Cycle 1 2018 Funding Cycle

PCORI Funding Announcement:
Pharmacological Treatment of Anxiety Disorders in Children, Adolescents and/or Young Adults

Published January 16, 2018

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes May 16, 2018, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/pharmacological-treatment-anxiety-children-adolescents-andor.
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.”
The Patient-Centered Outcomes Research Institute (PCORI) will screen Letters of Intent (LOIs) for responsiveness to this PCORI Funding Announcement (PFA) and for fit to program goals. Only those applicants with an approved LOI will be permitted to submit a full application. Notification of denial or approval to submit a full application will occur no later than March 14, 2018.

### Summary

The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund high-quality clinical studies that compare the effectiveness of two or more pharmacological treatments for moderate to severe anxiety in children, adolescents, and/or young adults (e.g., comparisons of shorter-acting to longer-acting selective serotonin reuptake inhibitors (SSRIs) or comparisons of SSRIs to selective serotonin norepinephrine reuptake inhibitors (SNRIs)); pharmacological treatments should be delivered in conjunction with Cognitive Behavioral Therapy (CBT) or another evidence-based psychological intervention.

For this PFA, PCORI is broadly interested in comparisons that are relevant and applicable to patients in the age range of 7 through 25 years; this age range represents a spectrum of developmental stages. Applicants will be asked to clearly define the specific age range to be studied, and to provide a scientific rationale justifying the coherence of the proposed study population, in terms of age, disease severity, proposed intervention approaches, and analytic plans.

Each proposed comparator must be clearly defined, evidence-based, and widely available, and applicants should ensure that all comparators are appropriate for the age range and disorder severity of the study population. Studies must include a minimum follow-up period of one year from baseline; two years of follow-up from baseline is preferred. In addition, all studies funded through this initiative must include robust sample sizes of at least 300 participants, with sufficient power demonstrated to conduct proposed primary analyses and subgroups as appropriate to the proposed population.

For this solicitation, applicants are not required to demonstrate that patients and other stakeholders are already engaged as research team members at the time an application is submitted. However, applicants should outline how patients and other stakeholders will participate as partners in various phases of the proposed research, once awarded. Applicants should describe their plan to form a Study Advisory Committee (SAC), and other appropriate engagement body, to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. PCORI may recommend additional representation in collaboration with the applicant, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. However, PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups, and other bodies, or involving individual patient and other stakeholder partners in various ways are also permissible to employ—either in addition to or instead of—the formation of the SAC. The SAC provision is not meant to require that a separate governance or advisory entity be established beyond the study governance and advisory structure the awardee has planned, if an applicant already has an approach for including the relevant and required patient and other stakeholder partners. For clarification in your application materials and for merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for in-person meetings at least two times per year and appropriate budgeting.

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1 The intent of the SAC described in the PFA is to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. PCORI may recommend additional representation in collaboration with the applicant, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. However, PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups, and other bodies, or involving individual patient and other stakeholder partners in various ways are also permissible to employ—either in addition to or instead of—the formation of the SAC. The SAC provision is not meant to require that a separate governance or advisory entity be established beyond the study governance and advisory structure the awardee has planned, if an applicant already has an approach for including the relevant and required patient and other stakeholder partners. For clarification in your application materials and for merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for in-person meetings at least two times per year and appropriate budgeting.
Regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. PCORI may recommend additional representation in collaboration with the applicant, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts.

Note that this funding program does not support applications in conducting cost-effectiveness analyses, systematic reviews (with or without meta-analyses), or developing or conducting efficacy evaluation of shared decision making. PCORI will not cover costs for interventions that are being compared in the proposed study. (See Appendix 3: Administrative Actions in the Pediatric Anxiety Application Guidelines for details.)

