patsopoulos³ and Thorpe et al.⁴

Examples of Successful Pragmatic Clinical Trials

- Choudhry and colleagues⁵ enrolled 5,855 patients to test whether elimination of out-of-pocket expenses for medications prescribed after a myocardial infarction would increase the percentage of patients who adhere to medication regimens and would 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 from 623 North American centers were randomized to chlorthalidone, amlopidine, or Lisinopril.⁶
- 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.⁷

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, palliative, 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 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 and delivery system interventions that are generally available in the settings where people access health care.
- Obtains the perspectives of stakeholders to address the burdens to individuals, access to care, quality of care, and requirements for technology and personnel.

**Research Characteristics and Objectives**

PCORI seeks to fund investigator-initiated research having the following characteristics:

- Studies the benefits and harms of different interventions and strategies that are delivered in typical clinical and community settings.
- Compares at least two alternative clinical approaches.
- Examines interventions such as specific drugs, devices, and procedures, as well as medical and assistive devices and technologies, behavioral change, complementary and alternative medicine, and delivery-system interventions. In some cases, “usual care” or no specific intervention may be an appropriate comparator, if this is a realistic choice faced by patients and other stakeholders (e.g., choosing not to have a cancer screening test). When “usual care” is proposed as an alternative, it should be described in detail, coherent as an alternative, properly justified as a legitimate comparator, and accompanied by an explanation of how appropriate inferences will be estimated (see Considering Usual Medical Care in Clinical Trial Design).
- Compares health outcomes that are meaningful to the patient population under study (e.g., morbidity, mortality, symptoms, functional status, quality of life, absenteeism from work or school). In selected instances, surrogate physiological measurements may be sufficiently linked to final health outcomes to be of interest, but they may not be the sole study outcome.

PCORI has two objectives in this solicitation. First and most importantly, PCORI seeks to commit adequate funding to address critical clinical and health-related questions faced by patients, their caregivers, and their clinicians. Second, PCORI is interested in testing novel methodological approaches within real-world environments and expects various randomization schemes to be proposed, including individual or cluster randomization. PCORI has particular interest in funding studies that focus on patient-reported outcomes (PROs) that have not been well studied previously; can be completed relatively 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); or employ strategies to enhance study efficiency, such as Bayesian adaptive designs in which trial characteristics (e.g., sample

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size, randomization proportions, treatment arms, or 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\(^9\)). Such studies will help determine not only how these approaches might be employed within real-world settings, but especially how such approaches might be integrated within a dynamic, rapid-learning environment (see Robert Wood Johnson Foundation’s Rapid Learning Project\(^10\)).

**Topic Selection**

High-priority questions (see Appendix) have been identified by PCORI’s multi-stakeholder advisory panels; other multi-stakeholder efforts, such as the Institute of Medicine (IOM) Priorities for CER\(^11\) and the Agency for Health Care Research and Quality (AHRQ) Future Research Needs Projects\(^12\); and specific stakeholder organizations, including payers and purchasers of health care. Applications submitted that address any of these questions would be of particular interest to PCORI. *Note that PCORI will also be open to receiving and reviewing Letters of Intent for studies on other priority CER questions.* Regardless of the research questions, applicants are expected to adhere to PCORI Methodology Standard RQ1\(^13\), which states “gap analysis and systematic reviews should be used to support the need for a proposed study.”

On the basis of Letters of Intent submitted for the first cycle of grant application, PCORI has invited full applications related to 11 of the high-priority research topics\(^14\) listed for this second cycle (see Appendix). Even though PCORI will consider topics for which it has invited full applications, it will only consider multiple pragmatic trials on the same topic if they are deemed complementary. Therefore, applicants should be aware that the topic of the application may be a factor in PCORI’s decision to invite a full application. *(Note: PCORI does not provide information about pending applications.)*

In all cases, PCORI will expect that in preparing applications, researchers have partnered with relevant patient organizations, specialty professional organizations, healthcare systems, insurers, and/or employer purchasers. Involvement of these organizations in finalizing and endorsing the research question and their participation in the proposed study are essential requirements for labeling a research question as high priority. If one or more key stakeholders have declined to endorse the study, PCORI would expect this to be explained clearly in the application.

