Cycle 1 2019 Funding Cycle

PCORI Funding Announcement:
Treatment of Post-Traumatic Stress Disorder (PTSD) in Adults

Published January 3, 2019

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes April 24, 2019, at 5 pm (ET). Application Guidelines, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/treatment-posttraumatic-stress-disorder-adults-cycle-1-2019.
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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Follow us on Twitter: @PCORI

PCORI Cycle 1 2019: Treatment of PTSD in Adults PFA
## Overview

<table>
<thead>
<tr>
<th>Published</th>
<th>January 3, 2019</th>
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<tbody>
<tr>
<td>Letter of Intent Deadline</td>
<td>January 31, 2019, by 5 pm (ET)</td>
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Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and for fit to program goals. Only those selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than February 26, 2019.

### Summary

Through this funding initiative, PCORI seeks to support patient-centered comparative clinical effectiveness research to generate important findings about which specific treatments for adults with PTSD are most effective, and for whom.

For this PFA, the proposed comparators may include psychological interventions, pharmacological interventions, or a combination of the two. All proposed comparators must have demonstrated evidence of efficacy (from systematic reviews, prior empirical investigations, or other scientific documentation). Study endpoints should include patient-centered outcomes such as symptom frequency and severity, functional endpoints, and quality of life.

Studies must include a minimum of 6 months of follow-up. PCORI is especially interested in studies that are inclusive of a broad patient population, including those with comorbidities, and in studies that are powered to assess the effectiveness of treatments in subgroups of interest.

### Applicant Resources


### Key Dates

<table>
<thead>
<tr>
<th>Event</th>
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<tbody>
<tr>
<td>Online System Opens</td>
<td>January 3, 2019</td>
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<tr>
<td>Town Hall</td>
<td>January 17, 2019; 12:00 - 1:00 pm ET</td>
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<tr>
<td>LOI Deadline</td>
<td>January 31, 2019, by 5 pm (ET)</td>
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<tr>
<td>LOI Status Notification</td>
<td>February 26, 2019</td>
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<tr>
<td>Application Deadline</td>
<td>April 24, 2019, by 5 pm (ET)</td>
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<tr>
<td>Merit Review</td>
<td>July 2019</td>
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<td>Awards Announced</td>
<td>September 2019</td>
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<tr>
<td>Earliest Project Start Date</td>
<td>December 2019</td>
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### Maximum Project Budget (Direct Costs)

<table>
<thead>
<tr>
<th>Amount</th>
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<td>$5 million</td>
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### Maximum Research Project Period

<table>
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<tr>
<th>Duration</th>
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<tr>
<td>3.5 years (42 months)</td>
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### Funds Available Up To

<table>
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<tr>
<th>Amount</th>
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<td>$15 million</td>
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### Eligibility

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.
<table>
<thead>
<tr>
<th>Review Criteria</th>
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<tbody>
<tr>
<td>1. Potential for the study to fill critical gaps in evidence</td>
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<td>2. Potential for the study findings to be adopted into clinical practice and improve delivery of care</td>
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<td>3. Scientific merit (research design, analysis, and outcomes)</td>
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<td>4. Investigator(s) and environment</td>
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<td>5. Patient-centeredness</td>
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<td>6. Patient and stakeholder engagement</td>
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<tr>
<th>Contact Us</th>
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<tr>
<td><strong>Programmatic Inquiries:</strong> Please contact the PCORI Helpdesk via email (<a href="mailto:sciencequestions@pcori.org">sciencequestions@pcori.org</a>), phone (202-627-1884), or online (<a href="http://www.pcori.org/PFA/inquiry">http://www.pcori.org/PFA/inquiry</a>). PCORI will respond within two business days. However, we cannot guarantee that all questions will be addressed in two business days prior to an LOI or application deadline.</td>
</tr>
<tr>
<td><strong>Administrative, Financial, or Technical Inquiries:</strong> Please contact the PCORI Helpdesk at <a href="mailto:pfa@pcori.org">pfa@pcori.org</a>. PCORI will respond within two business days. Please note that during the week of a deadline, response times may exceed two business days. 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.</td>
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<th>Other</th>
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<tr>
<td>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.</td>
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I. Introduction

Summary of Program

Through this initiative, PCORI seeks to fund high-quality clinical studies that compare the effectiveness of evidence-based psychological and/or pharmacological treatments for post-traumatic stress disorder (PTSD) in adults.