### Applicant Resources

### Key Dates
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<td>January 16, 2018</td>
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<td>January 31, 2018</td>
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<td>LOI Deadline</td>
<td>February 13, 2018, by 5 p.m. (ET)</td>
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<td>Application Deadline</td>
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### Maximum Project Budget (Direct Costs)
$15 million

### Maximum Research Project Period
Five years

### Funds Available Up to
$40 million

### Eligibility
Any private-sector research organization, including any nonprofit or for-profit organization; any public-sector research organization, including any university or college hospital or healthcare system; any laboratory or manufacturer; or unit of local, state, or federal government may submit applications. 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. Potential for the study to fill critical gaps in comparative clinical effectiveness evidence
2. Potential for the study findings to be adopted into clinical practice and improve delivery of care
3. Scientific merit (research design, analysis, and outcomes)
4. Investigator(s) and environment
5. Patient-centeredness
6. Patient and stakeholder engagement
| Contact Us | Programmatic Inquiries: 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 we can address all questions in a timely fashion when the inquiry is made three or fewer business days before 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. Applicants may also call the PCORI Helpdesk at 202-627-1885. Please note that during the week of the application deadline, response times may exceed two business days. We ask that applicants plan accordingly. It is the applicant’s responsibility to submit the application on or before the application deadline. |
| Other | Deadlines are at 5 p.m. (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday. |
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I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to generate needed scientific evidence to aid patients, families, and clinicians in making decisions about pharmacological treatments for pediatric anxiety. PCORI seeks to fund high-quality clinical studies that compare the effectiveness of two or more pharmacological treatments for moderate-to-severe anxiety in children, adolescents, and/or young adults delivered in conjunction with Cognitive-Behavioral Therapy (CBT) or another evidence-based psychological intervention. Pharmacological comparisons of interest include, but are not limited to, the following:

- Comparisons of shorter-acting to longer-acting selective serotonin reuptake inhibitors (SSRIs)
- Comparisons of SSRIs to selective serotonin norepinephrine reuptake inhibitors (SNRIs)

For this PFA, PCORI is broadly interested in comparisons that are relevant and applicable to patients in the age range of 7 through 25 years; this age range represents a spectrum of developmental stages. Applicants will be asked to clearly define the specific age range to be studied, and to provide a scientific rationale justifying the proposed study population—in terms of age and disease severity—and the proposed intervention approaches and analysis plan. In addition, studies must collect data on patient comorbidities.

Each proposed comparator must be clearly defined, evidence based, and widely available, and applicants should ensure that all comparators are appropriate for the age range and disorder severity of the study population. Studies must include a minimum follow-up period of one year from baseline; two years of follow-up from baseline is preferred. In addition, all studies funded through this initiative must include robust sample sizes of at least 300 participants, with sufficient power demonstrated to conduct proposed primary analyses and subgroups as appropriate to the proposed population.

Background

Anxiety disorders are one of the most common childhood-onset psychiatric disorders in the United States, with a lifetime prevalence of 31.9 percent among adolescents between the ages of 13 and 18, with 8.3 percent diagnosed as having severe anxiety. Pediatric anxiety disorders typically follow an unremitting course and impede the social, emotional, and academic development of youth. Early intervention may modify the trajectory of the disorder and prevent significant impairment. These disorders often persist into adulthood and are associated with severe mental health conditions such as depression, substance abuse, functional and occupational impairments, and suicidal behavior.

According to a 2017 systematic review published by the Agency for Healthcare Research and Quality (AHRQ), the main treatment options for pediatric anxiety disorders include psychological interventions, pharmacotherapy, and combination approaches. The AHRQ review found that, among the various psychological interventions, CBT is the most widely studied and has the strongest evidence of effectiveness. Among the pharmacological therapies, SSRIs and SNRIs have the strongest evidence of effectiveness in children and adolescents.\(^4\)

Despite the range of available evidence-based treatment options, clinical guidelines offer inconsistent and conflicting advice regarding the treatment for youth with moderate-to-severe symptomatology. Most guidelines recommend first-line treatment with CBT, but they differ regarding whether and when to introduce pharmacological treatment options.\(^3,5,6\) In general, pharmacotherapy might be appropriate when patients present with moderate or severe symptoms initially, when patients are unable to access psychotherapy, or when psychotherapy inadequately addresses symptoms.\(^4\) The benefits of pharmacotherapy must also be weighed against potential disadvantages such as possible adverse effects and diminished improvements after treatment discontinuation.\(^4\) In addition, there is a lack of information to help guide patients, families, and clinicians in deciding what medications to use as first-, second- or third-line therapies given a patient's individual characteristics.