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9 Available at pcori.org/assets/Standards-for-the-Design-Conduct-and-Evaluation-of-Adaptive-Randomized-Clinical-Trials.pdf

10 Available at rwif.org/en/grants/grantees/rapid-learning-systems.html

11 Available at iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20CER%20Priorities%20for%20web.ashx

12 Available at effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports?pagetype=displayproduct&productid=521

13 Available at pcori.org/assets/2013/11/PCORI-Methodology-Report.pdf

14 Available at pcori.org/blog/pcori-invites-full-proposals-under-first-round-of-pragmatic-studies-initiative/
It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment and/or primary data collection, length of follow-up, and analytic complexity. PCORI seeks efficient studies, such as those that take 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 is taken as further evidence of the importance of the research question.

II. Guidance for Preparing Applications

Specific Requirements
The proposed study should strive to meet all of the following requirements:

- Focus on a comparative effectiveness question that is important to patients and other decision makers.
- Address a research gap that has been substantiated either by an existing (recent or updated) rigorously conducted systematic review or specifically emphasized by an official professional society’s clinical practice guideline.
- Receive endorsement by relevant patient organizations, clinician organizations, payer/purchaser consortia, and/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 or for clear demonstration of non-inferiority; 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 effects).
- 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.
- Feature near-term outcomes and PROs as primary outcomes when appropriate.
• Plan to efficiently collect patient-centered outcomes data 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. 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.
• In the case of randomized trials, adhere to current best practices (standardized inclusion/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).
• Adhere to all applicable PCORI Methodology Standards.\(^\text{15}\)
• 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, 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:
• Identify and engage with major patient and stakeholder organizations that would implement study findings—as well as with existing local communities of patients and care providers—to formulate the research questions, design the study, help monitor progress, and disseminate the findings.
• 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, as seamlessly as possible, be integrated 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.
• If data standardization and interoperability across study sites has not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different electronic health record systems.

\(^{15}\) Available at pcori.org/research-we-support/research-methodology-standards/
Non-responsiveness
Applications will be considered non-responsive 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 in the form of dollar-cost per quality-adjusted life-year to compare two or more alternatives.
- Directly compares the costs of care between two or more alternative approaches.

Innovation and changes in healthcare systems and in the behavior of healthcare system participants are often driven by economic, political, and social needs to improve access to care or quality of care; attract patients or enrollees; and contain costs. Therefore, PCORI does have an interest in studies of 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. PCORI is also interested in studies that examine differentials in healthcare utilization. Applications proposing to examine costs that patients bear personally (“out-of-pocket” costs)—and may constitute a barrier to the receipt of care—are acceptable.

Further, PCORI considers it important for applicants to discuss cost-related issues, such as the resources needed to implement, replicate, or disseminate a successful intervention. PCORI is also interested in evaluation of interventions and system designs intended to reduce health-system waste or increase health-system efficiency. Applications that include studies of these issues without utilizing a formal cost-effectiveness analysis or comparing the costs of alternatives are considered responsive.

PCORI discourages applications that include studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or study of biological mechanisms. This funding announcement does not seek studies that evaluate new or existing decision aids or clinical prognostication tools.

Leveraging Existing Resources
Investigators are encouraged to propose studies that leverage existing resources, such as adding PCOR to an ongoing 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 include preliminary data that supports the proposed measures. Investigators are encouraged to consider those measures described in the Patient Reported Outcomes Measurement
Information System\textsuperscript{16} (PROMIS).

Documentation of Assumptions
PCORI specifically seeks studies that are sufficiently powered to detect clinically meaningful effects. To that end, investigators should justify the proposed sample sizes by explaining the assumptions used in all study power calculations. The application should clearly state all the necessary assumptions (e.g., the primary outcome measure, the estimated difference in the mean value of this measure between study arms, standard deviation of the measure, and type I error rate). All such estimates must be justified by referring to prior published research or preliminary data.

Studies in Rare Diseases
PCORI is interested in the investigation of 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 \textit{low prevalence} is defined as conditions that affect fewer than 200,000 individuals in the United States or have a prevalence of less than 1 in 1,500 persons.

