Cycle 1 2017 Funding Cycle

PCORI Funding Announcement: Optimized Multidisciplinary Treatment Programs for Nonspecific Chronic Low Back Pain

January 17, 2017

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes on May 17, 2017, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at http://www.pcori.org/cycle-1-2017-multidisciplinary-treatments-low-back-pain.

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 policy makers make better-informed health decisions by "advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions."

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Overview

Published	January 17, 2017
Letter of Intent Due	February 14, 2017 by 5 p.m. (ET) Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than March 15, 2017.
Summary	The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund large, randomized controlled trials (RCTs) or well-justified observational studies that compare the effectiveness of optimized, multidisciplinary nonsurgical treatment programs involving combined or sequenced interventions for patients with nonspecific chronic low back pain (LBP). Treatment programs that are proposed must be evidence-based. The treatment programs are expected to be well-characterized to facilitate replication and dissemination efforts. Proposed studies must address actual clinical choices faced by patients, caregivers, and clinicians in specific practice settings. They must involve patient populations that represent the U.S. population; be large enough to provide precise estimates of hypothesized effectiveness differences; and be large enough to support evaluation of potential differences in treatment effectiveness in patient subgroups. For this solicitation, applicants should document that they have consulted with patients and other stakeholders to identify the important decisional dilemmas and evidence needs that will drive development of the research questions or reference previously documented decisional dilemmas. Although PCORI does not require that relevant national patient organizations, professional organizations, and payer or purchaser organizations be formally included as partners and active participants prior to contract award, successful applicants may be required to develop such formal arrangements. PCORI may require a project Study Advisory Committee (SAC)[1] that is composed of national or regional organizations that represent—at a minimum—patients and families with lived experience; relevant clinicians; payers; and health plans. Scientific and methodological experts may also be recommended for this oversight role. The SAC advises and assists the research team with refining the study questions, outcomes, and protocol. PCORI expects applications to follow the RCT study design specified for the research question. **Note that this funding program does not support applications to conduct cost-effectiveness analysis, systematic reviews, or development and evaluation of shared decision making or decision-support tools.** The proposed studies must address the priority research question identified in the main body of the PFA.

[1] The intent of the SAC described in the PFA is to ensure that a broad spectrum of stakeholders and patients advise and assist the research team with refining the study questions, outcomes, and protocols. These stakeholders and patients must include national or regional organizations that represent—at a minimum—patients or families with lived experience; relevant clinicians; payers; and health plans. 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. 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

Applicant Resources	See http://www.pcori.org/cycle-1-2017-multidisciplinary-treatments-low-back-pain
Key Dates	Online System Opens: January 17, 2017 LOI Deadline: February 14, 2017, by 5 p.m. (ET) LOI Town Hall: January 25, 2017, 11 – 1 p.m. (ET) LOI Status Notification: March 15, 2017 Application Deadline: May 17, 2017, by 5 p.m. (ET) Merit Review: July 2017 Awards Announced: November 2017 Earliest Project Start Date: January 2018
Maximum Project Budget (Total Direct Costs)	$10 million
Maximum Project Period	Five years
Funds Available Up To	$50 million
Eligibility	Applications may be submitted by any private-sector research organization, including any nonprofit or for-profit organization; any public-sector research organization, including any university or college hospital or healthcare system, laboratory, or manufacturer; or any unit of local, state, or federal government. The Internal Revenue Service must recognize all U.S. applicant organizations. Nondomestic components of organizations based in the 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 clearly shown. 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 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:** 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 all questions will be addressed 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:** Contact the PCORI Helpdesk at pfa@pcori.org. PCORI will provide a response within two business days. Note that during the week of the application deadline, response times may exceed two business days. One week before an application deadline, applicants may also call the PCORI Helpdesk (202-627-1885). Applicants are asked to plan accordingly. It is the applicant's responsibility to submit the application on or before the application deadline.
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.

individual patient and 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 stakeholders and patient partners. For clarification in your application materials and 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.

