Cycle 2 2019 Funding Cycle

PCORI Funding Announcement:
Improving Methods for Conducting Patient-Centered Outcomes Research (PCOR)

Published May 1, 2019

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes on September 4, 2019, at 5 pm (ET). Application Guidelines, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/improving-methods-conducting-patient-centered-outcomes-research-4.

About PCORI

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

PCORI was authorized by Congress in 2010 as a nonprofit, nongovernmental organization. PCORI's purpose, as defined by our authorizing legislation, is to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders 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	May 1, 2019
Letter of Intent Due	May 29, 2019, by 5 pm (ET) Letters of Intent (LOIs) will be screened for responsiveness to program goals and for overlap with projects in the existing portfolio. Only those selected will be invited to submit full applications. Invitations to submit a full application will occur no later than June 24, 2019. PCORI encourages prospective applicants to contact us with questions prior to the deadline. See "Contact Us" below for additional details.
Summary	In this PCORI Funding Announcement (PFA), we seek to fund studies that address important methodological gaps and lead to improvements in the strength and quality of evidence generated by patient-centered outcomes research (PCOR) and comparative effectiveness research (CER).
Applicant Resources	See https://www.pcori.org/funding-opportunities/announcement/improving-methods-conducting-patient-centered-outcomes-research-4.
Key Dates	Online System Opens: May 1, 2019 Town Hall: May 9, 2019, 12 pm ET LOI Deadline: May 29, 2019, by 5 pm (ET) LOI Screening Notification: June 24, 2019 Application Deadline: September 4, 2019, by 5 pm (ET) Merit Review: November 2019 Awards Announced: February 2020 Earliest Project Start Date: May 2020
Maximum Project Budget (Direct Costs)	$750,000
Maximum Research Project Period	Three years
Funds Available up to	$12 million Because the nature and scope of the proposed research are expected to vary widely from application to application, it is anticipated that the size and duration of each award will also vary. PCORI reserves the right to change the funds available at any time.
Eligibility	*Organization:* 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. The Internal Revenue Service must recognize all U.S. applicant organizations. Nondomestic components of organizations based in the U.S. and foreign organizations may apply, as long as there is demonstrable benefit to the U.S. healthcare system and U.S. efforts in the area of patient-centered research can be shown clearly. Organizations may submit multiple applications for funding. Individuals are not permitted to apply.
Review Criteria	1. Study identifies critical methodological gap(s) in PCOR/CER 2. Potential for the study to improve PCOR/CER methods 3. Scientific merit (research design, analysis, and outcomes) 4. Investigator(s) and Environment 5. Patient-centeredness 6. Patient and stakeholder engagement

Contact Us	**Programmatic Inquires:** Please contact the PCORI Helpdesk via email (sciencequestions@pcori.org), phone (202-627-1884), or online (http://www.pcori.org/PFA/inquiry). PCORI will respond within two business days. However, we cannot guarantee that all questions will be addressed two business days prior to an LOI or application deadline. **Administrative, Financial, or Technical Inquiries:** Please contact the PCORI Helpdesk at (pfa@pcori.org). PCORI will respond within two business days. Please note that during the week of the application deadline, response times may exceed two business days. Applicants may also call the PCORI Helpdesk (202-627-1885). It is the applicant's responsibility to submit the application on or before the application deadline.
Other	*Deadlines are at 5 pm (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday.

New or Revised for the Cycle 2 2019 Funding Cycle:
- No changes to the Research Areas of Interest (RAIs):
  - Methods Related to Ethical and Human Subjects Protections (HSP) Issues in PCOR/CER
  - Methods to Improve Study Design
  - Methods to Support Data Research Networks
  - Methods to Improve the Use of Natural Language Processing
- New PCORI Methodology Standard categories (Standards for Qualitative Methods, Standards for Mixed Methods Research, and Standards for Individual Participant-Level Data Meta-Analysis) have been added—see pages 4-5
- See the Application Guidelines for updates to the templates and other requirements.

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I. Introduction

Summary

In this Patient-Centered Outcomes Research Institute (PCORI) Funding Announcement (PFA) for Improving Methods for Conducting Patient-Centered Outcomes Research (PCOR), also referred to as the "Methods PFA," PCORI aims to fund studies that address high-priority methodological gaps in PCOR and comparative effectiveness research (CER).

