Cycle 2 2018 Funding Cycle

PCORI Funding Announcement: Symptom Management for Patients with Advanced Illness

Published June 1, 2018

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes on September 25, 2018, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at http://www.pcori.org/Cycle-2-2018-symptom-management/.
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, caregivers, and the broader healthcare community.

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, clinicians, purchasers, and policymakers make better-informed health decisions by “advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions.”

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Overview

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<th>Published</th>
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<td>Letter of Intent Due</td>
<td>June 28, 2018 by 5 p.m. (ET)</td>
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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 full applications. Notification of denial or approval to submit a full application will occur no later than July 23, 2018.

Summary

PCORI seeks to fund multiple high-quality clinical studies that compare the effectiveness of evidence-based treatments for relief of common symptoms experienced by patients living with advanced illness. The goal of this initiative is to support patient- and caregiver-centered comparative clinical effectiveness research (CER) to generate important findings that will aid clinical decision making for symptom management. The proposed interventions must have proven efficacy in the population being studied or be in wide use. The proposed comparison should reflect important choices in contemporary clinical practice. Comparators may include evidence-based pharmacological or non-pharmacological interventions. This PFA is specifically focused on the following symptoms:

- Pain
- Fatigue
- Dyspnea
- Insomnia
- Anorexia/cachexia
- Nausea/vomiting
- Anxiety

For this PFA, applicants should consult with patients, caregivers, providers, and other stakeholders, in addition to scientific and methodological experts to identify the important decisional dilemmas and evidence gaps that will drive research question development.

Note that this PFA will not support applications proposing to conduct cost-effectiveness analysis; systematic reviews; or development and evaluation of shared decision making, decision-support tools, or clinical practice guidelines.

Applicant Resources

See https://www.pcori.org/funding-opportunities/announcement/symptom-management-patients-advanced-illness-cycle-2-2018

Key Dates

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<td>LOI Deadline:</td>
<td>June 28, 2018, by 5 p.m. (ET)</td>
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<td>LOI Status Notification:</td>
<td>July 23, 2018</td>
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<td>Application Deadline:</td>
<td>September 25, 2018, by 5 p.m. (ET)</td>
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<td>Merit Review:</td>
<td>December 2018</td>
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<tr>
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<td>Earliest Project Start Date:</td>
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Maximum Project Budget (Direct Costs) $2 million

Maximum Project Period Three years

Total Funds Available Up To $22 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 United States 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) or phone (202-627-1884), or complete the Research Inquiry Form (http://www.pcori.org/content/research-inquiry). PCORI will provide a response within three 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 provide a response 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 a deadline falls on a weekend or federal holiday, the deadline will be the following Monday or the next day after the federal holiday.
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## III. Merit Review
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What Has Changed for the Cycle 2 2018 Funding Cycle:

- Pharmacological intervention is encouraged but not required.
- Depression was removed from symptom list
- Population setting includes any setting where the proposed patient population typically receives care.
- Administrative requirements have changed: LOI can be 3 pages; however, the research plan will remain 12 pages.
I. Introduction

Summary of Program

Through this research initiative, the Patient-Centered Outcomes Research Institute (PCORI) seeks to generate needed scientific evidence to aid patients, caregivers, and providers in decision making about the clinical options for symptom management in advanced illness. PCORI aims to fund multiple high-quality clinical studies that compare evidence-based management strategies for a range of common symptoms. Proposed interventions should include the most relevant treatment choices currently available to patients with the symptoms and condition(s) proposed. These interventions may include pharmacological treatments or nonpharmacological alternatives. This PCORI Funding Announcement (PFA) focuses specifically on the following symptoms:

- Pain
- Fatigue
- Dyspnea
- Insomnia
- Anorexia/cachexia
- Nausea/vomiting
- Anxiety

This PFA is targeted toward advanced illnesses such as (but not limited to) advanced heart failure, advanced cancer, chronic obstructive pulmonary disease, and neurodegenerative diseases. Studies on populations with advanced illnesses other than cancer, which have not been heavily represented in prior research but have a range of palliative care options to consider, are of particular interest. This PFA is not limited to any age group, although PCORI is interested in improving the evidence base for pediatric and adolescent populations. We encourage applicants to include assessments of caregiver outcomes where appropriate. **PCORI is particularly interested in head-to-head comparisons of pharmacological and nonpharmacological approaches.** The studies funded under this initiative will provide substantial advances in understanding the range of approaches and their impact on outcomes that matter to patients and their families.