Table of Contents

I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is launching this funding initiative to support patient-centered comparative clinical effectiveness research (CER) that addresses important questions about the comparison of noninvasive treatment modalities for managing patients with nonspecific chronic low back pain (LBP). PCORI seeks to fund large, pragmatic, randomized controlled trials (RCTs) or well-justified observational studies of multidisciplinary, noninvasive interventions for patients with nonspecific chronic LBP. Each treatment program being compared should include two or more component interventions which are documented to be efficacious or in common use, and should also be well-characterized to facilitate replication and dissemination efforts. All proposed studies must be justified by the presence of an important and meaningful gap in the current base of clinical evidence. Through this PCORI Funding Announcement (PFA), PCORI seeks to fund studies with sufficient sample sizes to address the priority research question. This program's goal is to generate valid clinical evidence that is readily generalizable to the broader population of people with nonspecific chronic LBP.

For this PFA, applicants should follow the definition of the National Institutes of Health (NIH) Task Force on Research Standards for Chronic Low Back Pain. This definition is pain that is present on at least 50 percent of days during a six-month period, unaccompanied by pain or neurological symptoms and signs in the lower legs, and without abnormalities on imaging tests other than degenerative disk disease.[2] PCORI expects that the study population will include those individuals who have progressed from a period of intermittent episodes of LBP to the state of persistent pain. Similarly for this PFA, PCORI defines multidisciplinary programs as including professionals from two or more disciplines who deliver care in a coordinated fashion.

PCORI is particularly interested in large pragmatic studies that can investigate potential Heterogeneity of Treatment Effects (HTEs) with respect to important sociodemographic and clinical characteristics (e.g., overweight or obesity, prominent psychosocial stressors, comorbid mental health conditions or a history of substance use, older adults, or other clinical characteristics proposed by investigators with an accompanying strong rationale.) Investigators are encouraged to consult the minimal dataset requirements of the NIH Task Force on Research Standards for Chronic Low Back Pain when planning participant recruitment and data collection, including potential clinical characteristics of interest.

Applications must address the priority research question described in this PFA. Proposed studies should include comparison of two or more nonsurgical treatment programs that are combined or sequenced. Together these programs should be comprehensive, multidisciplinary, and justified on the basis of convincing evidence regarding their component interventions (from systematic reviews, prior empirical investigations, or other documentation). If applicants propose comparing interventions that are in

[2] Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., Weiner, D. K. (2014). REPORT OF THE NIH TASK FORCE ON RESEARCH STANDARDS FOR CHRONIC LOW BACK PAIN. *The Journal of Pain: Official Journal of the American Pain Society*, *15*(6), 569–585. http://doi.org/10.1016/j.jpain.2014.03.005.

common use but without clear evidence of efficacy, they must document the extensiveness of their use and demonstrate how they will interpret study results. Based on a 2016 Agency for Healthcare Research and Quality (AHRQ) systematic review by Chou et al.[3], interventions of interest may include but are not limited to the following:

- Active physical therapy modalities (e.g., exercise therapy)
- Complementary and integrative health (e.g., acupuncture)
- Non-opioid pharmacologic interventions (e.g., nonsteroidal anti-inflammatory drugs, duloxetine)
- Multidisciplinary and interdisciplinary rehabilitation interventions (e.g., having both behavioral and physical components)

Although there is evidence of the short-term benefits of opioid treatment in patients with chronic LBP, this PFA is not intended to include studies of treatment sequences that include opioids.

Proposed comparators must be adequately defined and structured as to how they will be carried out over time, and the proposed implementation must align with available evidence of efficacy. Proposed sequences of interventions must address actual clinical choices faced by patients, caregivers, and clinicians in specific practice settings.

In addition to including pain and function, applicants are strongly encouraged to include well-validated outcome measures from at least the following domains: quality of life, productivity and return to work/return to premorbid function, and healthcare utilization. Studies should conduct periodic outcome assessments, including an outcome assessment after a follow-up period of 12 months or longer.