Methodological Considerations
Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards.\textsuperscript{17} The PCORI Methodology Standards include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and are relevant to most PCORI studies. Researchers should refer to all of these standards when planning and conducting their research projects. These 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

Five other categories of standards are 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:

- 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

\textsuperscript{16} Available at http://nihpromis.org/
\textsuperscript{17} Available at pcori.org/research-we-support/research-methodology-standards/
Most of these standards should be considered minimal standards. Additional best practices, including guidelines for the conduct of clinical trials developed by other organizations, should be addressed in the application.

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

**Patient and Stakeholder Engagement**

PCORI encourages all applicants to clearly describe the patient and stakeholder engagement in their applications. PCORI understands that patient and stakeholder engagement in research can take many forms; it is not seeking one particular method of engagement. Rather, applicants should communicate how patients (those with lived experience), family members, caregivers, and the organizations that represent them, as well as any other relevant stakeholders, will be involved in study activities. Because this type of engagement in research is a relatively new concept, PCORI has developed a Patient and Family Engagement Rubric\(^\text{18}\) to guide both applicants and merit reviewers. Additionally, studies are expected to adhere to **PCORI’s Methodology Standards Associated with Patient-Centeredness**\(^\text{19}\) and to the PCOR Engagement Principles found within the rubric. These and additional resources are available in the Funding Center.

**Populations Studied**

PCORI seeks to fund research that includes diverse populations 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 importance of the study 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. Thus, comparisons should examine the impact of strategies in various subpopulations with attention to the possibility that the effects might differ across various populations. Populations of interest include those that are less frequently studied. PCORI has developed the following list of priority populations to guide our efforts in research and engagement:

- Racial and ethnic minority groups


\(^{19}\) Available at [http://www.pcori.org/research-we-support/research-methodology-standards/](http://www.pcori.org/research-we-support/research-methodology-standards/)
• Low-income groups
• Women
• Children (ages 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 make-up affects their medical outcomes
• Individuals with low health literacy or numeracy and/or limited English proficiency
• Lesbian, gay, bisexual, and transgender (LGBT) persons

Budget and Duration of Project
Applicants may request up to $10 million in total direct costs for a project period not to exceed five years. Applicants should submit realistic budgets and timelines. For those rare circumstances in which the estimated total direct costs exceed $10 million, please 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 project period longer than five years will be denied.

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, 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\(^ {20} \) for a list of additional project milestones specific to the PFA.

\(^ {20} \) Available at pcori.org/assets/2014/05/PCORI-PFA-2014-Fall-Pragmatic-Studies-Application-Guidelines.pdf
Collaboration
PCORI is particularly interested in applications that involve community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We encourage applications that include novel collaborations with accreditation organizations, credentialed bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

Human Subject Protection
Federal regulations (45CFR46)\(^\text{21}\) require that applications involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

Required Education of Key Personnel on the Protection of Human Subject Participants: PCORI requires all applicants to adhere to National Institute of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all personnel listed in the application as key personnel. The policy is available here.\(^\text{22}\)

Replication and Reproducibility of Research and Data Sharing Plan
PCORI strongly supports practical policies that promote transparency, replication, and reproducibility in research. The following policies are in effect.

Replication of research findings: This requirement refers to supporting efforts by other researchers to replicate study findings in other patient populations and datasets. It applies to all applicants, regardless of the size of the project.

Applicants must describe a replication plan that accommodates:

- Provision of a complete, final study protocol, describing the study population; primary and secondary hypotheses to be tested; and sources and methods of measuring exposures, outcomes, and all covariates used in analyses, including data definitions, coding instructions, discussion guides for qualitative research, and the analysis plan. PCORI reserves the right to share these materials with appropriate researchers, in consultation with the principal investigator of the study.
- Descriptions of study datasets including codebooks, metadata related to the datasets, and documented programming code used for creating the final study population, creating variables, and conducting all outcomes analyses.

