Cycle 3 2021 Funding Cycle

PCORI Funding Announcement:
Comparative Effectiveness of Novel Pharmacologic and Evidence-based Nonpharmacologic Treatments for Migraine Prevention

Published September 7, 2021

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes January 11, 2022, at 5 pm ET. Submission Instructions, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/pharmacologic-nonpharmacologic-treatments-migraine-prevention-cycle-3-2021.
About PCORI

PCORI was authorized by federal law in 2010 and reauthorized for an additional 10 years in 2019 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” and by promoting the dissemination and uptake of this evidence.

PCORI is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI uses a variety of forums and public comment periods to obtain public input to enhance its work. PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients and other stakeholders.
Important Considerations Related to COVID-19 and Research Studies

The significant global impact of the COVID-19 pandemic has markedly affected healthcare delivery and research. Substantial uncertainties exist about the nature and duration of its impact on research, including intervention delivery and the collection, analysis, and the interpretation of study data. Research staff may face conflicting local and institutional policies to promote safety and the provision of care for those afflicted with COVID-19. They may also face personal risks of exposure, illness, and incapacity related to the pandemic. PCORI considers the safety and well-being of study participants, research staff, and stakeholders to be paramount and advocates that safety be the foundational principle guiding research decisions.

In light of the risks and uncertainties of COVID-19 on population health, health care, and research, PCORI requests applications to this PFA to include an explicit assessment of potential risks and risk management plans/contingencies for the proposed research as it may be affected by COVID-19. In addition to risk assessment and management related to the planning and conduct of the research itself, applicants should also consider provisions in their leadership and staffing plan to assure study continuity in the event of personnel absences due to quarantine, illness, or the provision of clinical care.
### Key Dates

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<thead>
<tr>
<th><strong>Online System Opens:</strong></th>
<th>September 7, 2021</th>
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<tbody>
<tr>
<td><strong>Town Hall:</strong></td>
<td>September 15, 2021; 1:30 pm (ET)</td>
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<tr>
<td><strong>Letter of Intent (LOI) Deadline:</strong></td>
<td>October 5, 2021, by 5 pm (ET)</td>
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<td><strong>LOI Status Notification:</strong></td>
<td>November 2, 2021</td>
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<td><strong>Application Deadline:</strong></td>
<td>January 11, 2022, by 5 pm (ET)</td>
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<tr>
<td><strong>Merit Review:</strong></td>
<td>April 2022</td>
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<tr>
<td><strong>Awards Announced:</strong></td>
<td>July 2022</td>
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<tr>
<td><strong>Earliest Project Start Date:</strong></td>
<td>November 2022</td>
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### Maximum Project Budget (Direct Costs)

- $10 million

### Maximum Research Project Period

- 5 years

### Funds Available Up To

- $40 million

### 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:** sciencequestions@pcori.org, phone (202-627-1884), or online (http://www.pcori.org/PFA/inquiry).

**Administrative, Financial, or Technical Inquiries:** pfa@pcori.org or phone (202-627-1885).

PCORI will respond within two business days. However, we cannot guarantee that all questions will be addressed two business days prior to a LOI or application deadline. Applicants must plan accordingly; it is the applicant’s responsibility to submit on time.
# Table of Contents

Table of Contents ........................................................................................................................................ 5

## I. Introduction ........................................................................................................................................ 1

Summary of Program ................................................................................................................................ 1
Topic Background ......................................................................................................................................... 1
Evidence Gaps .............................................................................................................................................. 3
Specific Requirements for This Funding Announcement .............................................................................. 4
Funds Available and Duration of Studies ..................................................................................................... 5

## II. General Requirements for PCORI Research ..................................................................................... 5

Research Priorities ....................................................................................................................................... 6
Categories of Non-responsiveness ................................................................................................................ 6
Principles for Consideration of Full Range of Outcomes Data in PCORI Funded Research ......................... 7
Coverage of Intervention Costs .................................................................................................................... 8
Avoiding Redundancy .................................................................................................................................. 8
Methodological Considerations .................................................................................................................... 8
Patient-Centered Outcome Measures .......................................................................................................... 8
Leveraging Existing Resources, Including PCORnet ..................................................................................... 9
Patient and Stakeholder Engagement .......................................................................................................... 10
Populations Studied and Recruited ............................................................................................................ 10
Protection of Human Subjects ..................................................................................................................... 11
Required Education of Key Personnel on the Protection of Human Subject Participants ......................... 12