Background

LBP is an extremely prevalent and burdensome health issue in the United States. LBP is the most common type of pain and the second-most-common reason for doctor visits in the United States.[4] Up to 84 percent of adults experience LBP at some point in their lifetimes,[5,6] while chronic LBP affects an estimated 5–10 percent of U.S. adults.[7] LBP is the most common cause of job-related disability, a leading contributor to missed work days,[8] and as of 2008 accounted for 34 million office visits annually to family physicians and primary care internists.[9] The burden from LBP has worsened in recent years. In 2010 LBP

[3] Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M, Fu R, Dana T, Kraegel P, Griffin J, Grusing S, Brodt E. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2016.
[4] Institute of Medicine (U.S.) Committee on Advancing Pain Research C, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington DC: National Academy of Sciences; 2011.
[5] Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates. Spine (Phila Pa 1976). 2006;31(23):2724-7. PMID: 17077742.
[6] Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. J Spinal Disord. 2000;13(3):205-17. PMID: 10872758.
[7] Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012;64(6):2028-37.
[8] NINDS. "Back Pain Fact Sheet." Dec 2014. http://www.ninds.nih.gov/disorders/backpain/detail_backpain.htm.
[9] Licciardone JC. The epidemiology and medical management of low back pain during ambulatory medical care visits in the

was the third-most-prevalent cause of poor health, behind only ischemic heart disease and chronic lung disease.[5] The direct annual cost of caring for back pain in the United States is $40 billion and the indirect cost (including the impact of lost wages on family functioning) is estimated at over $100 billion annually—with the bulk of these expenses being accounted for by patients with chronic LBP.[10, 11,12]

CER on chronic LBP has been limited by several factors, including (1) a lack of consensus on the most clinically meaningful outcomes to measure; (2) small differences, if any, between most therapies within a given category when compared with one another (e.g., various types of psychological interventions); and (3) a lack of clarity regarding which patients respond to which therapies.[3] Because treatment options for LBP are aligned with different professional disciplines (e.g., acupuncture, physical therapy, spinal manipulation, and behavioral health), existing referral patterns and limited access to treatments could be a barrier to diffusion of best clinical practices (especially those that require combinations or sequences of treatments). Thus, insights that new CER provides could have an important clinical impact.

Evidence Gaps

In the recent systematic review commissioned by the AHRQ that addressed noninvasive treatment options for managing chronic LBP[3], several important evidence gaps were identified that applicants should consider when responding to this PFA. In addition to research on the effectiveness of various sequences of interventions, the review called for future studies that include a longer duration of follow-up; that include other outcomes of interest in addition to pain, such as return to work, quality of life and healthcare utilization; and that more consistently and rigorously report harms. The AHRQ review also calls for more studies examining which sociodemographic and clinical characteristics may affect treatment-related benefits and harms. Investigators responding to this PFA are encouraged to examine the HTEs among important patient characteristics.

Research Topic Prioritization

PCORI's multi-stakeholder Advisory Panel for the Assessment of Prevention, Diagnosis, and Treatment Options rated chronic nonspecific LBP as a high-priority topic. PCORI then hosted a multi-stakeholder workgroup to develop research questions focusing on the comparative clinical effectiveness of treatments for this patient population. On June 9, 2015, 16 participants representing patients, clinicians, researchers, payers, and purchasers met for a one-day workshop. The meeting was open to the public via teleconference, with slides and meeting materials posted on the PCORI website. Throughout the day, discussions centered around questions that stakeholders submitted and around defining the study population, interventions, and outcome measures.

Subsequently, PCORI met individually with representatives of five professional organizations that represent clinicians who specialize in spine conditions, including nonspecific chronic LBP (spine surgeons, orthopedic surgeons, neurosurgeons, physical therapists, and primary care physicians).[13] The

United States. Osteopath.Med.Prim.Care. 2008;2:11.

[10] UMHS Low Back Pain Guideline Update, December 2011.

[11] Frymoyer JW. Predictors of low back pain disability. J Clinical Orthop Relat Res. 1987;22:89-98. PMID: 2955993.

[12] Engel CC, Von Korff M, Katon WJ. Back pain in primary care: predictors of high health-care costs. Pain. 1996;65:197-204. PMID: 8826507.