Background

The availability of multiple options for prevention, diagnosis, and treatment in health care presents a significant challenge to patients and clinicians trying to make informed care decisions. Deciding between alternative options in health care requires an understanding of how to balance the benefits and risks of each treatment option and an understanding of how each option might apply differently to different patients, given their unique personal characteristics. However, limitations in the design, implementation, and analysis of clinical research may produce biased study results that can have serious consequences for patients.

The PCORI Methodology Standards address some of the challenges related to the planning, conduct, and reporting of PCOR/CER, but these standards are not exhaustive. PCORI and its Methodology Committee recognize the need to better understand and advance the appropriate use of these methods for PCOR/CER. PCORI seeks to fund projects that address important methodological gaps and lead to improvements in the strength and quality of evidence generated by PCOR/CER studies.

Research Areas of Interest and Program Priorities

PCORI has invested extensively in methodological research to advance the field of PCOR. The funded portfolio now includes more than 90 projects awarded under previous cycles of the Methods PFA. With the maturing of the current portfolio of funded projects, PCORI's funding priorities have focused on a specific set of program priorities.

For the Cycle 2 2019 Methods PFA, PCORI has identified four Research Areas of Interest (RAIs) as programmatic prioirites. (See the blue tables below for additional details.) Proposed research should be justified with respect to the published scientific literature and designed to advance methods for PCOR/CER. Projects that simply apply methods or approaches to a particular domain, seek to disseminate an approach, or focus on infrastructure development will not align with program priorities.

Regardless of a proposed project's status in regard to previous Letter of Intent (LOI) submissions and full applications, PCORI reserves the right to reject the LOI if the project overlaps significantly with other funded projects or in other ways no longer aligns with PCORI's program priorities.

Methods Related to Ethical and Human Subjects Protections (HSP) Issues in PCOR/CER

PCORI is interested in funding projects to address important ethical and HSP issues related to the conduct of PCOR/CER. Applications responding to this RAI must include an empirical component. PCORI will consider purely conceptual and theoretical work to be nonresponsive. Moreover, PCORI will give preference to proposals that seek to develop or test new approaches rather than those that conduct primarily descriptive work.

The following topics are priorities for this RAI:

a) Methods to improve consent processes for participation in clinical research in the context of conventional randomized controlled trials (RCTs), observational studies conducted in learning healthcare system settings, cluster randomized trials, pragmatic trials, or adaptive trials

   Note: PCORI will consider projects focusing on informed decision making and consent in the context of clinical care to be nonresponsive.

b) Methods to assess the concept of minimal risk in clinical research (including clinical trials)

c) Methods to improve review and monitoring of PCOR/CER, including protocol adherence and adjudication of study outcomes

Methods to Improve Study Design

PCORI is interested in funding projects that foster improvements in the use of specific study designs to address PCOR/CER questions. PCORI will give preference to proposals that seek to evaluate the proposed methods using both simulations and data from real-world studies.

The following topics are priorities for this RAI:

a) Methods to improve the design and conduct of cluster randomized trials, including methods to account for the dependence of observations within clusters

b) Methods to support the inclusion of patient preferences for allocation of interventions in randomized designs, while minimizing threats to internal validity

c) Methods to manage adaptation of treatment strategies, while minimizing threats to internal validity in studies of complex interventions

d) Methods to improve the design and conduct of PCOR/CER studies in circumstances limiting the use of RCTs

Methods to Support Data Research Networks

PCORI is interested in funding projects that improve the quality of data and analyses for multi-site PCOR/CER using data research networks. PCORI will consider projects that focus on infrastructure development and/or capacity building for specific platforms to be nonresponsive.

The following topics are priorities for this RAI:

a) Methods to improve distributed analyses in data research networks	• Methods to evaluate optimal network designs and analytical approaches (e.g., distributed regression and meta-analysis)
b) Methods to improve data quality in data research networks	• Methods to assess dimensions of data quality (e.g., completeness, accuracy, or consistency)
	• Methods to prevent, mitigate, or impute missing or inaccurate data and improve understanding of mechanisms of missingness and implausibilities in electronic health

	records (EHRs) and distributed data settings
	• Methods to evaluate optimal linkage of multiple data sources, such as EHRs, claims, and national registry data
	• Methods to conduct patient-level disambiguation for de-identified linkage of data across networks

Methods to Improve the Use of Natural Language Processing

PCORI is interested in funding projects that develop and evaluate natural language processing (NLP) and other related methods for leveraging free-text clinical information contained in EHRs for PCOR/CER. PCORI will consider proposals that simply seek to apply NLP to a particular clinical context to be nonresponsive.

