



Cycle 2 2018 Funding Cycle

PCORI Funding Announcement: Medication-Assisted Treatment (MAT) Delivery for Pregnant Women with Substance Use Disorders Involving Prescription Opioids and/or Heroin

Published June 1, 2018

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes September 25, 2018, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at <https://www.pcori.org/funding-opportunities/announcement/medication-assisted-treatment-cycle-2-2018>.



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

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Overview

Published	June 1, 2018
Letter of Intent Due	<p>June 28, 2018, by 5 p.m. (ET)</p> <p>The Patient-Centered Outcomes Research Institute (PCORI) will screen Letters of Intent (LOIs) for responsiveness to this PCORI Funding Announcement (PFA) and for fit to program goals. Only those applicants with an approved LOI will be permitted to submit a full application. Notification of denial or approval to submit a full application will occur no later than July 23, 2018.</p>
Summary	<p>PCORI seeks to fund large, randomized controlled trials (RCTs) or well-justified observational studies that compare the effectiveness of different strategies to support providers who offer office-based opioid treatment (OBOT) with buprenorphine to pregnant and postpartum women with opioid use disorder (OUD) with different levels of addiction severity. Comprehensive OUD treatment for pregnant and postpartum women includes perinatal care, medication-assisted treatment, and psychosocial care. Treatment must include maintenance medication, and delivery components must be evidence based or currently in use. PCORI expects the treatment programs to be well characterized to facilitate replication and dissemination efforts. Support for providers should address provider barriers such as patient induction (e.g., in an addiction clinic, emergency department, hospital, or at home versus the clinician’s office) and psychosocial services (e.g., different levels of medication management by provider, on-site individual or group counseling, online services, referral). Proposed studies must address actual choices faced by decision makers in the field of treatment delivery to pregnant women with OUD. They must involve patient populations that represent the US population; be large enough to address estimates of hypothesized effectiveness differences; and be large enough to support evaluation of potential differences in treatment delivery effectiveness between patient subgroups if such comparisons are planned.</p> <p>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. All studies should compare models or components of models that are ready for implementation on a large scale, should the study results be positive. Proposals should have strong endorsement and study input from patient organizations, professional organizations, payer or purchaser organizations, and other relevant stakeholder groups. Because close to 50 percent of US births are covered by Medicaid, partnerships and input from state Medicaid agencies or Medicaid Medical Directors or other representatives are particularly important. Successful applicants may have to develop formal arrangements. PCORI may require a project Study Advisory</p>

	<p>Committee (SAC)¹ that comprises national or regional organizations that represent—at a minimum—patients and families with lived experience; relevant clinicians; payers; and health plans. PCORI may also recommend scientific and methodological experts 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 or observational study designs specified for the research questions. Note that this PFA does not support applications to conduct cost-effectiveness analysis; systematic reviews; or development and evaluation of shared decision making, decision-support tools, or clinical practice guidelines.</p> <p>The proposed studies must address the priority research question identified in the main body of this PFA.</p>
Applicant Resources	See https://www.pcori.org/funding-opportunities/announcement/medication-assisted-treatment-cycle-2-2018
Key Dates	<p>Online System Opens: June 1, 2018</p> <p>LOI Town Hall: June 11, 2018, 12pm (ET)</p> <p>LOI Deadline: June 28, 2018, by 5 p.m. (ET)</p> <p>LOI Status Notification: July 23, 2018</p> <p>Applicant Town Hall: August 9, 2018, 12pm (ET)</p> <p>Application Deadline: September 25, 2018, by 5 p.m. (ET)</p> <p>Merit Review: December 2018</p> <p>Awards Announced: April 2019</p> <p>Earliest Project Start Date: June 2019</p>
Maximum Project Budget (Direct Costs)	\$4 million
Maximum Research Project Period	Four years
Funds Available Up to	\$6 million
Eligibility	<p>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 US applicant organizations. Nondomestic components of organizations based in the US and foreign organizations may apply, as long as there is demonstrable benefit to the US healthcare system and US 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.</p>

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

<p>Review Criteria</p>	<ol style="list-style-type: none"> 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
<p>Contact Us</p>	<p>Programmatic Inquiries: Please contact the PCORI Helpdesk via email (sciencequestions@pcori.org), phone (202-627-1884), or online (http://www.pcori.org/PFA/inquiry). PCORI will respond within two business days; however, we cannot guarantee that we can address all questions in a timely fashion when the inquiry is made three or fewer business days before an LOI or application deadline.</p> <p>Administrative, Financial, or Technical Inquiries: Please contact the PCORI Helpdesk at pfa@pcori.org. PCORI will respond within two business days. Applicants may also call the PCORI Helpdesk at 202-627-1885. Please note that during the week of the application deadline, response times may exceed two business days. We ask that applicants plan accordingly. It is the applicant's responsibility to submit the application on or before the application deadline.</p>
<p>Other</p>	<p>Deadlines are at 5 p.m. (ET). If deadlines fall on a weekend or a federal holiday, the deadline will be the following Monday or the next day after the federal holiday.</p>

