



PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Spring 2014 Funding Cycle

PCORI Funding Announcement:
Pragmatic Clinical Studies and Large Simple Trials to
Evaluate Patient-Centered Outcomes

This PCORI Funding Announcement applies to the funding cycle that closes August 8, 2014, at 5:00 p.m. (ET). Application guidelines, templates, and other resources are available at www.pcori.org/PFA/pragmatic-studies



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."

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Overview

Published	February 5, 2014																
Letter of Intent Due	March 7, 2014, by 5:00 p.m. (ET)																
Summary	<p>Letters of Intent will be screened for responsiveness and fit to program goals. Only those selected will be permitted to submit full applications. Notification of request to submit full application will occur no later than April 7, 2014.</p> <p>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 for eliminating health or healthcare disparities.</p> <p>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.</p> <p>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 new PCORI program will not support proposals to conduct evidence synthesis or to develop decision-support tools.</p> <p>This announcement is a collaborative effort of PCORI's Clinical Effectiveness, Improving Healthcare Systems, and Addressing Disparities research programs. Thus, proposals for pragmatic studies may fit within any of these three priority areas.</p>																
Applicant Resources	See pcori.org/PFA/pragmatic-studies																
Key Dates	<table><tr><td>Online System Opens:</td><td>February 5, 2014</td></tr><tr><td>Applicant Town Hall Session:</td><td>February 12, 2014, at 11:00 a.m.–12:00 p.m. (ET)</td></tr><tr><td>Letter of Intent (LOI) Deadline:</td><td>March 7, 2014, by 5:00 p.m. (ET)</td></tr><tr><td>LOI Screening Notification:</td><td>April 7, 2014</td></tr><tr><td>Application Deadline:</td><td>August 8, 2014, by 5:00 p.m. (ET)</td></tr><tr><td>Merit Review Dates:</td><td>November 2014</td></tr><tr><td>Awards Announced:</td><td>February 2015</td></tr><tr><td>Earliest Project Start Date:</td><td>April 2015</td></tr></table>	Online System Opens:	February 5, 2014	Applicant Town Hall Session:	February 12, 2014, at 11:00 a.m.–12:00 p.m. (ET)	Letter of Intent (LOI) Deadline:	March 7, 2014, by 5:00 p.m. (ET)	LOI Screening Notification:	April 7, 2014	Application Deadline:	August 8, 2014, by 5:00 p.m. (ET)	Merit Review Dates:	November 2014	Awards Announced:	February 2015	Earliest Project Start Date:	April 2015
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Maximum Project Budget (Direct Costs)	\$10 million																



Maximum Project Period	5 years
Funds Available Up To	\$90 million
Eligibility	Applications may be submitted by any private sector research organization, including any nonprofit or for-profit organization; any public sector research organization, including any university or college hospital or healthcare system, laboratory or manufacturer, unit of local, state, or federal government. All US applicant organizations must be recognized by the Internal Revenue Service. Non-domestic 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	<ol style="list-style-type: none">1. Impact of the condition on the health of individuals and populations2. Potential for the study to improve health care and outcomes3. Technical merit4. Patient-centeredness5. Patient and stakeholder engagement
Contact Us	<p>Programmatic Inquiries: 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.</p> <p>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.</p>



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I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching a new funding initiative to expand its support of patient-centered comparative clinical effectiveness research (CER). PCORI seeks to fund investigator-initiated large pragmatic clinical trials, large simple trials, or large-scale observational studies that will 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 allow precise estimates of effect sizes and support evaluation of potential differences in treatment effectiveness in patient subgroups. Funded studies will compare the relative effectiveness¹ of two or more alternatives for improving patient-centered outcomes. Proposed studies of comparative efficacy² will be considered non-responsive.

Background

While use of traditional randomized controlled trials (RCTs) are widely accepted for assessing the efficacy of medical interventions, it is also recognized that 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 be 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; to include broader and more diverse populations; and to be conducted in real-world clinical settings. Such trials are often referred to as pragmatic clinical trials (PCTs) because they are intended to provide information that can be directly adopted by healthcare providers. They often must be much simpler than traditional RCTs. 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, when large, they may pertain to only certain patient subgroups. For these and other reasons, such trials have also been called large simple trials

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 health care practice (modified from http://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 http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf).

(LSTs). Certainly, the protocols for these trials should be less complex and less intrusive to routine clinical practice than typical efficacy (RCT) studies. For more extensive discussion on pragmatic versus traditional explanatory trials, see Patsopoulos (A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*. 2011;13:217-224; <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181997/>) and Thorpe et al. (A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ*. 2009;180:E47-E57; <http://www.cmaj.ca/content/180/10/E47.full.pdf>).