\(^\text{21}\) Available at [http://hhs.gov/ohrp/humansubjects/guidance/45cfr46.html](http://hhs.gov/ohrp/humansubjects/guidance/45cfr46.html)
\(^\text{22}\) Available at [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html)
Reproduction of research findings: This requirement refers to reproducing research findings in the same dataset by another researcher (or researchers) not affiliated with the applicant’s research team. The ability to reproduce important findings from the original data is critical to establishing trust in PCORI findings. Therefore, PCORI will require a data-sharing plan (described below) for applications responding to this PFA. Although the plan described below is required of all applicants, subsequent data sharing would be requested by PCORI only after review of findings and a decision that the findings warrant the expense and time.

The data-sharing plan must:

- State that a complete, cleaned, de-identified copy of the final dataset used in conducting the final analyses will be made available within one year of study completion.
- Propose a plan by which investigators will make this dataset available, if requested.
- Propose a budget that would cover costs of data-sharing, if requested.

Note: Depending on the nature, uses, and potential impact of the study findings, PCORI will consider whether incremental funding will be made available to assist investigators in complying with data-sharing requests.

III. How to Submit an Application

PCORI Online System
You must register with the PCORI Online System23 to submit a Letter of Intent24 (LOI) and subsequently an application, if the LOI is approved. You must create a new LOI for each cycle in which you are applying.

Submission Dates
LOIs and applications must be submitted in accordance with the published dates and times listed in the Overview of this document and in the PCORI Funding Center.25

Applicant Resources

PCORI Funding Center pcori.org/funding-opportunities/funding-center/

23 Available at pcori.fluxx.io
24 Available at pcori.org/assets/2014/05/PCORI-PFA-2014-Fall-Pragmatic-Studies-Letter-of-Intent-Template.doc
25 Available at pcori.org/PFA/large-pragmatic-studies-fall/
IV. Merit Review

PCORI Merit Review is a multi-phase process that includes:

- Evaluation of Letters of Intent
- 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 on the basis of the preliminary review and program priorities)
- Post-panel review, leading to Selection Committee recommendation of applications for funding
- Board of Governors award approval (no later than June 2015)

Letter of Intent Review

Letters of Intent are evaluated on the following criteria:

- Whether the topics are related to those on the PCORI’s own priority list (see Appendix) versus the IOM/AHRQ lists versus other topics initiated by investigators themselves.
- Importance, as evidenced by critical gaps identified by clinical guidelines developers and/or recent relevant systematic reviews
• Clarity and credibility of applicants’ responses to the LOI questions, as well as their justification of the need for a large pragmatic study, including rationale for the estimated sample size citing published estimates and need for rigorous comparative analysis of important subgroups
• Prior relevant experience
• Programmatic fit and balance, taking into consideration whether the applications significantly overlap 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

Letters of Intent are reviewed qualitatively; they are not scored. Only LOIs deemed most responsive to this PFA will be invited to submit a full application. Notification of request to submit a full application will occur no later than July 31, 2014. Please refer to the Application Guidelines for due dates and information on how to submit your LOI in PCORI Online.

Application Review Criteria
The following five criteria are used by PCORI’s review panels during the preliminary and in-person phases to evaluate all submitted applications. Each application should address the listed questions.

Criterion 1. Impact of the condition on the health of individuals and populations
The proposal addresses the following question:
• Is the condition or disease associated with a significant burden in the US population, in terms of prevalence, mortality, morbidity, costs to society, individual suffering, or loss of productivity?