Previous research in PTSD has demonstrated the efficacy of many psychological interventions and some pharmacological treatments. However, few robust head-to-head comparisons of evidence-based interventions have been completed to date. Studies that assess the heterogeneity of treatment effect within subgroups of interest (e.g., military versus civilian populations, men versus women, type of trauma) and those that include patients with conditions that frequently co-occur with PTSD (e.g., substance use disorder) are especially needed. The goal of this funding initiative is to support patient-centered comparative clinical effectiveness research to generate important findings about which specific treatments for adults with PTSD are most effective, and for whom.

Proposed comparators may include psychological interventions, pharmacological interventions, or a combination of the two. All proposed interventions must have demonstrated evidence of efficacy that is at least moderate strength (from systematic reviews, prior empirical investigations, or other scientific documentation). Study endpoints should include patient-centered outcomes such as functional outcomes and quality of life in addition to symptom-related measures. Studies must include a minimum of six months of follow-up. PCORI is especially interested in studies that are inclusive of a broad patient population, including those with co-morbidities, and in studies that are powered to assess the effectiveness of treatments in subgroups of interest. Applicants should clearly define why the question and associated comparison they propose are of clinical interest, providing a rationale for the proposed study and describing how it has the potential to improve clinical care. All proposed studies need to be justified by an important gap in the current evidence base for guiding the delivery of clinical care.

Background

PTSD is characterized by a set of symptoms that occur following exposure to a traumatic event.¹ The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) categorizes PTSD symptoms into four groups: (1) intrusion, (2) avoidance, (3) negative alterations in cognition and mood, and (4) changes in arousal and reactivity. To be diagnosed with PTSD, an individual must experience at least one intrusion symptom, one avoidance symptom, two cognition and mood symptoms, and two arousal and reactivity symptoms for more than one month. Additionally, these symptoms must cause clinically significant distress or functional impairment.²

PTSD can occur after exposure to many different types of trauma, such as military combat, interpersonal violence (including sexual, physical, or emotional abuse), a natural or manmade disaster, the unexpected death of a loved one, or a severe motor vehicle accident. Among the US general adult population, the past-year and lifetime prevalence of PTSD are estimated as 4.7 percent and 6.1 percent, respectively. The prevalence of PTSD is greater among certain populations, such as active duty military personnel and veterans. For example, the estimated lifetime prevalence of PTSD among Vietnam veterans is 18.7 percent. Additionally, the 2009–2010 National Health Study for a New Generation of US Veterans found that 15.8 percent of Iraq and Afghanistan veterans screened positive for PTSD.

Individuals who present with PTSD are generally treated with psychological interventions, pharmacological agents, or a combination of the two, with psychological interventions recommended over pharmacological agents as first-line treatment in current clinical guidelines. In 2016, PCORI commissioned an update of a 2013 Agency for Healthcare Research and Evaluation (AHRQ) systematic evidence review on psychological and pharmacological treatments for PTSD in adults. The purpose of the update was to document important recent developments in the evidence base. The updated review, published in May 2018, found strong strength of evidence supporting the efficacy for psychological interventions including trauma-focused cognitive behavioral therapy with an exposure component, and moderate strength of evidence supporting the efficacy of three drugs—two selective serotonin reuptake inhibitors (paroxetine and fluoxetine) and one serotonin and norepinephrine reuptake inhibitor (venlafaxine).

Given the small number of direct comparisons of active interventions within the literature, the 2018 PCORI/AHRQ report concludes that the current evidence base is insufficient to determine the comparative effectiveness of psychological and pharmacological treatments. Moreover, the report emphasizes that the current evidence base is insufficient to determine whether any treatment approaches are more efficacious or effective for certain subgroups of patients, such as those with comorbid conditions or those who have faced one type of trauma versus another.

These findings are consistent with the research needs called out within current clinical guidelines, including US Department of Veterans’ Affairs (VA)/Department of Defense (DoD) and American Psychological Association (APA) guidelines, both published in 2017. Accordingly, the goal of this funding initiative is to support patient-centered comparative clinical effectiveness research to generate

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important findings about which specific treatments for adults with PTSD are most effective, and for whom.

Evidence Gaps

The 2018 AHRQ/PCORI systematic review update, 2017 APA clinical practice guideline, and 2017 VA/DoD clinical practice guideline describe evidence gaps and outline important areas for future research. The following four key areas emerged across the three sources:

1. There is a need for more head-to-head, direct comparisons of evidence-based psychological interventions, pharmacological interventions, and/or a combination of psychological and pharmacological interventions.