Examples of Successful Pragmatic Clinical Trials

- Choudhry and colleagues 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 (Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial; Choudhry, et al. *N Engl J Med*. 2011 Dec 1;365(22):2088-97).
- 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, amlodipine, or Lisinopril. (Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic; ALLHAT Collaborative Research Group, *JAMA* 2002; 288:2981-2997).
- A randomized, real-world, open-label comparative clinical effectiveness trial enrolled patients empirically 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 (Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs. tricyclic antidepressants. Simon, et al., *JAMA*. 1996; 275(24):1897-1902).

Research of Interest and Research Approach

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

- Studies of 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 are expected to be estimated (see Considering Usual Medical Care in Clinical Trial Design. Dawson, et al. *PLoS Med* 2009 6(9): e1000111. doi:10.1371).
- 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 not as 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. Of note, PCORI has particular interest in funding studies that focus on patient-reported outcomes (PROs) that have not been well studied previously; studies that can be completed relatively quickly because the primary outcomes focus on symptoms or other patient-reported measures; studies that examine interventions and outcomes that cut across specific diagnoses (e.g., studies with primary outcomes focused on symptoms such as pain), and studies that employ strategies to enhance study efficiency, such as Bayesian adaptive designs in which trial characteristics such as sample 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](#)³). Such studies will help determine not only how such approaches might be employed within real-world settings, but especially to learn how such approaches might be integrated within a dynamic, rapid-learning environment (see Robert Wood Johnson Foundation's [Rapid Learning Project](#)⁴).

High-priority questions have been identified by PCORI's multi-stakeholder advisory panels; by other multi-stakeholder efforts, such as the Institute of Medicine (IOM) [Priorities for CER](#)⁵ and the Agency for Health Care Research and Quality (AHRQ) [Future Research Needs Projects](#)⁶, and by specific stakeholder organizations, including payers and purchasers of health care (see Appendix). 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.

In all cases, PCORI will expect that applicant researchers have partnered with relevant patient organizations, specialty professional organizations, healthcare systems, insurers, and/ or employer purchasers in preparing applications. Involvement of these organizations in finalizing and endorsing the research question and in participating in the proposed study is an essential requirement for labeling this 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.

³ Available at pcori.org/assets/Standards-for-the-Design-Conduct-and-Evaluation-of-Adaptive-Randomized-Clinical-Trials.pdf

⁴ Available at rwjf.org/en/grants/grantees/rapid-learning-systems.html

⁵ Available at <http://iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx>

⁶ Available at <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=521>

It is expected that project budgets and duration will vary substantially, depending on the study topic and approach/method selected, needs for recruitment and/or primary data collection, required length of follow-up, and analytic complexity. PCORI seeks efficient studies, such as those that take advantage of having large populations under observation and supportive involvement of delivery systems or health plans to enhance recruitment and data collection. Prolonged recruitment periods are not a rationale for longer studies, except possibly in the case of a rare disease. 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.

Specific Requirements for Proposed PCORI Pragmatic Trials

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

- Focus on a comparative effectiveness question that is important to patients and decision makers.
- Address a research gap that has been substantiated either by an existing rigorously conducted systematic review or specifically emphasized by an official professional society's clinical practice guideline.
- Endorsement by relevant patient organizations, clinician organizations, payer/purchaser consortia, and/or life sciences industry representatives as being a critical question, one that if adequately answered would substantially improve decisionmaking.
- 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 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 in and support for the study 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 either known to be efficacious, or are commonly in use, and can be implemented in real-world settings.
- Feature near-term outcomes and PROs as primary outcomes when appropriate.
- Capacity to collect efficiently 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, adherence to current best practices for conducting pragmatic trials (standardized inclusion/exclusion criteria; proper randomization; techniques to minimize potential for missing data; appropriate safety monitoring (including establishment of a data-safety monitoring board, or discussion of why such a board is unnecessary).

- Adherence to all applicable [PCORI Methodology Standards](#)⁷.
- 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 be, as seamlessly as possible, integrated with routine clinic/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.

II. Guidance for Proposing Research

Research Priorities

PCORI funds patient-centered outcomes research (PCOR), a type of CER. The studies PCORI supports must include the perspectives of patients and other healthcare stakeholders. To be considered responsive, applications must meet the aforementioned requirements.

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.

⁷ Available at <http://www.pcori.org/research-we-support/research-methodology-standards/>

- Directly compares the costs of care between two or more alternative approaches.