Criterion 2. Potential for the study to improve health care and outcomes
The application has the potential to lead to meaningful improvement in the quality and efficiency of care and to improvements in outcomes that are important to patients.
• Does the research question address a critical gap in current knowledge as noted in systematic reviews, guideline-development efforts, or previous research prioritizations?
• Is there strong evidence of support by relevant patient, caregiver, clinician, payer, or purchaser organizations?
• Is the research novel or innovative in its methods or approach, the population being studied, or the intervention being evaluated, in ways that make it likely to improve care?
• Do wide variations in practice patterns suggest current clinical uncertainty?
• Do preliminary studies indicate potential for a sizeable benefit of the intervention relative to current practice?
• How likely is it that positive findings could be disseminated and implemented quickly, resulting in improvements in practice and patient outcomes?
• Are there adequate plans for sustainability of the successful intervention(s) in the chosen settings, or discussion of implementation of successful intervention(s) into similar care settings?
Criterion 3. Technical merit
The application has sufficient technical merit to ensure that the study goals will be met.
- Is there a clear research plan with rigorous methods that adhere to PCORI’s Methodology Standards and prevailing accepted best practices?
- Is there a clear comparison condition that is a realistic option in standard practice? Is the comparator sufficiently described to reasonably compare the two or more conditions in the trial?
- Are the proposed comparative conditions currently in use? Is there prior evidence of efficacy or effectiveness for the interventions being compared?
- Is there evidence that the outcome measures are sufficiently sensitive to identify differences between groups?
- Is the study conducted in a patient population that is relevant to the majority of patients with a condition or to a previously understudied subgroup?
- Are the pre-specified subgroups reasonable given the proposed interventions and condition? Are the subgroups sufficiently large to allow a rigorous and valid comparative analysis?
- Is the budget appropriate for the proposed research?
- Is there a clear and adequate justification for the study design choices in the proposed pragmatic trial?
- Is there an adequate plan for protection of human subjects participating in this study?
- Do the applicants provide evidence of study feasibility based on availability of participants and experienced staff for efficient start-up?
- Does the project include a realistic timeline that includes clear and specific scientific and engagement milestones?
- Does the research team have the necessary expertise and prior experience conducting large scale multicenter trials and an appropriate organizational structure to successfully complete the study?
- Is the research environment, including the delivery systems that will host the study, well-resourced and highly supportive of the proposed study?

Criterion 4. Patient-centeredness
The application demonstrates patient-centeredness:
- Does the research question (the comparison) reflect a choice or choices faced frequently by patients, their caregivers, or clinicians?
- Does the study protocol include outcomes, including patient-reported outcomes (PROs) if appropriate, that are relevant to patients?

Criterion 5. Patient and stakeholder engagement
The application demonstrates that people representing the population of interest and other relevant
stakeholders are engaged in ways that are appropriate and necessary in a given research context.

- Are patients and other stakeholders engaged in:
  - Formulating research questions
  - Defining essential characteristics of study participants, comparators, and outcomes
  - Identifying and selecting outcomes that the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform decision making relevant to the research topic
  - Monitoring study conduct and progress
  - Designing and/or suggesting plans for dissemination and implementation activities

- Are the roles and the decision-making authority of all research partners clearly stated?
- Does the application demonstrate the principles of reciprocal relationships, co-learning, partnership, trust, transparency, and honesty?

**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., non-responsiveness). An application may be eliminated if it is incomplete or submitted past the stated due date and time, or it does not meet the administrative or formatting criteria outlined in the Application Guidelines, in the PCORI templates, and in the PCORI Online System.²⁶ 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 the National Institutes of Health (NIH) and the Agency on Healthcare Research and Quality (AHRQ).

Responsive applications will be reviewed by one or more specially convened Merit Review panels. Each panel is recruited by PCORI Merit Review Officers, who identify a chair; scientist reviewers who are clinical experts familiar with the clinical content of submitted applications; methodological and statistical experts familiar with pragmatic clinical trials and large database analyses; patient representatives trained in review of scientific applications; and representatives of other stakeholder groups.

**In-Person Review**

Once preliminary review is complete, prior to the in-person Merit Review, each submitted application that has been determined to be compliant with administrative and programmatic requirements will be reviewed by a team of five members of the Merit Review panel using the five criteria and PCORI’s methodology standards.

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²⁶ Available at pcori.fluxx.io
During the in-person review, the full panels 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 in-person meeting is led by the panel’s chair and a PCORI Merit Review Officer, who ensure that all applications considered receive a fair and thorough review informed by the standards outlined in the funding announcement.

**Post-Panel Review**

After the in-person panel review, meritorious applications are reviewed by the Selection Committee, which includes members of PCORI’s Board of Governors and Methodology Committee. PCORI will invite those applicants who are being recommended for consideration by the Selection Committee to present their research and respond to reviewers’ critiques. This presentation will occur either in-person at PCORI’s expense or via webinar.

The Selection Committee then works with staff to identify a slate of applications for possible funding based on merit review scores, programmatic balance, PCORI’s strategic priorities, and other considerations. This slate is proposed to PCORI’s Board of Governors for its consideration and approval.