2. There is a need for more studies that assess the heterogeneity of treatment effects of evidence-based interventions for PTSD in subgroups of interest, including sex/gender, civilian versus military populations, and type of trauma.

3. There is a need for studies that include individuals with co-morbidities that commonly occur with PTSD, such as substance use disorder.

4. There is a need for studies that evaluate patient-centered outcomes, such as functional outcomes and quality of life.

Priority Research Question

PCORI seeks to fund high-quality clinical studies that address the following research question:

Which psychological and/or pharmacological treatments are most effective for the treatment of PTSD in adults, and for whom?

Applicants should consider the following parameters when responding to this PFA:

- **Population:** Patients included should be adults aged 18 years or older with a diagnosis of PTSD per DSM-5 criteria. PCORI is particularly interested in studies that allow the inclusion of individuals with conditions and diagnoses commonly co-occurring with PTSD (e.g., substance use disorder). Studies that examine the effectiveness of interventions in key subgroups (e.g., military versus civilian populations, men versus women) are also of interest. Applicants should clearly specify the proposed patient population(s) and delineate key inclusion and exclusion criteria.

- **Interventions:** Proposed interventions may include psychological interventions, pharmacological treatments, or combinations of the two. All proposed comparators must have demonstrated evidence of efficacy that is at least moderate strength, documented via systematic reviews, prior empirical investigations, or other scientific documentation. Moreover, applicants should clearly define why the question and associated comparison they propose are of clinical interest, providing a rationale for the proposed study and describing how it has the potential to improve clinical care.

- **Outcomes:** Applicants should propose appropriate patient-centered outcomes. In addition to measuring PTSD symptoms and remission, study endpoints should include functional outcomes...
and quality of life. Applicants should provide a clear rationale for the selection of study endpoints, and all proposed outcomes must be well validated.

- **Timing**: Applicants should clearly specify the duration, format, and dosage of each intervention. Studies must include a minimum of six months of follow-up, but longer follow-up is preferred.

### Funds Available

PCORI has allotted up to $15 million in total costs under this PFA to fund high-quality clinical comparisons of treatments for PTSD in adults. The proposed budget for studies under this initiative may be up to $5 million in direct costs, as appropriate. The maximum project period is 3.5 years (42 months).

PCORI will not cover costs for clinical services that constitute the procedures, treatments, interventions, or other standard clinical care (“patient care”) that an applicant is proposing for comparison in the research project (“patient care costs”). The host healthcare delivery system, third-party payer, product manufacturer, intervention owner/licensing entity, or other interested party must cover the patient care costs.

PCORI seeks efficient studies, such as those that take advantage of large civilian and/or military populations already under observation; registries; research cooperatives; and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of intervention-related costs.

### II. Guidance for Preparing Applications

#### Specific Requirements for this Funding Announcement

The proposed study should meet the following requirements:

- **Focus on the priority research question, with consideration of what is important to patients, clinicians, and other decision makers.**

- **Address a question of clinical interest to the field; the importance of this question, and the associated comparison, should have been substantiated by a recent, rigorously conducted systematic review or emphasized by an official professional society’s clinical practice guideline.**

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

- **Propose a sample size that is sufficiently large to allow for precise estimation of hypothesized effect sizes.** When determining anticipated effect sizes, please ensure that such estimates are based on results observed in prior publications of adequately powered and well-conducted clinical studies.

- **Present a well-defined plan to ensure that participant recruitment, enrollment, accrual, and retention will be maximized.** This plan should describe where participants will be recruited and document the available volume of likely eligible patients in each proposed clinical site. Specific
plans to retain enrolled participants should be included. Applicants should provide evidence that the proposed study will not encounter significant recruitment or participation barriers.

- Studies must include appropriate oversight by local or centralized Institutional Review Boards (IRBs) while avoiding undue burdens on patients or barriers to study participation.
- Examine diverse populations receiving care in real-world settings.
- Have strong interest and support from host delivery systems and clinical care settings.
- Specify broad and simple eligibility criteria that will allow for wide generalization of results while attending appropriately to any ethical concerns of excess risk in some patient subgroups.
- Include patient-reported outcomes (PROs) as primary outcomes, when appropriate.
- Adhere to all relevant PCORI Methodology Standards.10 The full application will require the applicant to identify the standards appropriate to the proposed study and to describe how the study team plans to address each standard.
- In the case of RCTs, also adhere to current best practices (standardized inclusion or exclusion criteria; proper randomization; techniques to minimize the potential for missing data; and appropriate safety monitoring, including establishing a Data and Safety Monitoring Board [DSMB] or indicating why such a board is unnecessary).