[13] Refer to http://www.pcori.org/events/2015/prioritizing-comparative-effectiveness-research-questions-systems-interventions-improve.

clinicians consistently described chronic nonspecific LBP as a heterogeneous condition for which they lacked evidence regarding factors associated with response to treatment. To address this problem, PCORI convened a second multi-stakeholder meeting that took place on January 8, 2016.[14] The meeting focused on identifying clinical characteristics that predict how well chronic nonspecific LBP patients respond to surgery and nonsurgical interventions. The multi-stakeholder panel suggested a number of predictors of response to treatment for exploration (e.g., obesity; current or past use of chronic opioid therapy; and history of substance abuse, mental health conditions, etc.).

In April 2016 PCORI released a targeted PFA on the comparison of surgical and nonsurgical options for managing nonspecific chronic LBP. Although the PFA examined the specific comparison of lumbar fusion versus an optimized nonsurgical comprehensive multidisciplinary program for nonspecific chronic LBP, stakeholder feedback indicated an additional evidence gap regarding the effectiveness of nonsurgical interventions for nonspecific chronic LBP. The current PFA is intended to address many of the evidence gaps that remain, particularly with regard to the most effective combinations or sequences of noninvasive treatment options.

Priority Research Question

Applications should propose pragmatic RCTs or well-justified observational studies that address the priority research question noted below. The study should take place in clinical settings where patients with chronic nonspecific LBP typically receive care. The studies must be relatively large, in part to be able to demonstrate differences in comparative clinical effectiveness in the study arms, but also to allow adequate power to detect the potential differences in treatment responses by patient clinical characteristics of interest. In considering pragmatic approaches to their study design, conduct, and analysis, applicants should refer to the multiple elements of the pragmatic-explanatory continuum[15] and explicitly consider the tradeoffs of each element on the continuum. Absolute pragmatism is not the ideal, particularly for the standardization of interventions chosen for comparison. Interventions require some degree of flexibility in their use but must be sufficiently well defined to be replicable in their dissemination and implementation in U.S. health care.

The priority research question is: What is the comparative clinical effectiveness of optimized, multidisciplinary nonsurgical treatment programs involving combined or sequenced interventions for patients with nonspecific chronic LBP?

Given the anticipated size and scope of proposed studies submitted under this funding initiative, applications should also carefully consider and provide details supporting how the target sample size will be met across all study sites (e.g., expected eligible patients, recruitment capacity, integration of research and clinical workflow, etc.). Details such as anticipated attrition—informed by past studies by the investigative team and studies found in the extant literature—should be factored into target sample size calculations. Similarly, recruitment timelines should include careful consideration of feasibility

[14] Refer to http://www.pcori.org/events/2016/prioritizing-comparative-effectiveness-research-questions-treatment-options-chronic-low.

[15] Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K: A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009, 62:464–475.

within the context of the proposed study. Additional considerations for the proposed study approaches include:

> The proposed study should have well-characterized interventions and comparators. The clinical options should be structured based on how they will be carried out over time, and the proposed operationalization must align with available evidence of efficacy. Proposed combinations or sequences of interventions must address actual clinical choices faced by patients, caregivers, and clinicians in specific practice settings.

PCORI is interested in receiving applications that propose to conduct direct comparisons of clinical programs having a strong empirical or clinical rationale. Applicants should include sufficient details about the staging of combinations or sequences of component treatments. For sequenced approaches, a rationale based on the available empirical evidence and documented common use should be included (e.g., simplest to most complex, patient-preferred, patient profile-determined, or randomized treatment sequence). PCORI is always interested in studying populations with important disparities, important comorbidities, or difficult social conditions.