## III. LOI Review ......................................................................................................................................... 12

## IV. Merit Review ...................................................................................................................................... 13

Preliminary Review ..................................................................................................................................... 13
In-Person Review ....................................................................................................................................... 16
Post-Panel Review ...................................................................................................................................... 17
Summary Statements and Funding Recommendations .................................................................................. 17

## V. PCORI Policies that Govern Awardees Related to Data Access, Privacy, and Public Reporting ................................................................................................................................. 18

Registering Research Projects .................................................................................................................... 18
PCORI Public Access Policy .......................................................................................................................... 18
Standards for Privacy of Individually Identifiable Health Information .......................................................... 18
Data Management and Data-Sharing Plan ................................................................. 18
Peer Review and Release of Research Findings......................................................... 19
I. Introduction

The Patient-Centered Outcomes Research Institute (PCORI) funds patient-centered outcomes research (PCOR), a type of comparative clinical effectiveness research that focuses on outcomes that matter to patients, their caregivers, and their families. PCORI-funded studies must include the perspectives of patients and other healthcare stakeholders.

The public entrusts PCORI to fund research that matters to patients, their caregivers, and other stakeholders (defined as clinicians and clinician societies, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, policy makers, and training institutions). By emphasizing the role of diverse research teams that include varying perspectives, PCORI seeks to change how research is conducted. PCORI distinguishes itself by supporting studies in which patients, caregivers, practicing clinicians, and the broader stakeholder community are actively engaged in generating research questions, reviewing research applications, conducting research, disseminating research findings, promoting the implementation of those findings, and using the results to understand and address patient and other stakeholder needs.

Summary of Program

Through this PFA PCORI seeks to fund rigorous large-scale pragmatic trials that compare newly available pharmacologic and/or evidence-based nonpharmacologic treatments for the prevention of migraine.

PCORI is particularly interested in studies that compare emerging pharmacologic options with standard prophylactic therapy or with each other. PCORI is also interested in studies that examine the comparative effectiveness of evidence-based nonpharmacologic options for migraine prevention as stand-alone therapy or as an adjunct to pharmacologic options. Studies should be large enough to enable precise estimates of effect sizes and to support evaluation of potential differences in treatment effectiveness in patient subgroups.

Applicants may request up to $10 million in direct costs for each project and a maximum study duration of five years. PCORI encourages study proposals with well-justified design and analysis plans that could be completed in a shorter timeframe.

Topic Background

Migraine is a highly prevalent chronic neurological disorder characterized by recurrent attacks; it is associated with symptoms that include nausea, pain, vomiting, and sensitivity to light and sound.\(^1\) Approximately 40 million Americans experience migraines, and in 2016 the Global Burden of Disease ranked migraine as the second leading cause of disability worldwide.\(^2\) The one-year prevalence of migraine is 18 percent in women and 6 percent in men, with the peak prevalence of attacks occurring

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PCORI Cycle 3 2021 Migraine Prevention Funding Announcement
between the ages of 25 and 55. The financial burden associated with migraine headaches is staggering, with the estimated adjusted incremental total direct healthcare expenditures for individuals with migraine at approximately $9 billion to $11 billion per year in the United States.

Migraines can be classified as episodic or chronic, depending on the frequency of symptoms. Episodic migraine is defined as fewer than 15 headache days per month. According to the International classification of Headache Disorders, chronic migraine is reserved for patients with a least 15 headache days per month for more than three months, including at least eight days per month that involve other common migraine symptoms. Chronic migraine affects about 8 percent of patients with headaches and usually develops from episodic migraine at a conversion rate of about 3 percent. Although chronic migraine is less common, it remains underdiagnosed and undertreated. It is associated with greater headache-related disability, worse health-related quality of life, and higher impact on physical and work-related functioning.