Numerous evidence gaps around the comparative effectiveness of available treatment options exacerbate the uncertainty around these treatment decisions. With respect to CBT, there is a lack of evidence for comparisons of different delivery models. In relation to the use of pharmacotherapy, the evidence base is characterized by a lack of head-to-head comparisons of medications, combination therapy of medication plus psychological therapy versus either treatment alone and treatment sequencing approaches.

To begin addressing these evidence gaps, PCORI released a series of funding announcements in 2017. In Cycle 2 2017, PCORI released a PCS Special Area of Emphasis funding announcement on *digital applications of CBT for treatment of mild-to-moderate anxiety in children, adolescents, and/or young adults*. This initiative aimed to address the comparative effectiveness of different forms of delivery of CBT (e.g., digital versus face-to-face CBT) for pediatric patients. In Cycle 3 2017, PCORI introduced a new PCS priority topic that broadly focused on the treatment of anxiety disorders in children, adolescents, and/or young adults, with an emphasis on the comparative effectiveness of different approaches to treatment initiation, sequencing, monitoring, maintenance, and/or relapse prevention.

This current targeted funding announcement aims to complement our work to date and expand PCORI’s investment in pediatric anxiety disorders by addressing a critical evidence gap: head-to-head comparisons of pharmacological therapies, in conjunction with evidence-based psychological therapies,

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\(^6\) Anxiety and Depression in Children and Youth – Diagnosis and Treatment. (2010). Guidelines & Protocols Advisory Committee, British Columbia Medical Services Commission.
for children, adolescents, and/or young adults with moderate-to-severe anxiety.

Evidence Gaps

The need for additional evidence on the comparative effectiveness of pharmacological and combination pharmacological/psychological treatment options for pediatric anxiety disorders has been highlighted both in the literature and by stakeholders. Within the 2017 AHRQ systematic review on treatments for pediatric anxiety disorders, only two randomized controlled trials (RCTs) conducted head-to-head comparisons of medications.

Additionally, only three RCTs compared the combination of CBT and a medication to CBT alone and/or to medication alone.\(^4\) Two of these RCTs had small sample sizes of only 62 patients each. The third RCT—the Child-Adolescent Anxiety Multimodal Study (CAMS)—included 488 patients. It found that the combination of CBT and sertraline (an SSRI) improved primary anxiety symptoms, function, and clinical response more than either CBT alone or sertraline alone.\(^7\) A secondary analysis of the CAMS data, published in 2017, showed that youth with mild-to-moderate anxiety at baseline achieved remission with CBT alone, sertraline alone, or combination therapy. In contrast, youth with severe anxiety at baseline needed combination therapy to achieve a significant improvement in the likelihood of remission.\(^8\)

While CAMS is a landmark study, more studies on head-to-head comparisons of medications and combination therapy are needed to increase the actionable evidence base for treatment of pediatric anxiety disorders.\(^9\) The AHRQ review notes that larger RCTs with longer follow-up periods are needed to assess the longer-term safety of medications. Also, more research is needed to evaluate the most beneficial components of CBT and the impact of comorbidities, family demographics, and stressors as treatment effect modifiers.\(^4\)

Priority Research Question

PCORI seeks to fund high-quality clinical studies that address this PFA’s research question:

Based on patient- and family-centered outcomes, what is the comparative clinical effectiveness of two or more pharmacological interventions (in combination with CBT or another evidence-based psychotherapeutic approach) for the treatment of moderate-to-severe anxiety disorders in children, adolescents, and/or young adults? Pharmacological comparisons of interest include, but are not limited, to the following:

- Comparisons of shorter-acting to longer-acting selective serotonin reuptake inhibitors (SSRIs)
- Comparisons of SSRIs to selective serotonin norepinephrine reuptake inhibitors (SNRIs)

Pharmacological comparators must be delivered in conjunction with CBT or an alternative evidence-based psychological intervention. Each proposed comparator must be clearly defined, evidence based,

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and widely available, and applicants should ensure that all comparators are appropriate for the age range and disorder severity of the study population. All studies must collect data on patient comorbidities. In addition, all studies funded through this initiative must include robust sample sizes of at least 300 participants, with sufficient power demonstrated to conduct proposed primary analyses. Applications that propose sample sizes of fewer than 300 participants will be considered nonresponsive. Where possible, studies should propose means to evaluate the comparative effectiveness of different approaches to treatment monitoring, maintenance, and/or relapse prevention following an initial effective course of treatment.