The characteristics that apply to this research question include:

- Population/Patient Problem: Adults with chronic nonspecific LBP as defined by the NIH Task Force on Research Standards for Chronic Low Back Pain (no neurological symptoms or structural abnormalities other than disc degeneration) on at least 50 percent of days during the past six months despite current treatment (i.e., inadequate response to one or more nonsurgical treatments).
- Intervention: A structured, optimized, and multidisciplinary program of nonsurgical treatments used in combinations or sequences. (PCORI defines "multidisciplinary programs" as including professionals from two or more disciplines who deliver care in a coordinated fashion.) Applicants should fully describe the range and structuring of the specific procedures and techniques that will be included. The program must be well defined and justified in terms of efficacy and its feasibility for dissemination and implementation within the U.S population and healthcare system.
- Comparator: An evidence-based program of care that is meaningfully different from the primary intervention and meets the same requirements as listed above for the intervention.
- Outcome: The NIH Low Back Pain Task Force on Research Standards for Chronic Low Back Pain outcome measures (function, pain, sleep, mood, medication use, productivity, and use of opioids); healthcare utilization (emergency room visits, surgery, and hospital admissions); safety (major medical complications and infections); quality of life; and both validated general and specific disability measures for low back pain (e.g., Oswestry Disability Index and Roland Morris Disability Questionnaire2).
- Time: Follow-up for at least 12 months after initiating treatment and at least six months after active treatment concludes.
- Setting: Settings representative of locations where patients with chronic nonspecific LBP

typically receive care.

"Usual care" is discouraged but not prohibited as a comparator. It is too often ill defined, difficult to quantify, and subject to considerable geographic and temporal variations, which limits interpretability, applicability and reproducibility. If an applicant proposes "usual care" as a rational and important comparator in the proposed study, then it must be described in detail, coherent as a clinical alternative, and justified properly as a legitimate comparator (e.g., "usual care" is guidelines based). It must also be accompanied by an explanation of how the care given in the "usual care" group will be measured in each patient (to the extent possible) and how appropriate inferences will be drawn from its inclusion.

Funds Available

PCORI has allotted up to $50 million in total costs under this PFA to fund high-impact studies related to treating nonspecific chronic LBP. The proposed budget for all studies under this initiative may be up to $10 million in direct costs as appropriate, depending on the specific priority research question or questions the study proposes to address. The maximum project period is five years.

For this solicitation, PCORI is not requiring that relevant national patient organizations, professional organizations, and payer or purchaser organizations be formally included as partners and active participants prior to contract award. However, applicants should document that they have consulted with patients and other stakeholders to identify the important decisional dilemmas and evidence needs that will drive development of the research questions or refer to previously documented decisional dilemmas. Successful applicants are required to work in collaboration with PCORI staff upon award of the proposed studies to establish a project Study Advisory Committee (SAC) or other appropriate engagement body that is composed of national or regional organizations that represent—at a minimum—patients or families with lived experience; relevant clinicians; payers; and health plans. Other representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, among them scientific and methodological experts. The SAC advises and assists the research team with further refining the study questions, outcomes, and protocol.

Given the significant treatment costs associated with some interventions, the applications must specifically address—in the context of the proposed studies—the support from payers, health plans, industry sponsors, or others in covering the study interventions and non-study, protocol-related clinical costs and services rendered in the care processes. Of particular concern would be different levels of co-payment between two arms in a comparative study. Ideally, cost-sharing barriers will be eliminated in the study arms or equalized. If the study design does not allow for either option, the applicant should describe why and should also discuss how differences in co-payment costs will be accounted for in the analysis of the study's findings.

It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment or primary data collection, length of follow-up, and analytic complexity. PCORI seeks efficient studies—such as those that take advantage of large populations already under observation, registries, and the supportive involvement of delivery systems or health plans—to enhance recruitment, data collection, and coverage of treatment-related costs. A prolonged

recruitment period is not an acceptable rationale for longer studies.

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 by 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 precise estimation of hypothesized effect sizes. The sample size must also support testing of *a priori* hypotheses related to potential differences in effectiveness, depending on sociodemographic and clinical characteristics (HTE). When determining anticipated effect sizes, pay appropriate attention to basing such estimates on efficacy results observed in prior and adequately 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 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. PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and should present evidence that the study will not encounter significant barriers to recruitment or participation.
- Adhere to all applicable PCORI Methodology Standards.[16] The full application will require the

[16] Available at pcori.org/research-we-support/research-methodology-standards/.

applicant to identify the standards appropriate to the proposed study and 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 establishment of a Data and Safety Monitoring Board [DSMB] or indication of why such a board is unnecessary).