PCORI does have an interest, however, 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 resources or costs as a determinant of, or barrier to, good outcomes. Examples include ways in which out-of-pocket costs may constitute a barrier to the receipt of care.

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 also is interested in evaluation of interventions intended to reduce health system waste or increase health system efficiency. Proposals that include studies of these issues without utilizing a formal cost-effectiveness analysis or comparing the costs of alternatives are considered responsive.

PCORI discourages proposals that include studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or study of biological mechanisms. It is not the intended purpose of this funding announcement to seek studies aimed to develop and evaluate new decision aids or clinical prognostication tools.

Features of Patient-Centered Outcomes Research

PCOR helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research:

- 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 interventions that are generally available in the settings that people use to access health care.
- 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, such as adding PCOR to an existing large clinical trial or analyzing existing large databases that contain valuable, relevant information that may be used to answer important CER questions.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures. Include preliminary data that supports the proposed measures. Investigators are encouraged to consider those measures described in the [Patient Reported Outcomes Measurement Information System](#)⁸ (PROMIS).

Documentation of Assumptions

PCORI specifically seeks studies that are sufficiently powered to detect clinically meaningful effects. To that end, justify the proposed sample sizes by explaining the assumptions used in all study power calculations. The application should clearly state all the necessary assumptions (i.e., the primary outcome measure, the estimated difference in the mean value of this measure between study arms, standard deviation of the measure, type I error rate, and any other assumptions). 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 *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.

Review Criteria

Applications will be reviewed in one or more specially convened merit review panels. Each panel will be constituted to include 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 proposals; and representatives of other stakeholder groups.

The following are PCORI's merit review criteria for these applications. PCORI's review panels will rate all submitted applications on the following five criteria:

Criterion 1. Impact of the condition on the health of individuals and populations

The proposal addresses the following questions:

- 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

⁸ Available at <http://www.nihpromis.org/>

The proposal 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. This criterion considers the following questions:

- 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?
- Do wide variations in practice patterns suggest current clinical uncertainty?
- Is the research novel or innovative in its methods or approach, in the population being studied, or in the intervention being evaluated in ways that make it likely to improve care?
- 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?

Criterion 3. Technical merit

The proposal has sufficient technical merit to ensure that the study goals will be met. It includes:

- A clear research plan with rigorous methods that adhere to PCORI's Methodology Standards and prevailing accepted best practices
- A clear and adequate justification for the study design choices in the proposed pragmatic trial
- A realistic timeline that includes specific scientific and engagement milestones
- A research team with the necessary expertise and an appropriate organizational structure
- A research environment, including the delivery systems that will host the study, that is well resourced and highly supportive of the proposed study

Criterion 4. Patient-centeredness

The proposal demonstrates patient-centeredness at every stage of the research. It addresses the following questions:

- 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 PROs if appropriate, that are relevant to patients?
- 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?

Criterion 5. Patient and stakeholder engagement

The proposal 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/suggesting plans for dissemination and implementation activities
- Are the roles and the decision-making authority of all research partners clearly stated?
- Does the proposal demonstrate the principles of reciprocal relationships, co-learning, partnership, trust, transparency, and honesty?

Methodological Considerations

Regardless of study design, proposals must adhere to all relevant [PCORI Methodology Standards](#)⁹. PCORI Methodology Standards 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 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 (HTE)

Five 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:

- 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

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 create or explain apparent differences in the effectiveness of the alternative interventions being compared in clinical populations.

⁹ Available at pcori.org/research-we-support/research-methodology-standards/

Patient and Stakeholder Engagement

PCORI encourages all applicants to clearly describe the patient and stakeholder engagement in their research proposals. PCORI understands that patient and stakeholder engagement in research can take many forms; it is not seeking one particular type or 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 (see the appendix to the Engagement Template) to guide both applicants and merit reviewers. 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. These and additional resources are available in [PCORI's Funding Center](#).

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 comparative clinical effectiveness research may be examined. 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 the strategies in various subpopulations with attention to the possibilities that the effects of the strategy 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, 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 make-up affects their medical outcomes
- Patients with low health literacy/numeracy and/or limited English proficiency
- Lesbian, gay, bisexual, and transsexual (LGBT) persons

Letter of Intent Review

LOIs will be evaluated based on their responsiveness to this PFA. Applicants will be notified as to whether they have been selected to submit full applications; PCORI will accept full applications from only those selected organizations. See the [PCORI Funding Center](#) for applicant resources, including guidelines and templates.