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

- **Population:** The population must be children, adolescents, and/or young adults diagnosed with an anxiety disorder and exhibiting moderate-to-severe symptomatology. Clinical diagnoses of study participants must be specified. PCORI is interested in comparisons that are relevant and applicable to a spectrum of developmental stages represented by patients in the age range of 7 through 25 years old. Applicants should clearly define the specific age range to be studied and provide a scientific rationale and specific benefit for the proposed study population. Special populations of interest include underserved populations, including racial and ethnic minorities, low-income youth, and youth living in rural areas.

- **Interventions:** Each proposed comparator must include an evidence-based pharmacological treatment option. For example, a study comparing shorter-acting to longer-acting SSRIs or a study comparing SSRIs to SNRIs. All pharmacological treatments must be delivered in conjunction with CBT or another psychological intervention with established evidence of efficacy. See Important Safety Considerations below for guidance on the inclusion of appropriate human subjects protections.

- **Outcomes:** Applicants should propose patient- and family-centered outcomes that are well validated, responsive to change where baseline measures are employed, and developmentally appropriate for the proposed study population. Outcomes should include the following domains: function (e.g., school attendance, avoidance behavior, engagement in social activities); symptoms (e.g., child, parent, and/or clinician report, as appropriate and scientifically justified); acceptability of treatment (e.g., family burden, dropout from therapy); and the measurement of adverse effects (e.g., behavioral activation).

- **Timing:** Applicants should specify the duration of each of the active interventions as well as the duration of any maintenance or booster sessions. Studies must include at least one year of follow-up from baseline, with two years of follow-up preferred.

- **Setting:** Studies may take place in pediatric primary care or combined primary and specialty care settings, reflective of community-based care. Models that employ care coordination and integration across settings are encouraged.

Applicants should consider the potential for attrition due to normal life changes within the study period for the proposed population, and should propose specific strategies (i.e., retention plans) to mitigate these as appropriate, particularly for studies that target young adults.
Important Safety Considerations

Applicants should consult with the Food and Drug Administration regarding any off-label use of medications in the proposed study and seek approval for an Investigational New Drug (IND) application, as required. Awardees must plan to have specific and adequate human subjects protection measures in place (e.g., inclusion of a data safety monitoring board, a risk monitoring plan, and discussion of potential risk and how it will be monitored in the consent process).

Funds Available

PCORI has allotted up to $40 million in total costs under this PFA to fund up to two high-quality and high-impact studies related to treating anxiety disorders in children, adolescents, and/or young adults. The proposed budget for studies under this initiative may be up to $15 million in direct costs as appropriate. Requested budgets should be appropriately scaled to the actual size and scope of the proposed project. The maximum project period is five years.

PCORI will not cover costs for study interventions 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 developer, or other interested party must cover the patient care costs.

PCORI seeks efficient studies, such as those that take advantage of large 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. A prolonged recruitment period is not an acceptable rationale for longer studies. Funding requests with the primary purpose of developing or building on initial collaboration between researchers and patient or stakeholder groups are also not appropriate for this PFA.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet the following requirements:

- Focus on a comparative clinical effectiveness question that is important to patients and other decision makers.

- Address an evidence gap in deciding among available options; this gap should have been substantiated by an existing (recent or updated), 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 or for clear demonstration of non-inferiority. The sample size must also support testing of a priori hypotheses related to potential differences in effectiveness among relevant patient subgroups (HTE).