To carry out pragmatic studies, readily adopt the findings in a real-world setting, and maximize the efficient use of resources, care must be taken to prevent these trials from becoming more complex and onerous than necessary. The applicant is encouraged to be creative and consider the following innovative strategies, as appropriate and feasible:

- Be prepared to 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 Letters of Intent (LOIs) and the full applications.
- Carefully describe the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients; caregivers and families; and other stakeholders, including clinicians and policy makers. Similarly, applicants should document why project outcomes are especially relevant to patients, and also document meaningful endpoints for patients and their families.
- Justify why the interventions being compared are viable treatment alternatives worthy of a significant PCORI investment to elucidate the best clinical options for subgroups of patients with nonspecific chronic LBP.
- Minimize disruption to participants' daily routines (e.g., minimize participant visits intended solely for study assessment purposes and capture PROs during office visits, electronically, or via phone).
- Design the study so that the conduct can, as seamlessly as possible, be integrated with 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 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 electronic health record systems.

Nonresponsiveness

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).
- Conducts a cost-effectiveness analysis in the form of dollar-cost per quality-adjusted life-year to compare two or more alternatives.
- 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, and fundamental science of 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 patients and clinicians.
- Develops clinical prediction or prognostication tools.

Applications that include studies of these issues may measure and report use of any or all health services, but may not employ direct measurements of care costs.

PCORI does have an interest, however, in studying conditions that lead to high costs to the individual or to society. Thus, PCORI is also interested in studies that do the following:

- 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.

Applications that include studies of these issues without using cost-effectiveness analyses or comparing the costs of alternatives are considered responsive.

Furthermore, PCORI discourages applications in the following categories and is likely to deem them nonresponsive:

- Study of the natural history of disease
- Instrument development
- Pharmacodynamics
- Fundamental science or study of biological mechanisms
- Establishing efficacy for a new clinical strategy
- Pilot studies intended to inform larger efforts

- Comparisons of 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 preventive, diagnostic, 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 in the clinical settings
- 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 may be used to answer important CER questions. Studies that leverage existing research networks or consortia that would facilitate the conduct of large, multi-site studies called for in this PFA are of interest.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures and to include preliminary data that supports the proposed measures. Investigators are encouraged to consider those measures described in the *Patient-Reported Outcomes Measurement Information System* (PROMIS).[17]

Methodological Considerations

Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards.[18] These include 47 individual standards that fall into 11 categories. The first five categories are cross-cutting and are relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These five categories are:

1. Standards for Formulating Research Questions
2. Standards Associated with Patient-Centeredness
3. Standards on Data Integrity and Rigorous Analyses

[17] Available at http://nihpromis.org/.
[18] Available at pcori.org/research-we-support/the-pcori-methodology-report/.

4. Standards for Preventing and Handling Missing Data
5. Standards for Heterogeneity of Treatment Effect (HTE)

Six other standards categories will be applicable to particular study designs and methods. The standards in each of these categories should be used for guidance when they are relevant to a particular study. 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 Diagnostic Tests
6. Standards for Systematic Reviews

Most of these standards should be considered minimal. Additional best practices, including relevant guidelines for conducting clinical trials developed by other organizations, should be addressed in the application for PCORI funding. To help reviewers quickly identify the adherence to a particular standard, applicants must cite each PCORI Methodology Standard within their applications as the standard is being addressed. For example, when applicants describe the need for their proposed study within the Background section, they should indicate the particular standard for Identify Gaps in Evidence in parentheses, such as "(RQ-1)."

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, applicants are encouraged to review PCORI's Engagement Rubric,[19] which can be found in the PCORI Funding Center. Applicants should also review the PCORI Methodology Standards Associated with Patient-Centeredness and PCORI's Sample Engagement Plans.[20] The rubric and Sample Engagement Plans are not intended to be comprehensive or prescriptive; instead, they provide a variety of examples to incorporate engagement, where relevant, into the research process.