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New or Revised for the Cycle 2 2018 Funding Cycle:

- Given the policy importance and the evidentiary need, this PFA has been reopened. Changes in this PFA include:
 - This PFA will solicit applications that respond to the following priority research question: What is the comparative effectiveness of different strategies for providing support or coordination of services for components of MAT (induction and/or psychosocial services) to providers who offer office-based opioid treatment to pregnant women, in terms of maternal and neonatal outcomes?
 - Support for providers should address provider barriers such as patient induction (e.g., in a methadone clinic, emergency department, hospital, or at home versus the clinician’s office) and psychosocial services (e.g., different levels of medication management by provider, on-site individual or group counseling, online services, referral).
 - PCORI is particularly interested in proposals that focus on or include urban, low-income, and racial-ethnic minority populations.
 - The total funds available for this announcement are \$6 million.

Added a new Methodology Standard category (Standards for Studies of Complex Interventions)—see page 10. There is a new Methodology Standards Checklist. Applicants are required to upload this with Research Plan Template.

I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is reissuing this funding initiative to support patient-centered comparative effectiveness research (CER) on strategies to support providers who offer office-based opioid treatment (OBOT) to pregnant women with opioid use disorder (OUD). Due to the continued concern about the opioid epidemic, PCORI leadership remains committed to supporting high-quality research in this area. Through this PCORI Funding Announcement (PFA), PCORI seeks to fund studies with sufficient sample sizes to address the priority research question:

- What is the comparative effectiveness of different strategies for providing support or coordination of services for components of medication-assisted treatment (MAT) (induction and/or psychosocial services) to providers who offer office-based opioid treatment to pregnant women, in terms of maternal and neonatal outcomes?

The goal of this PFA is to generate valid evidence that is readily generalizable to the broader population of pregnant women with OUD. The study designs that PCORI will consider include large randomized controlled trials (RCTs) or well-justified observational studies. PCORI is particularly interested in receiving applications that focus on or include urban, low-income, and racial/ethnic minority populations. PCORI is also particularly interested in receiving proposals for large studies that can investigate potential heterogeneity of treatment effects (HTEs) regarding important sociodemographic and clinical characteristics (e.g., addiction severity, socioeconomic status, comorbid mental health conditions, or other clinical or patient/demographic characteristics proposed by investigators with an accompanying strong rationale).

Applicants should follow the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) definition of opioid use disorder: “a problematic pattern of opioid use leading to clinically significant impairment or distress.”¹

There is concern that the term “medication-assisted treatment” suggests that medication is merely an ancillary part of the treatment rather than a central component. In this PFA, the term MAT is used because it is well defined and broadly used and recognized, and to distinguish it from approaches that focus on abstinence. Studies will be considered nonresponsive if they do not include maintenance medication.

Applications must address the priority research question described in this PFA. Proposed studies should include a comparison of two or more strategies to provide support or coordination of services for clinicians who provide OBOT to pregnant women (induction, psychosocial services, mentoring, education). Treatment should be comprehensive and include prenatal care, maintenance medication, and psychosocial services (on-site, remote, or by referral). Care may be delivered by more than one provider (e.g., a primary care provider offers OUD treatment, and an obstetrician or midwife offers

¹ American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Washington, DC: American Psychiatric Association; 2013. 541-46.

prenatal care) and in more than one location (e.g., clinician's office, Opioid Treatment Program, hospital, Federally Qualified Health Center, community programs). Based on a 2016 Agency for Healthcare Research and Quality (AHRQ) systematic review by Chou et al.,² strategies of interest may include education and outreach for the provider and additional components. Proposed strategies should address barriers to the use of MAT for clinicians and promote generalizability on a broader scale.

Proposed strategies must be evidence based or in current use. If applicants propose comparing strategies that are in common use but without clear evidence of efficacy, they must document the extensiveness of their use. Proposed comparators must be adequately defined and described regarding how they will be measured.

Outcomes should include maternal measures, including illicit drug use, relapse, treatment entry, treatment retention, continuation of OUD care following delivery, patient quality of life, and anxiety/depression; perinatal measures, including pregnancy complications, preterm birth, birthweight, neonatal complications, and Neonatal Abstinence Syndrome; and provider measures, including provider satisfaction and provider stress. Studies should conduct periodic outcome assessments, including a follow-up period of three months or longer postpartum to allow for the assessment of continuity of OUD care for the mother.