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 letter of intent a detailed justification that ties the extra expense to the success of the project. Please also indicate whether (and if so, how) the study will be possible if the additional funds are not approved. *Note: Not all requests for additional funds will be approved.*

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:

- Development of study protocol and manual of procedures for the intervention
- Roles and responsibilities of members of the study team for implementing this project
- Obtaining clearances from all institutional and community partners to include IRB approvals
- Establishing a data and safety monitoring board (DSMB), or a clear description of why a DSMB is not considered necessary
- Execution of all subcontractor agreements
- Clearly communicating to PCORI an understanding of eligible patient populations for study recruitment
- Identifying barriers to patient recruitment into the study and addressing these barriers effectively
- Demonstration of successful recruitment during a pilot phase (if indicated)

Refer to the application guidelines for a list of additional project milestones specific to the PFA.

Collaboration

Innovation and changes in healthcare systems and in the behavior of healthcare system participants are often driven by economic, political, and social imperatives to improve access to or quality of care, to attract patients/enrollees, and to contain costs. As such, 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 proposals that include

novel collaborations with accreditation organizations, credentialing bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

Protection of Human Subjects

PCORI adopts, by reference, the Human Subjects requirements of 45 CFR Part 46. If the proposed research will involve human subjects, refer to the Supplemental Instructions for Preparing the Protection of Human Subjects Section of the Research Plan in Part II of the Instructions for the PHS 398 Form provided by the [National Institutes of Health](#).¹⁰

Note: PCORI requires engagement in the research by patients and/or other stakeholders, as research partners. Research subjects protection requirements do not apply to co-investigators, members of the research team, or research partners.

III. How to Submit a Proposal

PCORI Online System

To submit a proposal, you must register with the [PCORI Online System](#)¹¹ and submit a Letter of Intent (LOI) and, if requested, an application for each cycle in which you are applying.

Submission Dates

Letters of Intent 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](#).

Applicant Resources

PCORI Funding Center pcori.org/pfa/pragmatic-studies

PCORI Online System pcori.fluxx.io

PCORI Funding Awards pcori.org/pfaawards

¹⁰ Available at <http://grants.nih.gov/grants/funding/phs398/phs398.html>

¹¹ Available at pcori.fluxx.io

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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IV. Appendix: Research Topics of Interest to PCORI

Institute of Medicine 100 Initial Priority Topics for Comparative Effectiveness Research

(<http://iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.ashx>)

AHRQ Future Needs Projects (<http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=521>)

PCORI Priority Topics

- *Diagnosis and management of bipolar disorder*
 - 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 (>2 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, 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*
 - 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.

- 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.
- In so far as possible, CVD interventions should focus on reducing disparities in care experienced by racial and ethnic minorities, low-income individuals, individuals with low literacy, and rural populations.
- *Strategies for preventing the progression of episodic acute back pain into chronic back pain*
 - 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/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, as well as increased time between low-back-pain episodes and decreased severity of episodes (i.e., decreased pain and increased function).
- *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.
- *Compare the effectiveness of innovative strategies for enhancing patients' adherence to medication regimens.*
 - Studies should take into account the needs of patients with chronic conditions who are prescribed medications for short- and/or long-term indications.

- *Compare the effectiveness of specific features of health insurance on access to care, use of care, and other outcomes that are especially important to patients.*
 - 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*
 - Compare pharmacologic and nonpharmacologic strategies to prevent the transformation from episodic to chronic migraine.
 - 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*
 - Compare methods for deciding when to have surgery for OA using outcomes such as patient satisfaction, functional status, clinical status, quality of life.
 - Compare the effectiveness of strategies for engaging early-stage OA patients to adopt behaviors that can prevent OA progression and disability.
 - Compare different nonsurgical therapies (pharmacotherapy, injections, physical therapy/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.
- *Treatment strategies for patients with autism spectrum disorder*
 - Perform a multicenter, randomized controlled trial comparing the effectiveness of Applied Behavioral Analysis (in children aged 2 to 5 years) 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.
- *Strategies for follow-up of pulmonary nodules identified by imaging studies*
 - Compare different protocols for managing people with lung nodules. Differences in protocols might include the types of imaging technologies; frequency of follow-ups; indications for invasive diagnostic procedures; and biomarkers.
- *Treatment options for people with opioid substance abuse*
 - Compare different combinations of treatment options for people with opioid substance abuse, focusing on long-term outcomes of interventions. Treatment options might include medication-assisted treatments; psychosocial therapies; complementary medicine alternatives; and others.

- *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.
- *Particle beam therapy for patients with lung , breast, and prostate cancer*
 - 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.

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