The following topics are priorities for this RAI:

a) Methods to improve concept parsing in the extraction of valid medical information from EHRs

b) Methods to develop the most effective use of annotation when extracting data from unstructured text in EHRs

c) Methods to address issues associated with negation in the extraction of data from EHRs

II. Requirements for PCORI Research

This section includes language that is specific to PCORI's requirements for applications for funding. Applicants should use this section as guidance when preparing their applications.

Non-responsiveness

Applications to the Methods PFA that propose the following types of research will be considered nonresponsive:

Non-methodological research

- Develops a discrete intervention or healthcare practice

- Compares the efficacy of two or more health interventions

- Develops best practices for healthcare delivery

Narrowly focused research

- Develops, refines, and validates disease- or condition-specific measures

Consistent with PCORI's authorizing law,[1] PCORI does **not fund** research whose findings will include:

- Coverage recommendations

- Payment or policy recommendations

- Creation of clinical practice guidelines or clinical pathways

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[1] Available at http://www.pcori.org/sites/default/files/PCORI_Authorizing_Legislation.pdf/.

- Establishing efficacy for a new clinical strategy

- Pharmacodynamics

- Study of the natural history of disease

- Basic science or study of biological mechanisms

Studies of Cost-Effectiveness

PCORI will consider an application nonresponsive if the proposed research:

- Conducts a formal cost-effectiveness analysis

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

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

PCORI does have an interest, however, in studies that address questions about conditions leading to high costs to the individual or to society. Thus, PCORI is interested in studies that:

- Examine the effect of costs on patients, such as patients' out-of-pocket costs, hardship, or lost opportunity, or costs as a determinant of or barrier to access to care

- Address cost-related issues, such as the resources needed to replicate or disseminate a successful intervention

- Evaluate interventions to reduce health system waste or increase health system efficiency

Avoiding Redundancy

PCORI encourages potential applicants to review funded research at pcori.org. We intend to balance our funded portfolio to achieve synergy and avoid redundancy where possible.

Methodological Considerations

Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards. These include 65 individual standards that fall into 16 categories. The first five categories are cross-cutting and relevant to most PCOR studies. Researchers should refer to these standards when planning and conducting their research projects. These categories are:

1. Standards for Formulating Research Questions

2. Standards Associated with Patient-Centeredness

3. Standards on Data Integrity and Rigorous Analyses

4. Standards for Preventing and Handling Missing Data

5. Standards for Heterogeneity of Treatment Effect (HTE)

In addition to these five sets of standards, the first standard of "Standards for Causal Inference Methods (CI-1)" is considered cross-cutting and applies to all PCOR/CER studies.

The 11 other standards categories will be applicable to certain study designs and methods. Use the standards in each of these categories for guidance when they are relevant to a study:

6. Standards for Data Registries

7. Standards for Data Networks as Research-Facilitating Structures

8. Standards for Causal Inference Methods

9. Standards for Adaptive and Bayesian Trial Designs

10. Standards for Studies of Medical Tests

11. Standards for Systematic Reviews

12. Standards on Research Designs Using Clusters

13. Standards for Studies of Complex Interventions

14. Standards for Qualitative Methods

15. Standards for Mixed Methods Research

16. Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)

Most of these standards are minimal. The PCORI Methodology Standards[2] reflect practices that applicants should follow in all cases, and all deviations need to be explained and well justified. Applicants should address additional best practices—including relevant guidelines for conducting clinical trials developed by other organizations—in the application for PCORI funding. To help reviewers quickly identify adherence to a particular standard, applicants must cite each relevant PCORI Methodology Standard within the Methodology Standards Checklist, following the instruction in the checklist itself and in the Application Guidelines. Program staff use the checklist to evaluate applications.

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

Leveraging Existing Resources

PCORI encourages investigators 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. PCORI is interested in studies that leverage existing research networks or consortia, as well as established data resources such as patient outcomes registries, especially when such patient outcomes registries can be linked to electronic medical record (EMR) data from healthcare delivery systems or administrative claim data from public or commercial insurers to facilitate the conduct of CER. PCORI does not intend for this PFA to support the development of new patient registries, but rather to support the effective utilization of established

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[2] Available at http://www.pcori.org/research-we-support/the-pcori-methodology-report/.

patient registries where comprehensive data on patient characteristics and patient outcomes have been collected and/or can be linked to the EMR data or claims data to evaluate treatment outcomes in the proposed CER studies. In circumstances where randomized control trials are not practical or ethically acceptable, studies leveraging established patient outcomes registries can have meaningful and complementary roles in evaluating patient outcomes.