Background

The prevalence of opioid use disorder has increased dramatically among pregnant women in parallel with the current opioid epidemic. The largest increase in heroin use between 2002 and 2013 was in women, and the proportion of *pregnant women* who entered Substance Use Disorder treatment and reported prescription opioids as their primary substance increased from 1 percent in 1992 to 19 percent in 2012. The rate of neonatal intensive care unit admissions for Neonatal Abstinence Syndrome nearly quadrupled between 2004 and 2013 (from 7 to 27 per 1000 admissions), while the median length of stay increased from 13 days to 19 days.

OUD in pregnant women is associated with potentially serious maternal, fetal, and neonatal risks, including increased morbidity and mortality, decreased quality of life, complications during pregnancy, Neonatal Abstinence Syndrome in the baby, and potential longer-term cognitive and behavioral effects for the child.

Medication-assisted treatment (MAT), in which maintenance medication (methadone or buprenorphine) is combined with psychosocial services, is an evidence-based, clinically effective treatment for pregnant women with OUD. Buprenorphine has a more favorable safety profile than methadone, and is associated with improved birth outcomes compared with methadone, including reduced incidence and severity of Neonatal Abstinence Syndrome. Psychosocial services include counseling, and may also include mental health screenings and assessments, hepatitis C screening, contingency management, psychiatric care, and other specialty care.

² Chou R, Korthuis P, Weimer M, et al. *Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings*. Rockville, MD: Agency for Healthcare Research and Quality; December 2016. Technical Brief 28 (Prepared by Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I). AHRQ Publication No. 16(17)-EHC039-EF. https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/opioid-use-disorder_technical-brief.pdf

Pregnancy may motivate women to seek treatment, but stigma (relating to such elements as treatment setting or methadone usage), lack of access to treatment, and, in some states, fear of legal consequences are important barriers. Unlike methadone, buprenorphine may be offered for OUD in physicians' offices (office-based opioid treatment); buprenorphine also is less well known than methadone and not associated with the same stigma. Thus, OBOT has the potential to address the important patient barriers of stigma and lack of access. However, fewer than half the counties in the United States offer buprenorphine delivery, and the need for treatment continues to exceed availability. The percentage of obstetricians who have obtained a waiver for buprenorphine prescribing remains especially low. Provider barriers include lack of expertise regarding the treatment, particularly in this patient population, lack of adequate support for its delivery, and lack of access to mental health providers or services necessary for OUD treatment.

Evidence suggests that comprehensive care for pregnant women with OUD consists of prenatal care, OUD care, and psychosocial services. Support to providers who offer OBOT to pregnant women may focus specifically on the aspects that are considered challenging by providers: patient induction, psychosocial services, lack of time, and lack of expertise regarding the treatment and the population. Induction may take place elsewhere (e.g., in an emergency department or hospital, in an Opioid Treatment Program (OTP), or at home). Psychosocial services may be delivered off-site by referral, by enhanced medical management by the provider, or by non-physician staff in a group rather than individual format. Non-physician staff may take care of service coordination. Guidance regarding the treatment and population may be provided by OTP staff or mentor providers experienced in treatment for pregnant women with OUD and may be offered in person or by telecommunication.

Recommendations included in the 2017 US Commission on Combating Drug Addiction and the Opioid Crisis interim report³ call for increased provider education initiatives as well as a Centers for Medicare & Medicaid Services mandate to require all federally qualified health centers and their staff to possess waivers to prescribe buprenorphine. Addressing provider barriers is essential to successful implementation of these and other efforts to respond to the current opioid crisis.

Evidence Gaps

AHRQ recently commissioned a systematic review of MAT models in primary care settings that identified 12 models of MAT delivery currently in use, including one focusing on integrated prenatal care and MAT. As its main conclusion, AHRQ recommends research "to clarify optimal MAT models of care and to understand effective strategies for overcoming barriers to implementation."⁴

Comprehensive care for pregnant women with OUD includes prenatal care, maintenance medication for opioid addiction, and psychosocial services. Research has identified several provider barriers to offering OBOT, including lack of expertise regarding the treatment, particularly in this patient population, lack of

³ United States, The President's Commission on Combating Drug Addiction and the Opioid Crisis. (2017). *Appendix 3. Interim Report, President's Commission on Combating Drug Addiction and the Opioid Crisis. Washington, D.C.*
<https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Meeting%20Draft%20of%20Final%20Report%20-%20November%201%2C%202017.pdf>