Clinical options for migraine include preventive and acute treatments. Acute treatments are used to resolve pain and symptoms once an attack occurs. Preventive treatments include both pharmacologic and nonpharmacologic options that seek to reduce the frequency, severity, and duration of attacks. The American Headache Society recommends that patients be considered for preventive treatment in cases where patients experience: four or more headache days per month, medication-overuse headaches, and attacks that significantly interfere with a patient’s daily routine despite acute treatment. When contemplating preventive therapy, physicians should also consider patient preference. Although many pharmacologic options are used for migraine prevention, most were originally developed to treat other conditions. Patients on preventive therapies frequently discontinue or switch treatments due to efficacy or tolerability concerns. Newly approved treatments such as calcitonin gene-related peptide (CGRP) antagonists have been developed specifically for migraine prevention and have been shown to be efficacious and well tolerated. However, uncertainties remain

regarding the long-term comparative effectiveness of CGRPs—compared with commonly prescribed preventives and with each other.\textsuperscript{14,15} Furthermore, there is growing interest among patients and other stakeholders in the use of nonpharmacologic therapies, and additional research is needed to understand the role of such options in the prevention of migraine.

Given the paucity of evidence on the effectiveness of novel pharmacologic and evidence-based nonpharmacologic treatments—and the high level of interest from the patient/stakeholder community—PCORI has identified migraine prevention as a priority clinical area. In 2021, PCORI published an evidence map assessing the evidence-base of pharmacologic therapies and devices for migraine prevention. Most recently, PCORI commissioned an extension of this report to include nonpharmacologic options for migraine prevention.

**Evidence Gaps**

The development of migraine-specific treatments has generated great interest from clinicians, patients, and their families; however, there is a lack of evidence to guide clinical decision making on the use of newer pharmacologic agents within the broader context of migraine treatment. An Institute for Clinical and Economic Review evidence report on emerging migraine preventive therapy highlighted the lack of head-to-head trials comparing newly available CGRPs with standard prophylactic therapy and with each other.\textsuperscript{14} The review indicated that the evidence for CGRPs is limited to placebo-controlled studies, many of shorter duration, with highly specified inclusion/exclusion criteria—often limiting the patient population to those who have experienced no more than two or three preventive therapy failures. Patients with comorbidities, particularly those with cardiovascular diseases, are often excluded from study participation. Limitations in prior designs also raise important concerns about the generalizability of findings. Additionally, the report notes important evidence gaps regarding the durability of effects and the limited data on long-term adverse events (≥ 12 weeks). The PCORI-commissioned evidence map reiterated the call for longer-term comparative effectiveness trials of CGRPs to support decision making for migraine management.\textsuperscript{15}

Significant evidence gaps about the use of nonpharmacologic treatment for migraine prevention also exist. Nonpharmacologic options may be effective for those patients for whom pharmacologic treatment is contraindicated, ineffective, poorly tolerated, or not preferred.\textsuperscript{10} These therapies may be used as stand-alone therapy or as an adjunct to pharmacologic treatment. Efficacious nonpharmacologic options include neuromodulation and biobehavioral therapies including cognitive behavioral therapy,
biofeedback, and relaxation training. Other options with less evidence include physical therapy, sleep management, acupuncture, and dietary modifications. Given that there are few rigorous head-to-head trials including nonpharmacologic interventions, there is a need for more high-quality studies that address this evidence gap.

The summary report for the PCORI-commissioned evidence map highlights patient preference and interest in nonpharmacologic options and the need for future studies to compare the effectiveness of nonpharmacologic interventions with that of traditional pharmacologic therapies. Evidence reviews of migraine preventive treatments have called for future studies to include longer follow-up periods and to report both the monthly reduction in migraine headaches and a list of patient-reported outcomes.

**Specific Requirements for This Funding Announcement**

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

**What is the comparative effectiveness of novel pharmacologic and/or evidence-based nonpharmacologic treatments for the prevention of migraine?**

PCORI is particularly interested in studies that compare emerging pharmacologic options such as CGRP antagonists with standard prophylactic therapy or with each other. PCORI is also interested in studies that examine the comparative effectiveness of evidence-based nonpharmacologic options for migraine prevention. As appropriate, studies may include nonpharmacologic interventions as stand-alone therapy or as an adjunct to pharmacologic options. Applicants should include clear evidence of efficacy that the proposed options can reduce the frequency/number of migraine days and/or improve important migraine-related patient-reported outcomes. Applicants should provide an evidence-based argument for the relevance of the treatment options being compared, citing evidence gaps to be addressed that are supported by systematic reviews.