Patient and Stakeholder Engagement

PCORI encourages all applicants to outline how patients and other stakeholders will participate as partners in various phases of the proposed research. Before completing this section of the Research Strategy, applicants are encouraged to review PCORI's Engagement Rubric,[3] which can be found in the PCORI Funding Opportunities page. Additionally, the Engagement in Health Research Literature Explorer[4], a searchable, catalogued resource for peer-reviewed literature, can help identify publications about engagement that are specifically relevant to your work. These resources are not intended to be comprehensive or prescriptive; instead, they provide examples of options to incorporate engagement, where relevant, into the research process.

If patient and caregiver engagement is deemed inappropriate in the planning, conduct, or dissemination of research because of the proposed project's technical nature, applications should justify why. Highly technical applications should consider whether engaging other stakeholders or end-users (e.g., data architects, clinicians, domain experts, health services researchers with different expertise than that of the research team members, policy makers, etc.) would be of value in the methodological research process.

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 outcomes may be examined in defined subpopulations, otherwise known as HTE. PCORI recognizes that some proposed studies might represent important PCOR opportunities even in the absence of a broadly diverse study population. However, the burden is on the applicant to justify the study's importance in the absence of diversity and to discuss which subgroups are most important and how they will be analyzed—including whether the study will be powered to examine the question of effectiveness in subgroups. PCORI is particularly interested in the inclusion of previously understudied populations for whom effectiveness information is especially needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of the strategies in various subpopulations, with attention to the possibility that the strategy's effects might differ across subpopulations. PCORI has developed a list of populations of interest to guide our efforts in research and engagement:

- Racial and ethnic minority groups

- Low-income groups

- Women

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[3] Available at http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf.

[4] Available at http://www.pcori.org/literature/engagement-literature

- Children (age 0–17 years)

- Older adults (age 65 years and older)

- Residents of rural areas

- Individuals with special healthcare needs, including individuals with disabilities

- Individuals with multiple chronic diseases

- Individuals with rare diseases

- Individuals whose genetic makeup affects their medical outcomes

- Patients with low health literacy, numeracy, or limited English proficiency

- Lesbian, gay, bisexual, transgender, and questioning (LGBTQ) persons

- Veterans and members of the Armed Forces and their families

Protection of Human Subjects

This component (up to five pages) is included in the Research Plan Template. Describe the protection of human subjects involved in your proposed research. PCORI follows the Federal Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, please see Section 5, titled "Human Subjects Research Policy," in the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports,[5] which is issued by the U.S. Department of Health and Human Services (HHS). In referencing the HHS Supplemental Grant Application Instructions, note that PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal-wide assurance and the inclusion of women, minorities, and children in the proposed studies. Instead, PCORI expects applicants to address diversity in study participants in the Research Plan, through a focus on subpopulations, as described in the above section on populations studied. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI requires awardees to ensure that there is a Data and Safety Monitoring Plan, which may include the need to appoint a Data and Safety Monitoring Board, as provided in the PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded Research.[6]

PCORI merit reviewers will examine plans for protection of human subjects in all applications and may provide comments regarding the plans (see How To Evaluate Human Subjects Protections[7]). Reviewers' comments on human subject research are not reflected in the overall application score, but PCORI staff might use them during potential funding negotiations. Final determinations about the adequacy of human subject protections rest with the Institutional Review Board (IRB) or international equivalent that has jurisdiction for the study.

The Awardee Institution, whether domestic or foreign, bears ultimate responsibility for safeguarding the

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[5] See http://grants.nih.gov/sites/default/files/supplementalinstructions.docx.
[6] See http://www.pcori.org/sites/default/files/PCORI-Policy-Data-Safety-Monitoring-Plans.pdf.
[7] See http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/.

rights and welfare of human subjects in PCORI-supported activities.

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

PCORI requires that all applicants adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. This applies to all individuals listed as key personnel in the application. The policy and FAQs are available on the NIH website.[8]

Data Management and Data-Sharing

PCORI encourages openness in research and making research data available for purposes of replication and reproducibility. As such, if an award is made, the awardee will be expected to adhere to PCORI's Policy for Data Management and Data Sharing. The policy articulates PCORI's requirement that certain awardees make the underlying data and data documentation (e.g., study protocol, metadata, and analytic code) from their PCORI-funded research projects available to third-party requestors.