**Board of Governors Approval**

The PCORI Board of Governors will consider the selected applications, factoring in the total available funds allotted for this announcement and programmatic needs. PCORI will inform applicants of Board of Governors’ decisions no later than June 2015.
Appendix: Research Topics of Interest to PCORI

PCORI Priority Topics
(Asterisks indicate topics for which full applications have been invited based on Letters of Intent from the previous funding cycle.)

- **Treatment strategies for patients with autism spectrum disorder**
  - Perform a multicenter, randomized control trial comparing the effectiveness of Applied Behavioral Analysis (in children two to five 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 take into account the natural history of autism spectrum disorder.

- **Treatment options for patients with multiple sclerosis**
  - Compare management options for modifying disease progression. These might include FDA-approved disease-modifying agents; behavioral interventions, including exercise and physical therapy; and complementary medicine alternatives.

- **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, other comorbidities)**

- **Biologic agents in the management of patients with Crohn’s disease (We are particularly interested in under-studied populations, including non-white, pediatric, and newly diagnosed patients. Sample size should be sufficiently large to ascertain heterogeneity of treatment effects, especially with regards to disease severity.)**
  - Compare the use of one TNF-alpha inhibitor with another, or with other biologics—administered for either induction or maintenance of remission in adults and children diagnosed with Crohn’s disease—in outcomes such as patient-reported outcomes, steroid reduction, Crohn’s Disease Activity Index (CDAI), pediatric CDAI, and mucosal healing.
  - Compare the use of a TNF-alpha inhibitor and a thiopurine with the TNF-alpha inhibitor alone in maintenance of remission in adults and children, considering outcomes such as patient-reported outcomes, steroid reduction, CDAI, pediatric CDAI, and mucosal healing.

- **Multi-component 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 use of tobacco and promote tobacco cessation among populations with known tobacco disparities, including high-risk and vulnerable populations.

- **Active involvement by patients and caregivers in the management of chronic mental illness**
  - Compare the effectiveness of strategies that incorporate involvement and/or support of patients and their families or other caregivers in care for patients with chronic mental illness (e.g., bipolar disorder, major depression, anxiety disorders, schizophrenia). Studies
comparing different delivery system designs and measuring patient and caregiver outcomes (e.g., health-related quality of life, symptom relief, caregiver stress) are of particular interest.

- **Integration of mental and behavioral health services into the primary care of the general population**
  - Compare the effectiveness of different sustainable and scalable models for integrating mental and behavioral health services into primary care provided by large and small practice organizations. These studies should account for contextual effects of different payment methods (e.g., fee-for-service, capitation, and accountable care organizations).

- **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 (e.g., 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/ethnic minorities, low-income individuals, and rural populations.

- **Diagnosis and management of bipolar disorder in children and adolescents**
  - Compare clinical outcomes when children and adolescents presenting with symptoms of bipolar disorder are diagnosed by clinical judgment alone or by standard DSM diagnostic criteria.
  - Compare the outcomes of long-term treatment (more than two years) with different treatment strategies (e.g., antipsychotic medication classes and types; monotherapy or combinations; psychotherapy; assertive community treatment; adjunct therapies such as antidepressants, anxiolytics, and stimulants). Outcomes should include but are not limited to symptoms and socio-developmental, adaptive behavioral, and adverse effects (including substance abuse).

- **Management of breast ductal carcinoma in situ (DCIS)**
  - Compare the effectiveness of standard treatment options for DCIS (lumpectomy with or without radiation therapy; mastectomy; hormonal therapy post-surgery) with non-standard options (hormonal therapy alone; active surveillance) on progression to invasive cancer, recurrence of DCIS, DCIS progression without invasive cancer, quality of life, satisfaction with treatment choice at study completion, decisional conflicts, and other patient-relevant outcomes such as self-image, sexual activity, or change in marital status.
  - Compare different approaches to informed decision making about management of DCIS. Outcomes to include decisional conflicts, treatments received (e.g., mastectomy, lumpectomy, contralateral mastectomy), satisfaction with decision, match of the chosen treatment with the woman’s strength of preference for having an intact breast, and aforementioned clinical outcomes.