Applicants should consider the following parameters when responding to this funding announcement:

- **Population:** The target population is patients with episodic and/or chronic migraine who are eligible for migraine preventive therapy. Pharmacologic studies should be adequately powered

to assess changes in the frequency of headache or migraine days; such power should be consistent with and/or exceeding that of prior efficacy trials. Pharmacologic studies must consider evidence gaps regarding long-term effectiveness. Given that migraine is a heterogenous disorder, studies should be large enough to enable precise estimates of effect sizes and to support evaluation of potential differences in treatment effectiveness in patient subgroups. Subgroups of specific interest include patients for whom prior preventive treatments have failed; patients with comorbidities including cardiovascular disease; migraine type (medication overuse, episodic/chronic migraine, migraine with aura); and menstrual-associated migraine.

- **Interventions:** Novel pharmacologic options (e.g., CGRP antagonists) and/or evidence-based nonpharmacologic interventions are eligible. Interventions must have established efficacy or be commonly used for migraine prevention. Novel pharmacologic options may be compared with standard prophylactic therapy or with each other. As appropriate, nonpharmacologic options may be compared alone or in combination with commonly prescribed prophylactic treatment(s).

- **Outcomes:** Applicants should propose well-supported patient-centered outcomes—for example, a 50 percent reduction in frequency of headache/migraine days and/or other clinically justified outcomes that may include quality of life, headache-related disability, functional impact, tolerability, adverse events, and use of abortive treatment.

- **Timing:** Follow-up data collection should continue for at least 24 weeks post-treatment to adequately measure the durability of treatment effects or other clinically significant time-points.

- **Setting:** Proposed healthcare settings should be representative of sites where the target population of study typically receives care (e.g., primary and/or specialty care clinics).

**Funds Available and Duration of Studies**

PCORI has allotted up to $40 million under this PFA to fund high-quality comparative effectiveness studies that respond to the research question of interest. The proposed budget for studies under this initiative may be up to $10 million in direct costs, as appropriate.

The maximum allowable project period is five years (60 months). PCORI encourages studies with rigorous, well-justified design and analysis plans that can be completed in a compact timeframe. An appropriate timeframe for the research question and study design should be chosen in consultation with stakeholders.

**II. General Requirements for PCORI Research**

This section includes language that is specific to PCORI’s requirements for programmatic responsiveness under this funding announcement. Applicants should use this section as guidance when preparing their applications. For information related to administrative and technical requirements for LOI and application submission, please consult the PCORI Submission Instructions.
Research Priorities

To be considered responsive, applications must:

- *Describe comparators.* Regardless of the approach being studied, all proposed research projects must compare at least two alternatives. If the 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 properly justified 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, and how appropriate inferences will be drawn from its inclusion. “Usual care” must be described as mentioned above to ensure that it accounts for geographic and temporal variations, and it has wide interpretability, applicability, and reproducibility.

- *Describe research that compares two or more alternatives, each of which has established efficacy.* PCORI expects the efficacy or effectiveness of each intervention to be known. If the efficacy or evidence base is insufficient, then data need to be provided to document that the intervention is used widely. The application must provide information about the efficacy of the interventions that will be compared; pilot data might be appropriate. Projects aiming to develop new interventions that lack evidence of efficacy or effectiveness will be considered out of scope.

- *Describe research that studies the benefits and harms of interventions and strategies delivered in real-world settings.* PCORI is interested in studies that provide practical information that can help patients and other stakeholders make informed decisions about their health care and health outcomes.

- *Describe consultation with patients and other stakeholders about how the study is answering a critical question.* Explain the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Describe why project outcomes are especially relevant and meaningful endpoints to patients and other stakeholders.