⁴ Chou R, Korthuis P, Weimer M, Bougatsos C, Blazina I, Zakher B, Grusing S, Devine B, McCarty D. Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings. Technical Brief No. 28 (Prepared by Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I). AHRQ Publication No. 16(17)-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2016. https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/opioid-use-disorder_technical-brief.pdf

adequate support for its delivery, and lack of available to mental health providers or services necessary for OUD treatment. Various models that offer support for OBOT providers are in use. These models vary by resource intensity. For example, patient induction may take place in an emergency department, in a hospital, in an OTP, or at home versus in a provider's office; psychosocial services may be offered on-site through enhanced medical management/brief counseling by the provider, or through individual or group counseling by non-physician staff, or by referral. Support may also be provided by OTP staff or mentor providers of OUD to pregnant women.

In summary, the need to increase the number of providers who offer OBOT is well recognized, and patient and provider barriers have been identified. Different strategies to address these barriers are in use, but there are no studies comparing the effectiveness of these different approaches for pregnant and postpartum women and their infants, or for provider experience.

Research Topic Prioritization

The Medicaid Medical Directors Network identified the treatment of pregnant women with OUD as a priority in 2015 and 2016. PCORI met individually with representatives from key stakeholder groups, including midwives and obstetricians working in addiction treatment settings, addiction specialists, researchers who have focused on treatment of pregnant women with OUD, and individual Medicaid Medical Directors. PCORI also consulted the Advisory Panel on Improving Healthcare Systems, which consists of patient representatives, clinicians, researchers, payers, and purchasers.

Priority Research Question

Applications should propose RCTs or well-justified observational studies that address the priority research question noted below. The study should take place in clinical settings where pregnant patients with OUD typically receive care. The studies must be sufficiently large to be able to demonstrate differences in comparative clinical effectiveness in the study arms and to allow adequate power to detect the potential differences in treatment responses by patient clinical characteristics of interest. In considering approaches to their study design, conduct, and analysis, applicants should explicitly consider the tradeoffs of each element on the continuum while ensuring the validity of comparative clinical effectiveness findings. Interventions require some degree of flexibility in their use but must be sufficiently defined to be replicable in their dissemination and implementation in US health care.

The priority research question is the following:

1. What is the comparative effectiveness of different strategies for providing support or coordination of services for components of MAT (induction and/or psychosocial services) to providers who offer office-based opioid treatment to pregnant women, in terms of maternal and neonatal outcomes?

Proposed strategies should address provider barriers to the use of MAT and promote generalizability on a broader scale.

Given the anticipated size and scope of proposed studies submitted under this funding initiative, applications should 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.). Applicants should factor into target sample size calculations of details such as anticipated attrition, informed by the investigative team's past studies and studies found in the extant literature. Similarly, recruitment timelines should include careful consideration of feasibility within the context of the proposed study. The proposed studies should have well-characterized interventions and comparators. Proposed treatment models or model components 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 strategies, models, or model components that have a strong empirical or clinical rationale and/or are supported by published literature. Applicants should include sufficient details about the organization and components of treatment delivery.

The characteristics that apply to this research question include the following:

Population/Patients: Pregnant women with OUD as defined by the DSM-5 and infants born to women with OUD. Although women with Medicaid insurance account for close to 50 percent of US births, applications can include women with private insurance and uninsured women. Applicants should justify their patient populations of interest (e.g., rural, low-income, urban, and/or racial and ethnic minorities). PCORI is particularly interested in proposals that focus on or include urban, low-income, and racial-ethnic minority populations.

Intervention and Comparators: Support for providers should address provider barriers such as patient induction (e.g., in an addiction clinic, in an emergency department, in a hospital, or at home versus in the clinician's office), psychosocial services (e.g., different levels of medication management/counseling by provider, on-site individual or group counseling, online services, referral) and treatment- and population-related expertise (e.g., consultations with OTP staff, experienced provider as mentor).

Models might offer remote support for providers, including hub-and-spoke models, in which the hub is a center with on-site addiction treatment expertise and spokes are office-based clinicians at geographical distance from the hub. The spokes serve women who live too far away from the hub. Core components of the spokes include prenatal care and office-based opioid treatment by the clinicians.

Compared models need to be meaningfully different from each other and may include usual care. However, usual care is 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 the applicant must describe it in detail and include 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.

Outcomes: Studies need to include maternal outcomes (e.g., illicit drug use, relapse, treatment entry, treatment retention, patient quality of life, anxiety/depression, patient experience), perinatal outcomes (e.g., preterm birth, pregnancy complications, birthweight, neonatal complications, Neonatal Abstinence Syndrome), and provider outcomes (e.g., provider satisfaction, provider stress).