Interventions proposed for study under this PFA must have sufficient evidence of efficacy (from systematic reviews, prior empirical investigations, or other scientific documentation) or documentation of widespread use in the population proposed. In other words, the proposed interventions in the comparative clinical effectiveness study should reflect realistic and meaningful decision making and choices in contemporary clinical practice for the condition being studied. If applicants propose comparing interventions that are used commonly, without clear evidence of efficacy, they must document the extensiveness of their use in the population proposed. Applicants must be sure that they characterize proposed interventions effectively so that replication, dissemination, and clinical implementation are facilitated. Without documentation of widespread use, PCORI will consider studies that compare interventions without sufficient evidence of efficacy or effectiveness to be nonresponsive to this PFA.
Study outcomes should include well-validated patient assessment measures, symptom measures, adverse events, and caregiver measures (as appropriate, especially in studies of pediatric or adolescent patients). PCORI is particularly interested in those studies that propose long-term follow-up; therefore, applicants should include a minimum of six months’ follow-up for patient participants.

Background

Patients with advanced illness face burdensome symptoms that they must manage, in addition to often complex treatments for their underlying disease. Providers also face clinical decisions about treatment and symptom management, often without having the benefit of comparative clinical effectiveness evidence for discussing choices with patients or their caregivers. The dearth of evidence from comparative clinical effectiveness studies, which is necessary to inform clinical practice, signals the need to address research gaps in symptom management. The results from studies this PFA supports will specifically inform the high-priority decisional dilemmas commonly faced by patients with advanced illness, their caregivers, and other relevant stakeholders, such as providers and healthcare systems.

A significant body of evidence demonstrates that patients with advanced illnesses who receive palliative care services (including effective symptom management) report clinically significant improvements in their quality of life, lower symptom burden and caregiver distress, and reduced hospitalizations and emergency department visits. The research has identified three specific palliative care areas as needing further comparative clinical effectiveness research (CER): (1) community-based models of care delivery; (2) advanced care planning; and (3) symptom management. Patients, caregivers, researchers, and stakeholder organizations have also highlighted these three areas. PCORI has previously responded to two of these CER gaps. In 2016, PCORI released a PFA on community-based palliative care delivery that focused on care models and advanced care planning for adult patients with advanced illness.

This current PFA is a reissue of a PFA that was first released in 2017. Research supported under this initiative will expand PCORI’s commitment to address critical evidence gaps in symptom management for patients of any age living with any advanced illness. This initiative also provides the opportunity to support studies of the appropriate size and scope to generate high-quality evidence to influence the way symptoms in advanced illness are managed.

5 Center to Advance Palliative Care. *America’s Care of Serious Illness. 2015 State-by-State Report Card on Access to Palliative Care in Our Nation’s Hospitals.* 2015.
Evidence Gaps

International organizations such as the James Lind Alliance and Marie Curie have called for the acceleration of research on symptom management in advanced illness. In 2014 the World Health Organization urged the development of strong evidence-based guidelines for palliative care across diseases and care settings. The 2014 Institute of Medicine report *Dying in America* underscored the need for comparative clinical effectiveness studies of different symptom-management approaches used in pediatric palliative care populations. In addition, the 2016 Cancer Moonshot Blue Ribbon Panel of experts recommended “management of patient-reported symptoms to minimize debilitating side effects of cancer and its treatment” as a top priority. A number of recent systematic reviews have identified pain, fatigue, dyspnea, insomnia, anorexia/cachexia, nausea/vomiting, and anxiety as the most prevalent symptoms in advanced illness and have reported on the lack of related evidence-based treatments. A review by Kelley and Morrison (2015) identified the need for randomized controlled trials (RCTs) of interventions for many symptoms experienced by patients with advanced illness, including dyspnea, fatigue, and pain.

Specific evidence gaps in research on symptom management in advanced illness extend across disease types, age groups, and symptoms. Evidence produced to date has largely been limited to trials with small sample sizes and few head-to-head treatment comparisons. Studies frequently lack caregiver outcomes and adequate follow-up. Consequently, the most effective way to treat pain, alleviate breathlessness, address fatigue, and so on is often unclear. Prior research on symptom management has shown the potential for clinically significant improvements in quality of life, symptom burden, use of hospital services, and caregiver stress. This funding opportunity will advance scientific knowledge from head-to-head studies about how various symptom management approaches convey benefits and harms to patients.

Priority Research Question

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

Based on patient- and caregiver-centered outcomes, what is the comparative clinical effectiveness of two or more pharmacological and/or nonpharmacological approaches to alleviate symptoms in patients living with advanced illness, for one or more of the following symptoms?

- Pain
- Fatigue
- Dyspnea
- Insomnia

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10 World Health Organization. *Strengthening of Palliative Care as a Component of Comprehensive Care Throughout the Life Course*. 2014.