Categories of Non-responsiveness

PCORI discourages proposals in the following categories, and will deem them nonresponsive:

- Instrument development, such as new surveys, scales, etc.
- Developing, testing, and validating new decision aids and tools, or clinical prognostication tools
- Pilot studies intended to inform larger efforts
- Comparing patient characteristics rather than clinical strategy options
- For Assessment of Prevention, Diagnosis, and Treatment Options, Improving Healthcare Systems, and Communication and Dissemination Research applicants ONLY: Comparing interventions for which the primary focus is the role of community health workers or patient navigators
Consistent with PCORI’s authorizing law,\textsuperscript{24} PCORI does not fund research whose findings will include:

- Coverage recommendations
- Payment or policy recommendations
- Creation of clinical practice guidelines or clinical pathways
- Establishment of efficacy for a new clinical strategy
- Pharmacodynamics
- Study of the natural history of disease
- Basic science or the study of biological mechanisms

Further, consistent with past funding announcements, PCORI will consider an application nonresponsive if the proposed research does the following:

- Conducts a formal cost-effectiveness analysis of alternative approaches to providing care
- Directly compares the costs of care between two or more alternative approaches to providing care, or relies on modeling to develop estimates of “total costs of care” designed to enable such comparisons

Principles for Consideration of Full Range of Outcomes Data in PCORI Funded Research

PCORI’s authorizing law was amended by reauthorization legislation in 2019 to include a new mandate to consider, as appropriate, the full range of clinical and patient-centered outcomes data relevant to patients and stakeholders. The reauthorizing language clarifies that, in addition to the relevant health outcomes and clinical effectiveness, relevant outcomes included within PCORI-funded projects may include the potential cost burdens and economic impacts of the utilization of medical treatments, items, and services when relevant to patients and caregivers or to other stakeholders. The parameters for appropriately including such outcomes are further described below and in the accompanying FAQs. PCORI’s intention is that PCORI-funded research will, when germane, capture such cost burdens and economic impacts to provide the full range of outcomes data relevant to decision makers.

Specifically, applications responding to this PFA may include the following:

- Data collection on cost burdens or economic impacts associated with interventions that are relevant to patients and caregivers. Examples of elements of cost burden and economic impacts important to patients and caregivers include patient time in hospital, caregiver time away from work, cost and time for transport, childcare and eldercare costs, and medical out-of-pocket costs.
- Data collection on cost burdens and economic impacts relevant to other stakeholders, when these outcomes have a near-term or longer-term impact on patients, such as cost of treatment/intervention, costs associated with impacts of treatment on healthcare utilization, costs of a new intervention (program costs), and employer burden.
PCORI-funded studies have often included impacts of healthcare utilization, and data that capture the costs of these impacts will now be considered responsive. However, proposed research may not measure economic impacts as the primary outcome of a proposed study. Proposals that have economic measures as the primary outcome will be considered nonresponsive.

For further information, please reference our cost-effectiveness analysis FAQs.

PCORI has a continued interest in studies addressing questions about conditions that lead to high costs to individuals or society. This interest is reflected in our review criterion on the condition’s impact on the health of individuals and populations. Thus, as addressed in the cost-effectiveness analysis FAQs, PCORI is interested in studies that do the following:

- 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.

In March 2021, PCORI’s Board of Governors approved Principles for the Consideration of the Full Range of Outcomes. These Principles will inform both PCORI’s expectations for applicants and the corresponding review evaluation of applications submitted in response to this PFA.

**Coverage of Intervention Costs**

In general, PCORI will not cover costs for study interventions that constitute the procedures, treatments, interventions, or other standard clinical care (“patient care”) that are being proposed for comparison in the research project (“patient care costs”).

**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**

The PCORI Methodology Standards represent minimal requirements for the design, conduct, analysis, and reporting of scientifically valid, patient-centered outcomes research. Regardless of study design, applications must adhere to all relevant PCORI Methodology Standards, and all deviations need to be justified. Applicants should address additional best practices—including relevant guidelines for conducting clinical trials developed by other organizations—in the application for PCORI funding.

**Patient-Centered Outcome Measures**

PCORI encourages investigators to design their research using validated outcome measures. Include preliminary data that support using the proposed measures in the study population. We encourage investigators to consider those measures described in the Patient-Reported Outcomes Measurement
Information System\textsuperscript{25} (PROMIS). Likewise, PCORI encourages the use of core outcome sets, such as those developed by the Core Outcomes Measures in Effectiveness Trials Initiative to facilitate cross-study analysis. See http://www.comet-initiative.org/.