- Examine diverse populations receiving care in real-world settings.
- For studies aiming to reduce or eliminate health or healthcare disparities, specify one or more of the Addressing Disparities Program target populations (i.e., racial or ethnic minorities; low-income groups; residents of rural areas; individuals with special healthcare needs [including individuals with disabilities]; individuals with low health literacy or numeracy or limited English proficiency; and lesbian, gay, bisexual, and transgender [LGBTQ] persons) that will be the focus of the study. Studies should test the ability of interventions to improve outcomes (including patient-centered, clinical, and structural outcomes) and reduce disparities for at-risk populations.
- Have strong interest from and support of 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 ethical concerns of excess risk in some patient subgroups.
- Compare interventions that are known to be efficacious, effective, or commonly used and that can be implemented in real-world settings.
- Feature near-term outcomes and PROs as primary outcomes, when appropriate.
- Plan to collect patient-centered outcome data efficiently and periodically during follow-up.
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions (if applicable). PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and present evidence that the study will not encounter significant recruitment or participation barriers. The relevant IRBs make the final determination of the adequacy of informed-consent procedures and participant protections.
- Adhere to all applicable PCORI Methodology Standards. 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 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 LOIs and full applications.

- Carefully describe the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Similarly, applicants should document why project outcomes are especially relevant and meaningful endpoints for patients and their families.

- 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).

- 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. PCORI specifically encourages applications that use the National Patient-Centered Clinical Research Network (PCORnet) infrastructure.

- 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.

**Project Budget and Duration**

Applicants may request up to $15 million in total direct costs for a research project period not to exceed five years (not including peer review). At the time of contract execution, PCORI sets aside all 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. (Please refer to the Application Guidelines for further details.) In general, PCORI will not cover costs for interventions that are being compared in the proposed study. (Appendix 2: Allowable and Unallowable Costs in the Application Guidelines for details.) Applicants should submit a realistic budget and timeline reflecting the proposed study’s scope and requirements. In some rare circumstances, the estimated budget may exceed $15 million total direct costs, depending on the nature of the research question, the design and analytical requirements of the proposed study, the expected size of the patient enrollment, or the complexity and frequency of the outcomes assessment. PCORI expects these to be selective cases, which include high-priority topics that are of greatest interest to us. Applicants who intend to propose such studies must provide evidence of prior approval by PCORI scientific staff to exceed the budgetary limit and succinct justifications in their LOI, documenting the budget requirements with respect to the scope of the proposed research and the data-collection and analysis efforts. Please note that this justification counts toward the LOI three-page limit. PCORI will deny any request for a project period longer than five years. 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.

A contract is the funding mechanism for this program. A milestones and deliverables schedule, as well as specified recruitment targets, should be linked directly to and included in the proposed budget that will be subject to negotiation at the time of award. Some of the other activities that will be considered during negotiations include:

- Developing a study protocol and procedure manual for the intervention
- Assigning roles and responsibilities to study team members for project implementation
- Forming a SAC or other appropriate engagement body
- Providing a detailed task-based budget with level of effort for project staff, specified by task
- Obtaining clearances from all institutional and community partners, including IRB approvals
- Establishing a DSMB or providing a clear description of why one is unnecessary
- Executing all subcontractor agreements
- Agreeing on eligible patient populations for study recruitment
- Identifying barriers to patient recruitment in the study and addressing these barriers effectively
- Structuring a feasibility phase to demonstrate the potential for successful recruitment

Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Awardees must provide corroborating evidence to receive continuous funding support. Specifically, after 12 months of study performance, but no later than 18 months, PCORI will use information from the awardee to conduct a formal programmatic assessment of the study's progress and specified recruitment targets to determine the study’s viability and sustainability. Only studies that are deemed satisfactory in this assessment will receive continuous funding support.

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

Non-responsiveness

Applications will be considered nonresponsive to this PFA if the proposed research:

- Proposes a study with a sample size of less than 300 patients.
- Tests efficacy (or comparative efficacy) of interventions that are novel or with limited evidence of efficacy.
- Involves studies conducted within tightly controlled research environments instead of in clinical settings reflective of real-world healthcare delivery.
- Conducts a formal cost-effectiveness analysis.
- Directly compares the costs of care between two or more alternative approaches to providing care.
• Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science or biological mechanisms.