To carry out studies that allow for adoption of the findings in a real-world setting, and to maximize the efficient use of resources, take care to prevent these trials from becoming more complex and onerous than necessary. We encourage the applicant to be creative and consider the following innovative strategies, as appropriate and feasible:

- Consult with patients and other stakeholders on their decisional dilemma and evidence needs, or reference previously documented decisional dilemmas in preparation for submitting the LOI and full application.
- Carefully describe pertinent evidence gaps and why the project questions represent decisional dilemmas for stakeholders (i.e., patients, clinicians, and policy makers). Similarly, applicants should document why project outcomes are especially relevant and meaningful endpoints for patients and their families.
- 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 refine the research questions and study protocol, help monitor progress, and disseminate the findings.
- Minimize disruption to participants’ daily routines (e.g., minimize participant visits intended for study-assessment purposes and capture PROs during office visits, electronically, or via phone).

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10 Available at pcori.org/research-we-support/research-methodology-standards/.
• Design the study so that you can conduct it using routine clinic or office operations.

• Use efficient methods to obtain participant consent while still meeting ethical and legal requirements.

• Capitalize on the existing electronic health records (EHRs) 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 have not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different EHR systems.

**Non-responsiveness**

Applications will be considered non-responsive to this PFA if the proposal:

• Includes any interventions for which there is not demonstrated evidence of efficacy that is of at least moderate strength

• Proposes the development, testing, and validation new decision aids and tools, or clinical prognostication tools

• Fails to include analyses of subgroups of interest

• Compares patient characteristics rather than clinical strategies

Consistent with PCORI's authorizing law, 11 PCORI does not fund research whose findings will include:

• Coverage recommendations

• Payment or policy recommendations

• Creation of clinical practice guidelines or clinical pathways

• Establishment of efficacy for a new clinical strategy

• Pharmacodynamics

• Study of the natural history of disease

• Basic science or the study of biological mechanisms

**Studies of Cost-Effectiveness**

PCORI will consider an application nonresponsive if the proposed research:

• Conducts a formal cost-effectiveness analysis of alternative approaches to providing care

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

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

PCORI does have an interest, however, in studies addressing questions about conditions leading to high costs to the individual or to society. This interest is reflected in our review criterion on the condition’s impact on the health of individuals and populations. Thus, PCORI is interested in studies that:

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

Avoiding Redundancy

PCORI expects potential applicants to review funded research at pcori.org, clinicaltrials.org, and through other sources, and to include documentation in that appropriate steps have been taken by the applicant to ensure that duplication is avoided. 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 54 individual standards that fall into 13 categories. The first five categories are cross-cutting and relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These cross-cutting 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 cross-cutting and applicable to all PCOR studies.

The eight other standards categories will be applicable to particular study designs and methods. Applicants should use the standards in each of these categories as guidance when they are relevant to a study. These categories are:

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

Most of these standards are minimal. The PCORI Methodology Standards reflect practices that applicants should follow in all cases, and all deviations need to be explained and 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.

**Patient-Centered Outcome Measures**

PCORI encourages investigators to design their research using validated outcome measures. Include preliminary data that support using the proposed measures in the study population. We encourage investigators to consider those measures described in the Patient-Reported Outcomes Measurement Information System\(^\text{12}\) (PROMIS).

**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 network 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 commercial or public insurers (including the U.S. military and veteran health care system) to facilitate the conduct of comparative clinical effectiveness research. PCORI does not intend for this PFA to support the development of new patient registries, but rather to support the effective utilization of established 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.

\(^{12}\) Available at http://www.nihpromis.org/.
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 the Engagement Rubric\(^\text{13}\), which can be found in the PCORI Funding Center. Applicants should also review the PCORI Methodology Standards Associated with Patient-Centeredness and PCORI’s Sample Engagement Plans.\(^\text{14}\) The rubric and Sample Engagement Plans are not intended to be comprehensive or prescriptive; instead, they provide a variety of examples to incorporate engagement, where relevant, into the research process.

Applicants are expected to consult with patients and other stakeholders on their decisional dilemma and evidence needs, or to reference previously documented decisional dilemmas in preparation for the submission of Letters of Intent (LOIs) and applications. To describe the decisional dilemma, state the specific clinical decision(s) or treatment choice(s) confronted by the decision makers and explain how the findings from the proposed research will inform those decisions. State why this decision—such as choosing a specific medication, psychological intervention, or combination of the two to treat a condition or manage a specific population—is important to patients. Document the uncertainty patients and other stakeholders face in making this decision. Identify the patients and other stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continue engaging them actively in the conduct of the study. Similarly, applicants should document how the project outcomes are especially relevant and meaningful endpoints to patients and other stakeholders.