• Anorexia/cachexia
• Nausea/vomiting
• Anxiety

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

- **Population**: Patients with advanced illness and their caregivers (as appropriate) of any age group. This population should not include individuals near the end of life. Conditions may include (but are not limited to) advanced heart failure, advanced cancer, chronic obstructive pulmonary disease, or neurodegenerative diseases. PCORI is particularly interested in studies that will increase the evidence for treatments that are effective in pediatric and adolescent populations, for which fewer studies exist. Studies on populations with advanced illnesses other than cancer are also of interest. The applicant should propose a sufficient sample size to provide robust study results. The applicant should justify the hypothesized effect size and justify these assumptions with citations. Power calculations should support the proposed sample size.

- **Interventions**: Proposed interventions may include pharmacological treatments or nonpharmacological approaches, which could include complementary therapies. Interventions proposed for study must comprise the basis of symptom management decisions encountered by patients, caregivers, and clinicians. A justification for the appropriateness of the interventions within the proposed population must be provided. PCORI is interested in comparing interventions that have adequate evidence of efficacy, as well as those treatments that are used commonly in the proposed population. The applicant should demonstrate evidence of efficacy for proposed interventions using systematic reviews, prior empirical investigations, or other scientific documentation and/or documented widespread use in the proposed population. Attention to relevant comorbidities and possible interactions or contraindications should be considered.

- **Outcomes**: Applicants should propose appropriate patient- and caregiver-centered outcomes. Study outcomes should include well-validated patient assessment measures (e.g., quality of life), symptom measures, adverse events, other key clinical outcomes, and caregiver measures (e.g., burden), as appropriate.

- **Timing**: Follow-up of patient participants should be performed after a minimum of six months. Applicants should make reasonable estimates of participant attrition and estimate the necessary sample size accordingly.

- **Setting**: Proposed healthcare settings should be representative of locations where the patient population typically receives care.

**Funds Available**

PCORI has allotted up to $22 million in total costs under this PFA to fund multiple high-quality and impactful studies related to treating symptoms in advanced illness populations. The proposed budget for studies under this initiative may be up to $2 million in direct costs, as appropriate. The maximum project period is three years.

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 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.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet the following requirements:

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

• 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.

• Receive endorsement from relevant patient organizations, clinician organizations, payer or purchaser consortia, and life sciences industry representatives as potentially answering a critical question—one that, if adequately answered, would substantially improve decision making.

• Propose a sample size that is sufficiently large to allow for comparison of hypothesized effect sizes. When determining anticipated effect sizes, pay attention to basing such estimates on efficacy results observed in prior publications of adequately powered and well-conducted clinical studies.

• 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.

• As applicable, compare interventions that can be implemented in real-world settings and are known to be efficacious, effective, or in common use.

• Include patient-reported outcomes (PROs) as primary outcomes, when appropriate.

• 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 should present evidence that the study will not
encounter significant recruitment or participation barriers.

- Adhere to all relevant **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 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:

- 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.

- 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.

- 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.

- 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.

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15 Available at pcori.org/research-we-support/research-methodology-standards/.
Non-responsiveness
Applications will be considered nonresponsive to this PFA if the proposed research:

- Tests efficacy (or comparative efficacy) within a tight, protocol-controlled research setting (as opposed to a more real-world and pragmatic CER study).
- Conducts a cost-effectiveness analysis based on the ratio of treatment costs to measures of quality-adjusted life-years.
- Directly compares the costs of care between two or more alternative approaches.
- Measures the relative costs of care of two or more alternative approaches as the primary criteria for choosing the preferred alternative.
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, or biological mechanisms.
- Evaluates new or existing decision-support tools. This includes developing and evaluating a decision-support or shared-decision tool or system for patients, clinicians, or both.
- Develops clinical prediction or prognostication tools.
- Establishes efficacy for a new clinical strategy.
- Conducts only pilot studies intended to inform larger efforts.
- Compares patient characteristics rather than clinical strategy options.

Features of Patient-Centered Outcomes Research (PCOR)
PCOR helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research:

- Assesses the benefits and harms of therapeutic and palliative care to inform decision making, highlighting the choices that matter to people.
- Is inclusive of an individual’s preferences, autonomy and needs, focusing on outcomes that people notice and care about (including survival, functioning, symptoms, and health-related quality of life).
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination.
- Directly compares clinical interventions that are available to a broad segment of the patient population.
- Obtains stakeholder perspectives to address the burdens to individuals, availability of services, and requirements for technology and personnel.

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.

Applicants proposing use of an existing research network infrastructure (e.g., the National Patient-Centered Clinical Research Network [PCORnet]); research consortia; or related data resources (e.g., electronic medical records [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.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcome measures. Include preliminary data that supports 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).¹⁶

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¹⁶ Available at http://nihpromis.org/.
Methodological Considerations

Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards.\footnote{Available at pcori.org/research-we-support/the-pcori-methodology-report/.} These include 54 individual standards that fall into 13 categories. The first categories are cross-cutting and are relevant to most PCOR studies. Researchers should refer to these standards when planning and conducting their research projects. These five 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 Effects (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 for guidance when they are relevant to a particular 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 on Research Designs Using Clusters
8. 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 and program staff 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 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 applicants 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. Additionally, the Engagement in Health Research Literature Explorer, a searchable, catalogued resource for peer-reviewed literature, can help identify publications about engagement that are specifically relevant to your work. These resources are not intended to be comprehensive or prescriptive; instead, they provide examples 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.