• Evaluates validity or efficacy of (rather than the comparative clinical effectiveness of) new or existing decision-support tools. This includes the development and efficacy evaluation of decision-support or shared-decision tools or systems for patients, clinicians, or both.

• Develops clinical prediction or prognostication tools.

• Establishes efficacy for a new clinical strategy.

• Pilots studies intended to inform larger efforts.

• Compares patient characteristics rather than clinical strategy options.

• Compares interventions for which the primary focus or the sole intervention is examining the role of compensated or volunteer community health workers, including patient navigators.

Proposals may report use 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 is included in our review criterion on the potential for research to fill a critical gap in knowledge or practice. As a result, 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 48 individual standards that fall into 12 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 seven 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:

1. Standards for Data Registries
2. Standards for Data Networks as Research-Facilitating Infrastructures
3. Standards for Causal Inference Methods
4. Standards for Adaptive and Bayesian Trial Designs
5. Standards for Studies of Medical Tests
6. Standards for Systematic Reviews
7. Standards for Research Designs Using Clusters

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 valid patient-centered outcome measures. Include preliminary data that support using the proposed measures in the study population. We also encourage investigators to consider those measures described in the Patient-Reported Outcomes Measurement Information System (PROMIS).\(^{10}\)

**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 and relevant information that can be used to answer important CER questions. PCORI is interested in studies that leverage existing research networks or consortia that would facilitate the conduct of large, multi-site studies called for in this PFA.

Applicants proposing use of an existing research network infrastructure (e.g., PCORnet); research

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\(^{10}\) Available at [http://www.nihpromis.org/](http://www.nihpromis.org/).
consortia; or related data resources (e.g., patient outcomes registries and/or electronic medical record [EMR] data from healthcare delivery systems or administrative claims data from public or commercial insurers) should address the following in the Research Plan (as appropriate), with sufficient specificity:

- Identify and justify all participating research network entities (e.g., health plans, consortia projects and members, etc.) or, in the case of PCORnet, identify the names of the participating Clinical Data Research Networks (CDRNs), Patient-Powered Research Networks (PPRNs), and PCORnet Collaborative Research Groups) that will be collaborating on the project. Also, identify the affiliated study performance sites.
- Demonstrate that the data source can comprehensively capture the study variables needed to assess the interventions, covariates, and outcomes.
- Describe how you will manage data across study sites within the research network or the proposed research consortia, and whether you will use any dedicated data-coordinating functions or facilities.
- As applicable, demonstrate familiarity with the existing network governance policies or data-use restrictions. Provide a study management structure that identifies roles, responsibilities, and decision-making authority across the proposed research consortia.
- As applicable, provide a timeline for establishing data-use agreements.
- As applicable, describe the network infrastructure resource(s) used to conduct the study (i.e., core research-support facilities, streamlined IRBs, contracting, engagement and consenting processes, standardized data resources training, etc.). Indicate the percentage of sites that have previously used centralized versus localized IRBs.
- As applicable, provide documentation supporting the involvement of network leadership throughout the study (e.g., detailed Letters of Support, budgets, and Budget Justifications that cover the costs of the network’s efforts). You can obtain Letters of Support from PCORnet from the Coordinating Center by submitting a request via the PCORnet Front Door.

Collaboration
PCORI is particularly interested in applications involving community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We encourage applications that include novel collaborations with accreditation organizations, credentialing bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

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, we encourage to review PCORI’s Engagement Rubric, which can be found in the PCORI Funding Opportunities. Applicants should also review the PCORI Methodology Standards Associated with Patient-Centeredness, and PCORI’s Sample Engagement Plans. 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.

PCORI expects applicants 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 LOIs and applications. To describe the decisional dilemma, state the specific clinical decision(s) or treatment choice(s) the decision makers confront and explain how the findings from the proposed research will inform those decisions. State why this decision—such as choosing a specific medication, surgical approach, or care delivery strategy to treat a condition or manage a specific population—is important to patients. Document the uncertainty patients and other stakeholders face when making this decision. Identify the patients and other stakeholders you consulted when determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continue engaging them actively in the study. Similarly, applicants should document how the project outcomes are especially relevant and meaningful endpoints for patients and other stakeholders.