- **Reduction of cardiovascular disease (CVD) risk in underserved populations, such as racial and ethnic minorities and those living in rural communities**
o Compare the effectiveness of multi-disciplinary, systems-focused, and data-driven interventions to improve efficiency, effectiveness, and reliability of care to reduce CVD disparities in underserved populations. Targets for reducing disparities include improvements in hypertension control, treatment for hyperlipidemia, smoking cessation, and/or appropriate use of aspirin. The studies should examine which components of the interventions are critical for achieving risk reduction and provide details on patient-centered outcomes.

o Compare the effectiveness of various interventions to support self-management of hypertension, hyperlipidemia, tobacco addiction, and/or appropriate use of aspirin in underserved populations. The studies should examine which components of the interventions are critical for achieving risk reduction and provide details on patient-centered outcomes.

o In so far as possible, CVD interventions should focus on reducing disparities in care experienced by racial and ethnic minorities, low-income individuals, people with low literacy, and rural populations.

- **Strategies for preventing the progression of episodic acute back pain into chronic back pain**
  
o Compare the effect of different combinations of multimodal approaches to patients with episodic back pain (including self-care with or without over-the-counter medications; movement-based therapies, such as exercise and yoga; manipulation and/or mobilization; complementary medicine alternatives; and cognitive-behavioral therapies) on the transition from episodic acute back pain to chronic back pain, symptom relief, patient satisfaction, quality of life, and functional outcomes. Specific outcomes might also include reduction in pain-medication use, reduction in patient visits for low-back pain, increase in quality of life, increased time between low-back-pain episodes, and decreased severity of episodes (i.e., decreased pain and increased function).

- **Innovative strategies for enhancing patients’ adherence to medication regimens**
  
o Studies should take into account the needs of patients with chronic conditions who are prescribed medications for short- and/or long-term indications.

- **Specific features of health insurance on access to care, use of care, and other outcomes that are especially important to patients**
  
o Examples of specific insurance design features that may be considered include: utilization management approaches, consumer-directed care benefits, prior authorization programs, value-based insurance designs, and alternative patient cost-sharing schemes. Studies should take into account the preferences and needs of chronically ill patients and account for variations in care settings and providers’ payer mix, where applicable.

- **Treatment strategies for adult patients with migraine headache**
  
o Compare pharmacologic and nonpharmacologic strategies to prevent the transformation from episodic to chronic migraine.

o Compare pharmacologic and nonpharmacologic strategies for treatment of individual headache episodes on the incidence of medication-overuse headache in patients with high-frequency episodic or chronic migraine.
• **Treatment strategies for symptomatic osteoarthritis (OA), including joint replacement**
  o Compare methods for deciding when to have surgery for OA; use outcomes such as patient satisfaction, functional status, clinical status, quality of life.
  o Compare the effectiveness of strategies for engaging early-stage OA patients to adopt behaviors that can prevent OA progression and disability.
  o Compare different nonsurgical therapies (pharmacotherapy, injections, physical therapy and/or exercise, weight loss alone and in combination with other therapies, complementary medicine alternatives) to prevent OA progression and disability. The studies should seek to identify heterogeneity of treatment response among important subgroups of patients.

• **Strategies for follow-up of pulmonary nodules identified by imaging studies**
  o Compare different protocols for managing people with lung nodules. Differences in protocols might include the types of imaging technologies, frequency of follow-up, indications for invasive diagnostic procedures, and biomarkers.

• **Treatment options for people with opioid substance abuse**
  o Compare different combinations of treatment options for people with opioid substance abuse, focusing on long-term outcomes. Treatment options might include medication-assisted treatments, psychosocial therapies, and complementary medicine alternatives.

• **Particle beam therapy for patients with lung, breast, and prostate cancer**
  o Compare the use of particle beam radiation therapy with other forms of radiation therapies in patients with lung, breast, or prostate cancer. Short- and long-term outcomes of interest might include tumor site–specific toxicities, severity of adverse effects, cancer-specific and overall mortality, quality of life, and functional outcomes.

Institute of Medicine 100 Initial Priority Topics for Comparative Effectiveness Research[^27] *(Note: Decision-support topics within the IOM list are not supported in this funding announcement.)*

AHRQ Future Needs Projects[^28]

[^27]: Available at iom.edu/~/media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx
[^28]: Available at effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=521