A full data management and data sharing plan is <u>not</u> required at the time of application. If an award is made—specifically for the Pragmatic Clinical Studies and the targeted PFA studies—the awardee is required to develop and maintain such a plan, which is described in detail in the PCORI Methodology Standards for Data Integrity and Rigorous Analyses, specifically Standard IR-7. This plan must be appropriate for the nature of the research project and the types of research project data, and consistent with applicable privacy, confidentiality, and other legal requirements. The policy includes details about what data certain awardees will be expected to deposit into a PCORI-designated data repository and when that data would be available for third-party requests.

For research awards funded under a <u>Broad funding announcement</u> (Assessment of Prevention, Diagnosis, and Treatment Options, Improving Healthcare Systems, Addressing Disparities, Communication and Dissemination Research, Improving Methods for Conducting PCOR), the policy calls for awardees to maintain the Full Data Package for seven years. PCORI may, in selective cases, notify the researcher of its intent to provide funds for the deposition of the Full Data Package in a PCORI-designated repository in circumstances where PCORI requests such deposition.

The information here is meant for informational purposes only and does not attempt to be an exhaustive representation of the Policy for Data Management and Data Sharing. Refer to the Policy in its entirety for additional information.

Recruitment (if applicable)

Proposals should include information about the size and representativeness of the potential pool of patients from which recruitment will occur and describe how this size estimate was determined. Likewise, proposals should provide evidence-based estimates of how many participants are expected in the study, based on expected recruitment and applying the study's inclusion and exclusion criteria; anticipated acceptance (or refusal) rates; and other factors, such as failure to follow up. Such estimates must be discussed in the application, specified in the milestones, reviewed by merit reviewers and PCORI staff, and monitored by PCORI in the funded research.

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[8] See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html.

PCORI has a legislative mandate to ensure the scientific integrity of the primary research it supports and to make study findings widely available and useful to patients, clinicians, and the general public within a specific timeframe. Accordingly, the PCORI Board of Governors (Board) adopted the Process for Peer Review of Primary Research and Public Release of Research Findings.[9]

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

PCORI will post the following materials on its website no later than 90 days after the draft final research report is accepted: (1) a 500-word abstract for medical professionals; (2) a 500-word standardized abstract summarizing the study results for patients and the general public; (3) a link to the study record on ClinicalTrials.gov (as applicable); and (4) ancillary information, including conflict of interest disclosures. The final research report, along with anonymized reviewer comments, will be made publicly available on the PCORI website no later than 12 months after its acceptance, except by prior mutual agreement with the Awardee Institution.

III. How To Submit an Application

Applying for funding from PCORI is a two-stage process. An LOI must be submitted and an applicant must be invited to submit an application.

Letter of Intent (LOI)

Applicants should download the LOI Template for the Improving Methods for Conducting Patient-Centered Outcomes Research PFA from the PCORI Funding Opportunities page. They must complete the document and convert it to a PDF file. The LOI is limited to two pages, excluding references. PCORI suggests including all references as in-text citations using American Medical Association citation style, but other citation styles are accepted. Do not upload additional documents as part of your LOI, including Letters of Endorsement or Support, because they are not requested at this stage. Their inclusion will result in LOI rejection without review. Please visit the PCORI Funding Opportunities page for additional applicant resources, including the PFA and required templates.

For the Methods PFA, LOIs for proposed studies must include the following sections:

- **Specific Aims:** State the goals of the proposed research, including the specific aims that will address the identified methodological gap and the expected outcomes.

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[9] See http://www.pcori.org/sites/default/files/PCORI-Peer-Review-and-Release-of-Findings-Process.pdf.

- **Background:** State the methodological gap the research is designed to address and indicate the specific topic in the Methods PFA to which this project responds.

- **Significance:** Describe how the proposed research will advance methods for patient-centered outcomes research/comparative clinical effectiveness research (PCOR/CER) and the importance of this research to the relevant stakeholders (e.g., patients, clinicians, and policy makers).