Leveraging Existing Resources, Including PCORnet

PCORI encourages applicants to consider the potential merits of using the clinical research infrastructure and data resources of PCORnet®, the National Patient-Centered Clinical Research Network. PCORnet is designed to improve the nation’s capacity to conduct efficient large-scale clinical research, by drawing upon a network of clinical research networks that capture the healthcare experiences of millions of Americans. PCORnet enables connections to patients, clinicians, researchers, and health systems across the country interested in supporting research to improve health care and health outcomes.

The network currently includes clinical research networks and a coordinating center. PCORnet infrastructure resources include access to electronic health record data from over 60 million patients across the United States, encompassing a diverse range of care settings including hospitals, primary care practices, outpatient specialty care practices, emergency and urgent care centers, federally qualified health centers, and community clinics. PCORnet can be a source of research-ready clinical sites to enroll participants for feasibility testing of recruitment or for participation in a full-scale trial. It can also be used to provide preparatory data in support of clinical trial design through its large longitudinal data sets that capture clinical outcomes and details of specific procedures, treatments, disease severity, and comorbid illnesses.

PCORnet offers:

- Clinical research networks that are able to participate as clinical sites in randomized research trials
- Actively engaged patients, clinicians, and health systems
- Preexisting, standardized, curated, and research-ready clinical data to inform clinical trial design, conduct, and operations
- A readiness among network members to collaborate and a willingness to share data in pursuit of patient-centered research aims

Outside of participation as clinical sites, PCORnet data resources may inform aspects of clinical trial design, feasibility assessment, effect sizes, and potential study power. Examples include, but are not limited to, the following:

- Providing background to the research question or feasibility of study
- Documenting the importance of the research question
- Estimating the size of the potentially eligible population

\textsuperscript{36}–345 (2018). https://doi.org/10.1007/s
• Determining the range of current treatment practices and sequencing
• Assessing the duration of continuous treatment, care, and follow-up

Applicants interested in using PCORnet resources are encouraged to contact the PCORnet Front Door to explore opportunities for collaboration.

Patient and Stakeholder Engagement

In PCORI-funded research, patients and other healthcare stakeholders are viewed as partners who leverage their lived experience and/or professional expertise to influence research to be more patient centered, relevant, and useful. When developing an engagement strategy, PCORI encourages applicants to consider the time and resources needed to identify, confirm, and prepare stakeholders for collaborating; the infrastructure needed to manage stakeholder engagement activities; and the specific decision points that will draw on the expertise of stakeholder partners. Research partners must include representatives of the populations most impacted by the condition or issue addressed by the study. Applicants’ use of multiple approaches that are along a continuum of engagement from input to shared leadership are allowable and encouraged.26 For example, study teams may find it useful to solicit input from a large group of stakeholders using quick-turnaround methods (e.g., focus groups, surveys, crowdsourcing, virtual or in-person roundtables and community forums) in addition to engaging stakeholders via ongoing consultative groups (e.g., advisory committees, working groups), collaborative arrangements, and leadership positions (e.g., co-investigators, multidisciplinary steering committees) that are sustained over the course of the study.

Applicants should provide an overview of their engagement approach that should include (1) a proposed list of patient and other healthcare research partners (include names and affiliations, if available), the perspectives they will represent, and justification for their inclusion; (2) the goals for working with stakeholders, which may include affecting the acceptability, feasibility, rigor, and/or relevance of the study; and (3) a description of how the team will collaborate with and/or gather input from stakeholders at key decision points throughout the study. Funded awardees are required to submit a more detailed engagement plan six months after contract execution.

Populations Studied and Recruited

PCORI seeks to fund research that includes diverse populations with respect to age, gender, race, ethnicity, geography, or clinical status, so that possible differences in outcomes may be examined in defined subpopulations. PCORI recognizes that some proposed studies might represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant to justify the study’s importance in the absence of diversity; to discuss which subgroups are most important; and to discuss how the subgroups will be analyzed, including whether or not the study will be powered to examine the question of effectiveness in subgroups.

PCORI is particularly interested in including previously understudied populations for whom effectiveness information is especially needed, such as hard-to-reach populations or patients with multiple conditions.