Applicants are expected to consult with patients and other stakeholders on their decisional dilemma and evidence needs or to reference previously documented decisional dilemmas in preparation for submitting LOIs and applications. To describe the decisional dilemma, state the specific clinical decision(s) or treatment choice(s) confronted by the decision makers and explain how the findings from the proposed research will inform those decisions. State why this decision—such as choosing a specific

[19] Available at http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf.
[20] Available at http://www.pcori.org/sites/default/files/PCORI-Sample-Engagement-Plans.pdf.

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 in making this decision. Identify the patients and other stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continue engaging them actively in the conduct of the study. Similarly, applicants should document how the project outcomes are especially relevant and meaningful endpoints to patients and other stakeholders.

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 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, or clinical status, so that possible differences in CER may be examined (otherwise known as HTE). PCORI recognizes that some proposed studies may represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant in such cases to justify the study's importance in the absence of diversity and to discuss which subgroups are most important and how they will be analyzed, including whether there will be power to examine the question of effectiveness in subgroups. PCORI is particularly interested in including previously understudied populations for whom effectiveness information is particularly needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of the strategies in various subpopulations, with attention to the 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

- 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 persons
- Veterans and members of the Armed Forces and their families

Budget and Duration of Project

PCORI has devoted up to $50 million in total costs to this announcement. Applicants may request up to $10 million in total direct costs for a research project period not to exceed five 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, in general, PCORI will not cover costs for interventions that are being compared in the proposed study. (See Appendix 2 in the Application Guidelines for details.) In rare cases where this policy would preclude conducting a CER study addressing the priority questions outlined in this PFA, such as research in underserved or hard-to-reach populations or settings, PCORI may consider a waiver on this policy. In such cases, the applicant will need to address the issue of scalability, sustainability, and potential for broad dissemination of the intervention beyond the project period. The applicant should demonstrate that payers and health systems will likely cover the intervention costs if study results demonstrate its effectiveness. Request for such a waiver and the accompanying justification must be made in the LOI, and PCORI staff must approve the waiver at the LOI stage before a full application is submitted.

Applicants should propose realistic budgets, project duration, 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. Not all requests for additional funds will be approved. Any request for a project period longer than five years will be denied. For further information regarding PCORI's policies about allowable and unallowable costs, refer to Appendix 2 of the Application Guidelines. Note that although subcontractor indirect costs are included in the prime applicant's direct-cost budget, subcontractor indirect costs are not factored in 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. Awardees will be expected 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
- Forming a SAC or other appropriate engagement body
- Obtaining clearances from all institutional and community partners, including IRB approvals
- Establishing a DSMB or providing a clear description of why a DSMB is not necessary
- 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 that involve 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,[21] 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 that refer to requirements for federal-wide assurance or that refer 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

[21] See 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.[22]

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[23]). 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 Subject Participants

PCORI requires all applicants to adhere to the 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.[24]

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 is required to develop and maintain a plan that addresses data management and data sharing of research project data in a manner that is appropriate for the nature of the research project and the types of research project data, and that is 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.[25]

In summary, Awardee Institutions are required to submit to PCORI for peer review a draft final research report that provides the methodological details, describes the main study results, and interprets the findings in clinical or other decisional contexts. Subject matter experts; individuals with expertise 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

[22] See http://www.pcori.org/sites/default/files/PCORI-Policy-Data-Safety-Monitoring-Plans.pdf.
[23] See http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/.
[24] See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html.
[25] See http://www.pcori.org/sites/default/files/PCORI-Peer-Review-and-Release-of-Findings-Process.pdf.

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.