- **Approach:** Provide a detailed description of the methodological work that is planned for each of the specific aims and the ways in which it addresses the identified methodological gap. Include a sufficient description of the following elements to demonstrate the scientific rigor of the proposed research:

    o Study design

    o Study population and sample size (if applicable)

    o Primary data collection methods (if applicable)

    o Data sources and data sets (if applicable)

    o Analytic methods

The LOI Template provides guidance on responding to each item. Please refer to the Application Guidelines for due dates and information on how to submit an LOI via the PCORI Online System. **The deadline for LOI submission is May 29, 2019, by 5 pm (ET).**

LOI Review

LOIs are evaluated based on the following:

- Responsiveness to the Methods PFA

- Importance and relevance of the topics to PCORI priorities, as evidenced by critical gaps in current methodological understanding and supported by the scientific literature

- Clarity and credibility of responses to each section of the LOI

- Sufficient detail and scientific rigor of the proposed methods

- Programmatic fit and balance, taking into consideration whether an LOI significantly overlaps with funded studies or concurrent LOIs

Only applicants with LOIs deemed **most responsive** to this PFA will be invited to submit a full application. PCORI staff review the LOIs, which are not scored during review. Notification of the request to submit a full application will occur no later than June 24, 2019.

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

- Research question(s)

- Specific aims

- Study design

- Comparators (if applicable)

- Principal Investigator (PI)

- Institution

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

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

Project Budget and Duration

Applications submitted under the Methods research funding stream will not be granted an exception to the research project duration limit of three years (not including peer review) and/or the project budget limit of $750,000 in direct costs. At the time of contract execution, PCORI sets aside all of the funds associated with an awarded project to be made available throughout the contract's period of performance. The maximum budget includes all research- and peer-review-related costs. Refer to the Application Guidelines for further details. Refer to Appendix 2 in the Application Guidelines for a list of allowable and unallowable costs. Note that, although subcontractor direct and indirect costs are considered direct costs to the prime, subcontractor indirect costs should not be included when determining whether the budget exceeds the $750,000 limit. Note that although subcontractor indirect costs are included in the prime applicant's direct-cost budget, subcontractor indirect costs are not factored when determining adherence to the PFA's direct-cost limit.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the Overview section of this document and on the PCORI Funding Opportunities page.

PCORI Online System

To submit an application, you must register with PCORI Online and submit an LOI and an application for each cycle to which you are applying.

Applicant Resources

PCORI Funding Center	https://www.pcori.org/funding-opportunities/announcement/improving-methods-conducting-patient-centered-outcomes-research-4

PCORI Online System	https://pcori.force.com/engagement
PCORI Funding Awards	http://www.pcori.org/research-results-home

IV. Merit Review

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

- Identify applications that have the strongest potential to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders make informed decisions to improve patient outcomes.

- Implement a transparent, fair, objective, and consistent process to identify these applications.

- Elicit high-quality feedback that reflects a diversity of perspectives to ensure that the PCORI-funded research reflects the interests and views of patients and other stakeholders and those who care for them, and that it meets the criteria for scientific rigor.

- Fund projects that fill important evidence gaps and have strong implementation potential.

- Regularly evaluate and continually improve the merit review process and policies in support of PCORI's mission.

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

Preliminary Review

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

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

The table below is designed to help applicants understand how the PCORI merit review criteria align with criteria from other funding organizations with which applicants might be familiar (e.g., NIH). Though

PCORI's criteria do map to most NIH criteria, there are areas where we ask for different information (i.e., PCORI does not include a criterion that tracks to NIH's innovation criterion, but does include criteria evaluating patient-centeredness and engagement) reflecting PCORI's unique approach.

Crosswalk of PCORI Merit Review Criteria with NIH Criteria	
SIGNIFICANCE	1. Study identifies critical methodological gap(s) in PCOR/CER 2. Potential for the study to improve PCOR/CER methods
APPROACH	3. Scientific merit (research design, analysis, and outcomes) 4. Investigator(s) and environment
PCORI-only Merit Review Criteria	
PATIENT-CENTEREDNESS/ENGAGEMENT	5. Patient-centeredness 6. Patient and stakeholder engagement

Below are PCORI's merit review criteria. PCORI's merit review panels use these criteria during the preliminary and in-person review phases to evaluate and score all submitted applications, and to ensure consistency and fairness in how applications are evaluated.

Criterion 1. Study identifies critical methodological gap(s) in PCOR/CER
The application should address the following:

- Does the application identify and make a persuasive argument for addressing critical gaps in current PCOR/CER methods and provide sufficient support from the published scientific literature?