Time: Studies should include repeated assessments to measure maternal, pregnancy, and infant outcomes. Continuity of care for the mother should be assessed post-pregnancy, with an assessment at

least three months postpartum. Provider assessments should occur as appropriate throughout the study.

Setting: Focus on settings representative of locations where pregnant and postpartum women with OUD typically receive care.

Important Safety Considerations

Applicants must plan to have specific and adequate human subjects protection measures in place (e.g., inclusion of a data safety monitoring board, a risk monitoring plan, and discussion of potential risk and how it will be monitored in the consent process).

Funds Available

PCORI has allotted up to \$6 million in total costs under this PFA to fund high-quality and high-impact studies related to providing support or coordination of services for components of MAT to providers who offer OBOT to pregnant and postpartum women with OUD. The proposed budget for all studies under this initiative may be up to \$4 million in direct costs as appropriate. The anticipated project period is three to four years; in no case should the project period exceed four years. For this solicitation, applicants should document that they have consulted with representatives from key stakeholder groups to identify the important decisional dilemmas and evidence needs that will drive development of the research questions or refer to previously documented decisional dilemmas. Because Medicaid covers close to 50 percent of US births, partnerships and input from state Medicaid agencies, Medicaid Medical Directors, or other representatives are important. Successful applicants will collaborate with PCORI staff upon award of the proposed studies to establish a project Study Advisory Committee (SAC) or other appropriate engagement body that comprises national or regional organizations that represent—at a minimum—patients or families with lived experience, relevant clinicians, payers, and health plans. In collaboration with the applicant, PCORI might recommend other representation, 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.

PCORI will not cover costs for 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. 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. This is important because the interventions should be immediately implementable on a large scale if the study results provide significant evidence. 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 account for differences in co-payment costs in the analysis of the study’s findings.

PCORI seeks efficient studies, such as those that take advantage of large populations already under observation, registries, and research cooperatives, and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of intervention-related costs. A prolonged recruitment period is not an acceptable rationale for longer studies. Funding requests with the primary purpose of developing or building on initial collaboration between researchers and patient or stakeholder groups are not appropriate for this PFA.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet the following requirements:

- Focus on a comparative clinical effectiveness question that is important to patients, providers, and other decision makers.
- Demonstrate consultation with patients, providers, and other stakeholders or their representative groups, or reference previously documented decisional dilemmas to determine if the study is answering a critical question—one that, if adequately answered, would substantially improve decision making.
- Propose a sample size that is sufficiently large to allow for precise estimation of hypothesized effect sizes or for clear demonstration of non-inferiority. The sample size must also support testing of *a priori* hypotheses related to potential differences in effectiveness among relevant patient subgroups (HTE).
- Examine diverse populations receiving care in real-world settings.
- Have strong interest from and support of host delivery systems and clinical care settings.
- Compare interventions that are known to be efficacious, effective, or commonly used and that can be implemented in real-world settings.
- Feature near-term outcomes and PROs as primary outcomes, when appropriate.
- Plan to collect patient-centered outcome data efficiently and periodically during follow-up.
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions (if applicable). PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and present evidence that the study will not encounter significant recruitment or participation barriers. The relevant IRBs make the final determination of the adequacy of informed-consent procedures and participant protections.
- Adhere to all applicable [PCORI Methodology Standards](#). The full application will require the applicant to identify the standards appropriate to the proposed study and to describe how the

study team plans to address each standard.

- In the case of RCTs, also adhere to current best practices (standardized inclusion or exclusion criteria; proper randomization; techniques to minimize potential for missing data; and appropriate safety monitoring, including establishing a Data and Safety Monitoring Board [DSMB] or indicating why such a board is unnecessary).

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

- Consult with patients, providers, and other stakeholders on their decisional dilemma and evidence needs, or reference previously documented decisional dilemmas in preparation for submitting LOIs and full applications.
- Carefully describe the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Similarly, applicants should document why project outcomes are especially relevant and meaningful endpoints for patients and their families.
- Minimize disruption to participants' daily routines (e.g., minimize participant visits intended for study-assessment purposes and capture PROs during office visits, electronically, or via phone).
- Design the study so that you can conduct it using routine clinic or office operations.
- Use efficient methods to obtain participant consent while still meeting ethical and legal requirements.
- Capitalize on the existing electronic health records (EHRs) and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information. PCORI specifically encourages applications that use the National Patient-Centered Clinical Research Network (PCORnet) infrastructure.
- If data standardization and interoperability across study sites have not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different EHR systems.