III. How To Submit an Application

Letter of Intent

Applicants should download the Cycle 1 2017 Low Back Pain LOI Template from the PCORI Funding Center. They must complete the document and convert it to a PDF with a four-page limit. PCORI suggests including all references as in-text citations using American Medical Association citation style, but other citation styles are accepted. Do not upload additional documents as part of your LOI, 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 PFA 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 $10 million" is not sufficient. Upload your document to PCORI Online. The deadline for LOI submission is February 14, 2017, by 5 p.m. (ET).

Letter of Intent Review

LOIs are evaluated 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
- A size or scope sufficient enough to 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 are compliant with requirements in this PFA
- Adherence to the administrative and formatting requirements listed in the Application Guidelines, specifically the four-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 March 15, 2017. Please refer to the Application Guidelines for information on how to submit your LOI via PCORI Online.

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

- Research question(s)
- Specific aims
- Study design
- Comparators
- Principal Investigator (PI) (Contact PI and PI #2)
- Institution

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

Note: A PI can only submit one LOI per PFA. However, an individual listed as a PI on one LOI may be listed as and serve in another 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 which PFA he or she would like to apply to. 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 PFA and in the PCORI Funding Center.[26]

PCORI Online System

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

Applicant Resources

PCORI Funding Center	http://www.pcori.org/cycle-1-2017-multidisciplinary-treatments-low-back-pain
PCORI Online System	https://pcori.force.com/engagement
PCORI Funding Awards	pcori.org/pfaawards

IV. Merit Review

[26] Available at pcori.org/apply.

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., nonresponsiveness). 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 subject matter experts, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that they understand the programmatic and organizational goals of review.

The table below is designed to help applicants understand how the PCORI merit review criteria align with criteria from other funding organizations with which applicants might be familiar (e.g., NIH). Though PCORI's criteria do map to most NIH criteria, there are areas where we ask for different information (i.e., PCORI does not include a criterion that tracks to NIH's innovation criterion, but does include criteria evaluating patient-centeredness and engagement) reflecting PCORI's unique approach.

Crosswalk of PCORI Merit Review Criteria with NIH Criteria

SIGNIFICANCE	1. Potential for the study to fill critical gaps in evidence 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care
APPROACH	3. Scientific merit (research design, analysis, and outcomes) 4. Investigator(s) and environment
PCORI-only Merit Review Criteria	
PATIENT-CENTEREDNESS/ENGAGEMENT	5. Patient-centeredness 6. Patient and stakeholder engagement

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

Criterion 1. Potential for the study to fill critical gaps in evidence:
The application should address the following questions:

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

Criterion 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care
The application should describe how evidence generated from this study could be adopted into clinical practice and delivery of care by others. The application should also address the following questions:

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

reproduced by others, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder adoption of the intervention by others.

- Does the application describe a plan for how study findings will be disseminated 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 describe a clear conceptual framework anchored in background literature which informs the design, key variables, and relationship between interventions and outcomes being tested?
- Does the Research Plan describe rigorous methods that demonstrate adherence to the PCORI Methodology Standards?
- Is the overall study design justified?
- Are the patient population and study setting appropriate for the proposed research question?
- Does the application provide justification that the outcome measures are validated and appropriate for the population?
- Are each of the comparators (e.g., active intervention arm and comparator arm) described clearly and well justified? 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 well qualified are the PIs, collaborators, and other researchers to conduct the proposed activities? Is there evidence of sufficient clinical or statistical expertise (if applicable)?
- Does the investigator or co-investigator have demonstrated experience conducting projects of a similar size, scope, and complexity?
- If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate

for the project?

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

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

Criterion 5. Patient-centeredness

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

The application should also address the following questions:

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

Criterion 6. Patient and stakeholder engagement

The application should demonstrate the engagement of relevant patients and other stakeholders (e.g., patients, caregivers, clinicians, policy makers, 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 evaluation of 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 further the merits of the proposed research. They also identify areas for improvement. Each application is re-scored based on the content of discussion. The Panel Chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review according to the standards outlined in the PFA.

Post-Panel Review

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

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

Summary Statements and Funding Recommendations

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

- 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.

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to the Board for approval. Applicants to this current cycle's PFA will receive summary statements in November 2017 and notification of the funding status of their application no later than November 2017.