Criterion 2. Potential for the study to improve PCOR/CER methods
The application should address the following:

- Does the application articulate clearly how the development, refinement, or comparison of methods, and/or the novel application of methods to PCOR/CER improves the validity, trustworthiness, and usefulness of PCOR/CER findings?
- Are the PCOR/CER methods generated from this study likely to inform best practices or standards for PCOR/CER?

Criterion 3. Scientific merit (research design, analysis, and outcomes)
The application should address the following:

- Does the application provide a clear conceptual framework or theoretical model and empirical evidence that inform the study design, key variables or constructs, analytical approach, and relationships being tested or explored?
- Does the application demonstrate adherence to the relevant PCORI Methodology Standards and describe methods that reflect state-of-the-art thinking and practice in the relevant methodological area?
- Are the study scope and timeline realistic, including the completion of specific scientific and engagement milestones?

Criterion 4. Investigator(s) and environment
This criterion should assess the appropriateness (e.g., qualifications and experience) of the

investigator(s)/team and the environment's capacity (e.g., resources, facilities, and equipment) to support the proposed project. It should not be an assessment of the institution's quality.

The application should also address the following:

- How well-qualified are the PIs, collaborators, and other researchers to conduct the proposed activities? Is there evidence of sufficient clinical or statistical expertise (if applicable)?
- Does the investigator or co-investigator have demonstrated experience conducting projects of a similar size, scope, and complexity?
- If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate for the project?

    o (Dual-PI Option Only) Does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?

- Is the level of effort for each team member appropriate for successfully conducting the proposed work?
- Does the application describe adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research?
- Is the institutional support appropriate for the proposed research?

Criterion 5. Patient-centeredness
Note: A study can be patient-centered even if the end-user is not the patient, as long as patients will benefit from the study findings (e.g., methods to produce more valid, trustworthy, and useful PCOR/CER findings).

The application should address the following:

- Does the application articulate clearly how the study will improve PCOR/CER methods that address outcomes of interest to patients and their caregivers?

Criterion 6. Patient and stakeholder engagement
The application should address the following:

- Are patients and/or other relevant stakeholders meaningfully engaged in appropriate phases of the research?
- Does the proposed study demonstrate the principles of reciprocal relationships; co-learning; partnership; and trust, transparency, and honesty?
- If engagement is deemed inappropriate in some or all aspects of the proposed study, does the application justify why it is not appropriate?

In-Person Review

During preliminary review, all administratively and scientifically compliant applications are evaluated and scored by panels of external reviewers based on PCORI's merit review criteria, including evaluation of adherence to the PCORI Methodology Standards. After preliminary review, PCORI program staff members evaluate panel scores and critiques to identify a subset of applications for merit reviewers to discuss at the in-person review meeting. Not all submitted applications move forward to in-person review.

During the in-person review, merit reviewers meet to discuss applications and to clarify further the merits of the proposed research. They also identify areas for improvement. Each application is re-scored based on the content of discussion. The Panel Chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review according to the standards outlined in the PFA.

Post-Panel Review

After the in-person meeting, PCORI program staff evaluate final merit review panel scores and comments, identify duplication or synergy among funded projects, and consider the fit of applications within the programmatic vision. Program staff members then recommend projects to a Selection Committee, which includes members of the Board. The Selection Committee considers recommendations and works with staff to identify a slate of applications for possible funding based on merit review scores, programmatic balance and fit, and PCORI's strategic priorities. This slate is then proposed to the Board for consideration and approval.

In addition, PCORI evaluates applicant risk before issuing a PCORI award. Factors considered include financial stability, quality of management systems, audit findings, and past performance on PCORI awards (e.g., compliance with PCORI reporting requirements, conformance to PCORI terms and conditions on previous awards, and timely achievement of milestones). Based on the risk assessment, PCORI may impose special terms and conditions on awardees or withhold contract issuance until such business risks are mitigated. **PCORI will not award new contracts to current awardees with overdue reports (progress, interim, final, etc.) until the overdue reports have been submitted to PCORI.**

Summary Statements and Funding Recommendations

Summary statements are provided to applicants approximately two weeks before funding decisions are announced. **If an application progresses to in-person discussion**, the applicant will receive a summary statement which will include:

- In-person panel discussion notes
- Final average overall score
- Preliminary reviewer critiques
- Application quartile, to help applicants understand how they did relative to other discussed applications, as appropriate

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

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to the Board for approval. Applicants to this current cycle's PFA will receive summary statements and notification of the funding status of their application no later than February 2020.