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 CER can be examined (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 in such cases to justify the study’s importance in the absence of diversity and to discuss which subgroups are most important and how they will analyze them, including whether there will be power to examine the question of effectiveness in subgroups. PCORI is 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 the strategies in various subpopulations, with attention to the possibility that the effects might differ across subpopulations. PCORI has developed the following list of priority populations to guide our research and engagement efforts:

- Racial and ethnic minority groups

20 Available at http://www.pcori.org/literature/engagement-literature.
- 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 or numeracy and/or limited English proficiency
- Lesbian, gay, bisexual, and transgender (LGBT) persons
- Veterans and members of the Armed Forces and their families

**Project Budget and Duration**

PCORI has devoted up to $22 million in total costs to this PFA. Applicants may request up to $2 million in direct costs for a research project period not to exceed three years (not including peer review). The maximum budget includes all research and peer-review-related costs. (Please refer to the Application Guidelines for further details.) 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. Obligated funding is available for the duration of the project period. Note that PCORI will not cover costs for interventions that are being compared in the proposed study. (See Appendix 2: Allowable and Unallowable Costs in the Application Guidelines for details.)

Applicants should propose realistic budgets, project durations, and associated timelines. For those rare circumstances in which the estimated direct cost exceeds the maximum direct costs outlined in this PFA, please provide a detailed justification in your LOI that ties the extra expense to the project’s success. PCORI will not approve all requests for additional funds. We will deny any request for a project period longer than three years. For further information regarding PCORI’s policies about allowable and unallowable costs, refer to Appendix 2 in the Application Guidelines. Note that although subcontractor indirect costs are included in the prime applicant’s direct-cost budget, these costs are not considered when determining adherence to the PFA’s direct-cost limit.

A contract is the funding mechanism for this program. Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Milestones and targets—as well as possible pilot phases for the sole purpose of assessing recruitment feasibility—should be included in the budget and will be negotiated at the time of the award. PCORI will expect awardees to provide corroborating evidence to receive continual funding support. Some of the 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
• 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
• Demonstrating successful recruitment during a pilot phase (if indicated)

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

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.

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. PCORI does not require that applicants comply with sections of this policy referring to requirements for federal-wide assurance or to standards for including women, minorities, and children. 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 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

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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 all applicants to 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.23

**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.

**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].24

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 (SMEs); individuals with expertise on 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 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 standardized summary of 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.

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III. How to Submit an Application

Letter of Intent (LOI)

Applicants should download the Cycle 2 2018 Symptom Management LOI Template from the PCORI Funding Center. They must complete the document and convert it to a PDF with a three-page limit. 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 Center for additional applicant resources, including the 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 $2 million” is not sufficient. Upload your document to PCORI Online. The deadline for LOI submission is June 28, 2018, by 5 p.m. (ET).

LOI Review

PCORI evaluates LOIs based on the following criteria:

- Whether the proposed topic addresses the priority research question identified in this PFA
- Importance of the specific research question (comparison), as evidenced by critical gaps identified by clinical guidelines developers or recent relevant systematic reviews
- Two or more interventions with documented efficacy supported by citations or documentation that the interventions proposed are commonly in use by the proposed population.
- A size or scope that will have a significant impact on patient outcomes or healthcare practice
- Clarity and credibility of applicants’ responses to the LOI questions, as well as their justification of the proposed study 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 research study question and design comply with requirements in this PFA
- Adherence to the administrative and formatting requirements listed in the Application Guidelines, specifically the three-page limit for the LOI

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. Notification of denial or approval to submit an application will occur no later than July 23, 2018. Please refer to the Application Guidelines for information on how to submit your LOI via PCORI Online.

An invitation to submit an application is based on the information provided in the LOI. Any changes to the following require PCORI approval:
III. 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.

25 Available at http://www.pcori.org/funding-opportunities.
• 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 panel based on the number of and topic areas represented by 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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<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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PCORI-Only Merit Review Criteria
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-review 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 provide a clear conceptual framework anchored in background literature, which informs the design, key variables, and relationship between interventions and outcomes being tested?
• Does the application provide a Research Plan with rigorous methods that demonstrates 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)? Are 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 based on PCORI’s merit review criteria, including evaluating adherence to the PCORI Methodology Standards. After PCORI completes the 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.

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, which provides information for applicants to 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 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 April 2019.