For this PFA, applicants are not required to demonstrate that patients and other stakeholders are already engaged as research team members at the time an application is submitted. However, the Engagement Plan should outline how patients and other stakeholders will participate as partners in various phases of the proposed research, once awarded. Applicants should describe their plan to form a Study Advisory Committee (SAC), or other appropriate engagement body, to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. The SAC or other appropriate engagement body should meet in person at least two times per year, and the budget should account for these engagement costs.

PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups and other bodies, or involving individual patient and other stakeholder partners in various ways, are also permissible to employ—either in addition to or instead of—the formation of the SAC. For clarification in your application materials and for merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for in-person meetings at least two times per year and appropriate budgeting.

**Populations Studied**

PCORI seeks to fund research that includes diverse populations with respect to age, gender, race, ethnicity, geography, and clinical status. PCORI recognizes that some proposed studies might represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant in such cases to justify the study’s importance in the absence of diversity.
Alternatively, PCORI is particularly interested in including previously understudied populations for whom effectiveness information is needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of strategies in various subpopulations, with attention to the possibility that the strategy’s effects might differ across subgroups. Populations of interest include those that are less frequently studied. PCORI has developed the following list of populations of interest to guide our research and engagement efforts:

- Racial and ethnic minority groups
- Low-income groups
- Women
- Children (age 0–17 years)
- Older adults (age 65 years and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Individuals 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,\(^\text{11}\) 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

\(^{11}\) See [http://grants.nih.gov/sites/default/files/supplementalinstructions.docx](http://grants.nih.gov/sites/default/files/supplementalinstructions.docx)
the need to appoint a DSMB, 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 human subject protections rest with the IRB or international equivalent that has 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 Research Participants**

PCORI requires that all applicants adhere to the National Institutes of Health (NIH) policy on education in the protection of human research 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.12

**Data Management and Data-Sharing Plan**

PCORI encourages openness in research and making research data available for purposes of replication and reproducibility. Although not required to be submitted as a component of the research application, if an award is made, the awardee must develop and maintain a plan addressing data management and data sharing of research project data. This must be done in a manner that is appropriate for the research project and the types of research project data, and in a manner consistent with applicable privacy, confidentiality, and other legal requirements.

**Recruitment**

Applications should include information about the size and representativeness of the potential recruitment pool of patients and the means by which this size estimate was determined (e.g., EMRs, claims records, clinic logs, or other administrative systems). Likewise, applications should provide evidence-based estimates of how many participants are ultimately 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 loss to follow-up. Such estimates must be discussed in the application, specified in the milestones, reviewed by Merit Review Officers (MROs) 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 time frame. Accordingly, the Board adopted the Process for Peer Review of Primary Research and Public Release of Research Findings.

In summary, Awardee Institutions must submit to PCORI for peer review a draft final research report

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that provides the methodological details, describes the main study results, and interprets the findings in clinical or other decisional contexts. Subject matter experts (SMEs); 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 the earlier of 13 months after the Final Progress Report OR 90 days from the date the Final Research Report is approved by PCORI: (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

Letter of Intent (LOI)

Applicants should download the Pediatric Anxiety LOI Template from the PCORI Funding Opportunities. They must complete the document and convert it to a PDF with a three-page limit, excluding references. PCORI suggests including all references as in-text citations using American Medical Association citation style, but we do accept other citation styles. Do not upload additional documents as part of your LOI, such as 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 for additional applicant resources, including FAQs and required templates.

Please answer all of the questions in the LOI Template. This includes the question on brief justification for the proposed cost of the study. Providing the answer, “costs not to exceed $15 million in direct costs” is not sufficient. Upload your document to PCORI Online. The deadline for LOI submission is February 13, 2018, by 5 p.m. (ET).