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; to discuss which subgroups are most important; and to discuss how the subgroups will be analyzed, including whether or not the study will be powered to examine the question of effectiveness in subgroups. PCORI is particularly interested in including 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 the following list of populations of interest to guide our efforts in research and engagement. (Note that the Addressing Disparities Priority Area requires that proposed research focus on at least one of the groups indicated by an asterisk below.)

- Racial and ethnic minority groups*  

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\(^{13}\) Available at http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf.

\(^{14}\) Available at http://www.pcori.org/sites/default/files/PCORI-Sample-Engagement-Plans.pdf
Low-income groups*
Women
Children (age 0–17 years)
Older adults (age 65 years and older)
Residents of rural areas*
Individuals with special healthcare needs, including individuals with disabilities*
Individuals with multiple chronic diseases
Individuals with rare diseases
Individuals whose genetic makeup affects their medical outcomes
Patients with low health literacy, numeracy, or limited English proficiency*
Lesbian, gay, bisexual, transgender (LGBT) 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, 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 that 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.

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

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15 See http://grants.nih.gov/sites/default/files/supplementalinstructions.docx
human subject protections rest with the Institutional Review Board or international equivalent that have jurisdiction for the study.

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

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

PCORI requires 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.18

**Data Management and Data-Sharing Plan**

PCORI encourages openness in research and making research data available for purposes of replication and reproducibility. As such, if an award is made through this targeted Funding Announcement, the Awardee will be required to adhere to PCORI’s Policy for Data Management and Data Sharing.

The Policy articulates PCORI’s requirement that certain Awardees—specifically those funded through the Pragmatic Clinical Studies (PCS) and all targeted Funding Announcements—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. 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.

A full data management and data sharing plan is not required at the time of application. If an award is made, the Awardee will be 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. Awardees are also strongly encouraged to include, as appropriate, language in the research project’s informed consent forms that allows for the de-identification and sharing of study data for secondary research purposes.

As part of the Policy, PCORI intends to cover reasonable costs associated with the time and effort needed for preparing, depositing, and maintaining the Full Data Package in the repository for a period of at least seven (7) years following acceptance by PCORI of the Final Research Report. PCORI will negotiate with Awardees on the specific budget needs associated with this Policy requirement at the time of Award, in addition to the requested research project budget.

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. Please refer to the Policy in its entirety for additional information.

**Recruitment**

Proposals should include information about the size and representativeness of the potential pool of patients from which recruitment will occur, and describe the means by which 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; 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.

Peer Review and Release of Research Findings

PCORI has a legislative mandate to ensure the scientific integrity of the primary research it supports and to make study findings widely available and useful to patients, clinicians, and the general public within a specific timeframe. Accordingly, the PCORI Board of Governors (Board) adopted the Process for Peer Review of Primary Research and Public Release of Research Findings.\textsuperscript{19}

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 from the PCORI Funding Center. They must complete the document and convert it to a PDF file. The LOI is limited to three 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 Letters of Support, because they are not requested at this stage. Their

inclusion will result in LOI rejection without review. Please visit the PCORI Funding Center for additional applicant resources, including the PFA and required templates.

The LOI for the proposed study should contain the following information:

- Title of the proposed study that preferably captures the comparative nature of the study
- Specific aims (clearly stated)
- How the study will improve the quality and relevance of evidence available to help patients and stakeholders make informed health decisions
- Knowledge gap addressed by research question(s)
- Concise description of study design
- Study population (description of participants and participating study sites)
- Outcomes (identification and description of why they are important to patients)
- Sample size
- Comparators (described and listed clearly, with demonstrated efficacy specified for each and details on how the strategies will be delivered in real-world settings)
- Patient and other stakeholder engagement (involvement through planning, conducting, and disseminating)

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 PCORI Online. The deadline for LOI submission is January 31, 2019, by 5 p.m. (ET).