Project Budget and Duration

Applicants may request up to \$4 million in total direct costs for a research project period not to exceed four years (not including peer review). At the time of contract execution, PCORI sets aside all funds associated with an awarded project to be made available throughout the contract's period of performance. The maximum budget includes all research and peer-review-related costs. (Please refer to the Application Guidelines for further details.) In general, PCORI will not cover costs for interventions that are being compared in the proposed study. (Appendix 2: Allowable and Unallowable Costs in the [Application Guidelines](#) for details.) Applicants should submit a realistic budget and timeline reflecting the proposed study's scope and requirements. In some rare circumstances, the estimated budget may

exceed \$4 million total direct costs, depending on the nature of the research question, the design and analytical requirements of the proposed study, the expected size of the patient enrollment, or the complexity and frequency of the outcomes assessment. PCORI expects these to be selective cases. Applicants who intend to propose such studies must provide evidence of prior approval by PCORI scientific staff to exceed the budgetary limit and succinct justifications in their LOI, documenting the budget requirements with respect to the scope of the proposed research and the data-collection and analysis efforts. Please note that this justification counts toward the LOI three-page limit. PCORI will deny any request for a project period longer than four years. Note that although subcontractor indirect costs are included in the prime applicant's direct-cost budget, subcontractor indirect costs are not factored when determining adherence to the PFA's direct-cost limit.

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

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

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

Refer to the [Application Guidelines](#) for a list of additional project milestones specific to this PFA.

Non-responsiveness

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

- Tests efficacy (or comparative efficacy) of interventions that are novel or with limited evidence of efficacy and are currently not in use.

- Involves studies conducted within tightly controlled research environments instead of in clinical settings reflective of real-world healthcare delivery.
- Conducts a formal cost-effectiveness analysis.
- Directly compares the costs of care between two or more alternative approaches to providing care. Studies may propose to compare cost of care to patients.
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, fundamental science or biological mechanisms.
- Is a pilot study intended to inform larger efforts.
- Compares patient characteristics rather than clinical strategy options.
- Compares interventions for which the primary focus or the sole intervention is examining the role of compensated or volunteer community health workers, including patient navigators.

Proposals may report use of any or all health services, but may not employ direct measurements of care costs. For further information, please reference our [cost-effectiveness analysis FAQs](#).

PCORI does have an interest, however, in studies addressing questions about conditions leading to high costs to the individual or to society. This is included in our review criterion on the potential for research to fill a critical gap in knowledge or practice. As a result, PCORI is interested in studies that:

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

Avoiding Redundancy

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

Methodological Considerations

Regardless of study design, applications must adhere to all relevant [PCORI Methodology Standards](#). These include 54 individual standards that fall into 13 categories. The first five categories are cross-cutting and relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These cross-cutting categories are:

1. Standards for Formulating Research Questions
2. Standards Associated with Patient-Centeredness
3. Standards on Data Integrity and Rigorous Analyses
4. Standards for Preventing and Handling Missing Data
5. Standards for Heterogeneity of Treatment Effect (HTE)

In addition to these five sets of standards, the first standard of “Standards for Causal Inference Methods” -(CI-1)- is cross-cutting and applicable to all PCOR studies.

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

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 quickly identify adherence to a particular standard, applicants must cite each relevant [PCORI Methodology Standard](#) within the [Methodology Standards Checklist](#), following the instruction in the checklist itself and in the [Application Guidelines](#). Program staff use the checklist to evaluate applications.

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

Patient-Centered Outcome Measures

PCORI encourages investigators to design their research using valid patient-centered outcome measures. Include preliminary data that support using the proposed measures in the study population. We also encourage investigators to consider those measures described in the [Patient-Reported Outcomes Measurement Information System \(PROMIS\)](#).⁵

Leveraging Existing Resources

PCORI encourages investigators to propose studies that leverage existing resources, such as adding PCOR to an existing large clinical trial or analyzing existing large databases that contain valuable and relevant information that can be used to answer important CER questions. PCORI is interested in studies that leverage existing research networks or consortia that would facilitate the conduct of large, multi-site studies called for in this PFA.

⁵ Available at <http://www.nihpromis.org/>.

Applicants proposing use of an existing research network infrastructure (e.g., PCORnet); research consortia; or related data resources (e.g., patient outcomes registries and/or electronic medical record [EMR] data from healthcare delivery systems or administrative claims data from public or commercial insurers) should address the following in the Research Plan (as appropriate), with sufficient specificity:

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

Collaboration

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

Patient and Stakeholder Engagement

PCORI encourages all applicants to outline how patients and other stakeholders will participate as partners in various phases of the proposed research. Before completing this section of the Research Strategy, we encourage to review [PCORI's Engagement Rubric](#), which can be found in the PCORI Funding Opportunities. Applicants should also review the PCORI Methodology Standards Associated with Patient-

Centeredness, and PCORI's Sample Engagement Plans. Additionally, the [Engagement in Health Research Literature Explorer](#)⁶, 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 a variety of examples to incorporate engagement, where relevant, into the research process.