LOI Review

PCORI evaluates LOIs based on the following criteria:

- Whether the topics are related to those on PCORI’s own priority list, versus the IOM/AHRQ lists, versus other topics initiated by investigators
- Importance to current clinical decision making, as evidenced by critical gaps identified by clinical guidelines developers or recent relevant systematic reviews
- A size or scope sufficient to have a significant impact on patient outcomes or healthcare practices
- Clarity and credibility of applicants’ responses to the LOI questions, as well as their justification
of the need for a large pragmatic study—including the rationale for the estimated sample size—
citing published estimates, including effect sizes, standard deviations, and the need for rigorous
comparative analysis of important subgroups

- Prior relevant experience
- Programmatic fit and balance, considering whether the application significantly overlaps with
  concurrent applications or previously funded studies or, conversely, whether the application fills
  a gap in PCORI’s portfolio, considering such characteristics as disease category, topics, priority
  population, and methodologies
- Adherence to the administrative and formatting requirements listed in the Application
  Guidelines, especially the three-page limit for the LOI

LOIs are reviewed qualitatively; they are not scored. Only applicants whose LOIs are deemed most
responsive to this PFA will be invited to submit a full application. At least two PCORI staff review LOIs,
and they are not scored during review. Notification of denial or approval to submit a full application will
occur no later than March 14, 2018. Please refer to the Application Guidelines in the PCORI Funding
Opportunities for due dates and information on how to submit your LOI in PCORI Online.

All applicants are required to submit an LOI for PCORI staff to review. This allows PCORI to determine
whether proposed revisions and changes made to specific aims or methodological approaches from the
original applications align with our evolving strategic priorities.

If you are invited to submit an application, do not make significant changes to your proposed project
without consulting a program officer. For example, you should not revise your major aims and study
design. Any significant changes are grounds for removal from the review process.

Note: A Principal Investigator (PI) can only submit one LOI per PFA. However, an individual listed as a PI
on one LOI can 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 may 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 the PFA to which he or she would like to apply. This applies to single and dual-PI
submissions.

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 Opportunities.

PCORI Online System
To submit an application, you must register in PCORI Online and submit an LOI and an application for
each cycle to which you are applying.
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 SMEs, 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.
We designed the table below 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.

<table>
<thead>
<tr>
<th>Crosswalk of PCORI Merit Review Criteria with NIH Criteria</th>
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<tr>
<td>SIGNIFICANCE</td>
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<tr>
<td>1. Potential for the study to fill critical gaps in evidence</td>
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<tr>
<td>2. Potential for the study findings to be adopted into clinical practice and improve delivery of care</td>
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<tr>
<td>APPROACH</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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<tr>
<td>PCORI-Only Merit Review Criteria</td>
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<tr>
<td>PATIENT-CENTEREDNESS/ENGAGEMENT</td>
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<tr>
<td>5. Patient-centeredness</td>
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<td>6. Patient and stakeholder engagement</td>
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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 application evaluation.

**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 others could reproduce positive findings, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder others from adopting the intervention.

- Does the application describe a plan for how to disseminate study findings 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 justified? If “usual care” is one of the arms, is it adequately justified and will it be sufficiently measured?

- Are the sample sizes and power estimates appropriate? Is the study design (e.g., cluster randomized design, RCT, 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 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 patients and their healthcare providers would choose them 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, hospitals and health systems, 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., researchers, patients, caregivers, clinicians, policy makers and other healthcare system stakeholders) 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 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.

**In-Person Applicant Presentation**

Based on the results of the merit review and PCORI’s programmatic priorities, PCORI invites a selective subset of applicants whose proposed studies are deemed to be highly meritorious or aligned with PCORI’s strategic priorities to participate in follow-up discussions with PCORI on study methodological and execution issues. We expect applicants to address concerns and critiques identified in the merit review in this presentation. We will notify the selected applicants of the logistics for this presentation (including travel arrangements) in separate communications.

**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 then goes to the Board for consideration and approval.

In addition, PCORI evaluates applicant risk before issuing an 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 awardees have submitted the overdue reports.**

**Summary Statements and Funding Recommendations**

Applicants receive summary statements approximately two weeks before funding decisions are announced. **If an application progresses to in-person discussion,** the applicant will receive a summary statement that includes:

- 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.

PCORI makes funding recommendations by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. PCORI also considers the funds allotted for the current PFA 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 December 2018.