LOI Review

LOIs are evaluated based on the following:

- Importance and relevance of the topics to PCORI priorities, as evidenced by critical gaps identified by clinical guidelines developers and recent systematic reviews
- Clarity and credibility of responses to the LOI questions
- The investigators’ prior relevant experience
- Programmatic fit and balance, considering whether the application overlaps with previously funded studies or concurrent applications to a significant degree or, conversely, whether the application fills a gap in the portfolio with certain characteristics, including disease category, topics, priority population, methodologies, and other variables

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. A minimum of two 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 February 26, 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
- Principal Investigator (PI)
- Institution

If you need to change any of this information or have 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 non-PI 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**

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 additional details. Appendix 2 within the guidelines provides a list of allowable and unallowable costs. This PFA does not consider exceptions to the budget or to period-of-performance limits. PCORI will not review requests exceeding the stated maximum budget or period of performance. 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 in the PCORI Funding Center.

**PCORI Online**

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 Online System**  [https://pcori.force.com/engagement](https://pcori.force.com/engagement)
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, describes research that is not comparative, 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.
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. Potential for the study to fill critical gaps in evidence:**

The application should address the following questions:

- Does the application convincingly describe the clinical burden?
- Does the application identify a critical gap in current knowledge as noted in systematic reviews, guideline development efforts, or previous research prioritizations?
- Does the application identify a critical gap in current knowledge, evidenced by inconsistency in clinical practice and decision making?
- Would research findings from the study have the potential to fill these evidence gaps?

**Criterion 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care**

The application should describe how evidence generated from this study could be adopted into clinical practice and delivery of care by others. The application should also address the following questions:

- Does the application identify who will make the decision (i.e., the decision maker) or use (i.e., the end-user) the study findings (not the intervention) this study produces, such as local and national stakeholders?
- Does the application identify potential end-users of study findings—such as local and national stakeholders—and describe strategies to engage these end-users?
- Does the application provide information that supports a demand for this kind of a study from end-users?
- Would this study’s research findings have the potential to inform decision making for key stakeholders? If so, provide an example. How likely is it that positive findings could be
reproduced by others, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder adoption of the intervention by others.

- Does the application describe a plan for how study findings can be disseminated beyond publication in peer-reviewed journals and at national conferences?

Criterion 3. Scientific merit (research design, analysis, and outcomes)

The application should show sufficient technical merit in the research design to ensure that the study goals will be met. The application should also address the following questions:

- Does the application describe a clear conceptual framework anchored in background literature which informs the design, key variables, and relationship between interventions and outcomes being tested?
- Does the Research Plan describe rigorous methods that demonstrate adherence to the PCORI Methodology Standards?
- Is the overall study design justified?
- Are the patient population and study setting appropriate for the proposed research question?
- Does the application provide justification that the outcome measures are validated and appropriate for the population?
- Are each of the comparators (e.g., active intervention arm and comparator arm) described clearly and well-justified?
- Are the sample sizes and power estimates appropriate? Is the study design (e.g., cluster randomized design, randomized controlled trial, or observational study) accounted for and is the anticipated effect size adequately justified?
- Is the study plan feasible? Is the project timeline realistic, including specific scientific and engagement milestones? Is the strategy for recruiting participants feasible? Are assumptions about participant attrition realistic, and are plans to address patient or site attrition adequate?

Criterion 4. 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 questions:

- 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

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

The application should also address the following questions:
• Does the application include a thorough description about which outcomes (both benefits and harms) are important to patients, and are those outcomes included in the study plan?
• Does the application provide information that indicates that closing the evidence gap is important to patients and other stakeholders?
• Are the interventions being compared in the study available to patients now, and are they the best options for comparison (including whether they would be chosen by patients and their healthcare providers for managing the condition being studied)?

Criterion 6. Patient and stakeholder engagement

The application should demonstrate the engagement of relevant patients and other stakeholders (e.g., patients, caregivers, clinicians, policy makers, hospital and health system representatives, payers [insurance], purchasers [business], industry, researchers, and training institutions) in the conduct of the study. Quality of engagement should be evaluated based on scope, form, and frequency of patient and stakeholder involvement throughout the research process.

The application should also address the following questions:
• Does the application provide a well-justified description of how the research team incorporates stakeholder involvement? Does the study include the right individuals (e.g., patients, caregivers, clinicians, policy makers, hospital and health system representatives, payers, purchasers, industry, researchers, and training institutions) to ensure that the projects will be carried out successfully?
Does the application show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, and implementing)? Is the frequency and level of patient and stakeholder involvement sufficient to support the study goals?

- Is the proposed Engagement Plan appropriate and tailored to the study?
- Are the roles and the decision-making authority of all study partners described clearly?
- Are the organizational structure and resources appropriate to engage patients and stakeholders throughout the project?

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

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 September 2019.