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

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

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

⁶ Available at <http://www.pcori.org/literature/engagement-literature>

Populations Studied

PCORI seeks to fund research that includes diverse populations with respect to age, gender, race, ethnicity, geography, and clinical status. PCORI recognizes that some proposed studies might represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant in such cases to justify the study's importance in the absence of diversity.

Alternatively, PCORI is particularly interested in including previously understudied populations for whom effectiveness information is needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of strategies in various subpopulations, with attention to the possibility that the strategy's effects might differ across subgroups. Populations of interest include those that are less frequently studied. PCORI has developed the following list of populations of interest to guide our research and engagement efforts:

- Racial and ethnic minority groups
- Low-income groups
- Women
- Children (age 0–17 years)
- Older adults (age 65 years and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Individuals with low health literacy, numeracy, or limited English proficiency
- Lesbian, gay, bisexual, transgender, and questioning (LGBTQ) persons
- Veterans and members of the Armed Forces and their families

Protection of Human Subjects

This component (up to five pages) is included in the Research Plan Template. Describe the protection of human subjects involved in your proposed research. PCORI follows the Federal Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, please see Section 5, titled "Human Subjects Research Policy," in the [Supplemental Grant Application Instructions for All Competing Applications and Progress Reports](#),⁷ which is issued by the US Department of Health and Human Services (HHS). In referencing the HHS Supplemental Grant Application Instructions, note that PCORI does not require that applicants comply with sections of that policy that refer to requirements for federal-wide assurance and the inclusion of women, minorities, and children in

⁷ See <http://grants.nih.gov/sites/default/files/supplementalinstructions.docx>

the proposed studies. Instead PCORI expects applicants to address diversity in study participants in the research plan, through a focus on subpopulations, as described in the above section on ‘Populations Studied.’ Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

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

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

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

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

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

Data Management and Data-Sharing Plan

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

Recruitment

Applications should include information about the size and representativeness of the potential recruitment pool of patients and the means by which this size estimate was determined (e.g., EMRs, claims records, clinic logs, or other administrative systems). Likewise, applications should provide evidence-based estimates of how many participants are ultimately expected in the study, based on expected recruitment applying the study’s inclusion and exclusion criteria; anticipated acceptance (or refusal) rates; and other factors, such as loss to follow-up. Such estimates must be discussed in the application, specified in the milestones, reviewed by Merit Review Officers (MROs) and PCORI staff, and monitored by PCORI in the funded research.

⁸ Available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html>.

Peer Review and Release of Research Findings

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

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

PCORI will post the following materials on its website the earlier of 13 months after the Final Progress Report OR 90 days from the date the Final Research Report is approved by PCORI: (1) a 500-word abstract for medical professionals; (2) a 500-word standardized abstract summarizing the study results for patients and the general public; (3) a link to the study record on ClinicalTrials.gov (as applicable); and (4) ancillary information, including conflict-of-interest disclosures. The final research report, along with anonymized reviewer comments, will be made publicly available on the PCORI website no later than 12 months after its acceptance, except by prior mutual agreement with the Awardee Institution.

III. How To Submit an Application

Letter of Intent (LOI)

Applicants should download the [Medication Assisted Treatment LOI Template](#) from the PCORI Funding Opportunities. They must complete the document and convert it to a PDF with a three-page limit, excluding references. PCORI suggests including all references as in-text citations using American Medical Association citation style, but we do accept other citation styles. Do not upload additional documents as part of your LOI, such as Letters of Endorsement or Support, because they are not requested at this stage. Their inclusion will result in LOI rejection without review. Please visit the [PCORI Funding Opportunities](#) for additional applicant resources, including FAQs and required templates.

Please answer all of the questions in the LOI Template. This includes the question on brief justification for the proposed cost of the study. Providing the answer, "costs not to exceed \$4 million in direct costs" 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 topics are related to those on PCORI's own priority list, versus the IOM/AHRQ lists, versus other topics initiated by investigators

- Importance to current clinical decision making, as evidenced by critical gaps identified by clinical guidelines developers or recent relevant systematic reviews
- A size or scope sufficient to have a significant impact on patient outcomes or healthcare practices
- Clarity and credibility of applicants' responses to the LOI questions, as well as a rationale for the estimated sample size—citing published estimates, including effect sizes, standard deviations, and the need for rigorous comparative analysis of important subgroups
- Prior relevant experience
- Programmatic fit and balance, considering whether the application significantly overlaps with concurrent applications or previously funded studies or, conversely, whether the application fills a gap in PCORI's portfolio, considering such characteristics as disease category, topics, priority population, and methodologies
- Adherence to the administrative and formatting requirements listed in the [Application Guidelines](#), especially the three-page limit for the LOI

LOIs are reviewed qualitatively; they are not scored. Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. At least two PCORI staff review LOIs, and they are not scored during review. Notification of denial or approval to submit a full application will occur no later than July 23, 2018. Please refer to the Application Guidelines in the PCORI Funding Opportunities for due dates and information on how to submit your LOI in PCORI Online.

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

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

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

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the Overview section of this document and in the [PCORI Funding Opportunities](#).

PCORI Online System

To submit an application, you must register in [PCORI Online](#) and submit an LOI and an application for each cycle to which you are applying.

Applicant Resources

PCORI Funding Opportunities	https://www.pcori.org/funding-opportunities/announcement/medication-assisted-
PCORI Online System	https://pcori.force.com/engagement
PCORI Funding Awards	http://www.pcori.org/research-results-home

IV. Merit Review

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

- Identify applications that have the strongest potential to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders make informed decisions to improve patient outcomes.
- Implement a transparent, fair, objective, and consistent process to identify these applications.
- Elicit high-quality feedback that reflects a diversity of perspectives to ensure that the PCORI-funded research reflects the interests and views of patients and other stakeholders and those who care for them, and that it meets the criteria for scientific rigor.
- Fund projects that fill important evidence gaps and have strong implementation potential.
- Regularly evaluate and continually improve the merit review process and policies in support of PCORI's mission.

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

Preliminary Review

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

PCORI Merit Review Officers (MROs) recruit each review panel based on the number of invited LOIs and

topic areas represented by the invited LOIs. MROs recruit the panel chair, scientist reviewers who are SMEs, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that they understand the programmatic and organizational goals of review.

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

Crosswalk of PCORI Merit Review Criteria with NIH Criteria	
SIGNIFICANCE	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 3. Scientific merit (research design, analysis, and outcomes) 4. Investigator(s) and environment
PCORI-Only Merit Review Criteria	
PATIENT-CENTEREDNESS/ENGAGEMENT	<ol style="list-style-type: none"> 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 application evaluation.

Criterion 1. Potential for the study to fill critical gaps in evidence

The application should address the following questions:

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

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

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

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

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

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

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

Criterion 4. Investigator(s) and environment

This criterion should assess the appropriateness (e.g., qualifications and experience) of the

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

The application should also address the following questions:

- How qualified are the PIs, collaborators, and other researchers to conduct the proposed activities? Is there evidence of sufficient clinical or statistical expertise (if applicable)?
- Does the investigator or co-investigator have demonstrated experience conducting projects of a similar size, scope, and complexity?
- If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate for the project?
 - (Dual-PI Option Only) Does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?
- Is the level of effort for each team member appropriate for successfully conducting the proposed work?
- Does the application describe adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research?
- Is the institutional support appropriate for the proposed research?

Criterion 5. Patient-centeredness

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

The application should also address the following questions:

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

Criterion 6. Patient and stakeholder engagement

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

stakeholder involvement throughout the research process.

The application should also address the following questions:

- Does the application provide a well-justified description of how the research team incorporates stakeholder involvement? Does the study include the right individuals (e.g., researchers, patients, caregivers, clinicians, policy makers and other healthcare system stakeholders) to ensure that the projects will be carried out successfully?
- Does the application show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, and implementing)? Is the frequency and level of patient and stakeholder involvement sufficient to support the study goals?
- Is the proposed Engagement Plan appropriate and tailored to the study?
- Are the roles and the decision-making authority of all study partners described clearly?
- Are the organizational structure and resources appropriate to engage patients and stakeholders throughout the project?

In-Person Review

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

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

In-Person Applicant Presentation

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

Post-Panel Review

After the in-person meeting, PCORI program staff evaluate final merit review panel scores and comments, identify duplication or synergy among funded projects, and consider the fit of applications within the programmatic vision. Program staff members then recommend projects to a Selection Committee, which includes members of the Board. The Selection Committee considers

recommendations and works with staff to identify a slate of applications for possible funding based on merit review scores, programmatic balance and fit, and PCORI's strategic priorities. This slate then goes to the Board for consideration and approval.

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

Summary Statements and Funding Recommendations

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

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

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

PCORI makes funding recommendations by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. PCORI also considers the funds allotted for the current PFA when deciding which applications to recommend to the Board for approval. Applicants to this current cycle's PFA will receive summary statements and notification of the funding status of their application no later than April 2019.