13311-018-0623-6.
Thus, comparisons should examine the impact of the strategies in various subpopulations, with attention to the possibility that the strategy’s effects might differ across subpopulations. PCORI has developed the following list of populations of interest to guide our efforts in research and engagement. (Note that the Addressing Disparities Priority Area requires that proposed research focus on at least one of the groups indicated by an asterisk below.)

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

Regardless of the population studied, investigators are expected to provide evidence-based estimates regarding the representativeness of the potential pool of participants from which recruitment will occur; the target sample size; and recruitment and retention rates, reflecting the study’s inclusion and exclusion criteria as well as factors that may impact the final sample size (e.g., loss to follow-up).

Protection of Human Subjects

PCORI follows the Federal Regulation for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, please see Section 5, titled “Human Subjects Research Policy,” in the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports, which is issued by the U.S. Department of Health and Human Services (HHS). In referencing the HHS Supplemental Grant Application Instructions, note that PCORI does not require that applicants comply with sections of that policy that refer to requirements for federal-wide assurance and the inclusion of women, minorities, and children in the proposed studies. Instead, PCORI expects applicants to address diversity in study participants in the research plan, through a focus on subpopulations, as described in the above section on Populations Studied and Recruited. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to

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27 See http://grants.nih.gov/sites/default/files/supplementalinstructions.docx
the use of human subjects in research.

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

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

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

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

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

### III. LOI Review

Applying for funding for this PFA is a two-stage process. An LOI must be submitted, and an applicant must be invited to submit an application.

LOIs are evaluated based on the following:

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

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. A minimum of two PCORI staff members review the LOIs, which are not scored during review.

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The LOI Template provides guidance on responding to each item. Please refer to the Submission Instructions for information on how to submit an LOI via PCORI Online.

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 the review panel’s preliminary review of full applications and an in-person panel discussion of a subset of applications (identified by PCORI’s Program staff and based on the preliminary review and program priorities). After merit review, key steps include: post-panel review of application by PCORI staff; 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 Submission Instructions, in the PCORI templates, and in PCORI Online. An application may be scientifically withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes a cost-effectiveness analysis, or otherwise does not meet PCORI programmatic requirements.

PCORI Merit Review Officers (MROs) recruit each review panel based on the number of invited LOIs and topic areas represented by the invited LOIs. MROs recruit the panel chair, scientist reviewers who are subject matter experts, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that they understand the programmatic and organizational goals of review.

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-reviewed journals and at national conferences?

Criterion 3. Scientific merit (research design, analysis, and outcomes)
The application should show sufficient technical merit in the research design to ensure that the study goals will be met. The application should also address the following questions:

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

**Criterion 4. Investigator(s) and environment**

The application should demonstrate 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. Assessment of this criterion should not focus on the institution’s reputation, but rather on the breadth and depth of its available personnel and resources. The application should also address the following questions:

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

**Criterion 5. Patient-centeredness**

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

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

**Criterion 6. Patient and stakeholder engagement**

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

The application should also address the following questions:

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

**In-Person Review**

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

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

Post-Panel Review

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

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

Summary Statements and Funding Recommendations

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

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

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

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to the Board for approval. Applicants to this current cycle’s PFA will receive summary statements and notification of the funding status of their application no later
than July 2022.

V. **PCORI Policies that Govern Awardees Related to Data Access, Privacy, and Public Reporting**

Applicants should be aware that all PCORI awardees are required to comply with the following requirements:

**Registering Research Projects**

PIs are required to use the naming convention “PCORI-PCORI application number” (i.e., PCORI-XXXX-XXXX). Clinical trials must be registered before enrollment of the first patient. All trials that meet the definition on the [NIH database](https://prsinfo.clinicaltrials.gov/) (see Data Element Definitions) are required to register, if funded.

Funded clinical trials or observational outcomes studies must be registered at [ClinicalTrials.gov](https://clinicaltrials.gov).

Funded evidence-synthesis studies must be registered at [PROSPERO](http://www.crd.york.ac.uk/prospero). Funded patient registries must be registered at [https://patientregistry.ahrq.gov/](https://patientregistry.ahrq.gov/).

**PCORI Public Access Policy**

PCORI requires all awardees to adhere strictly to PCORI’s publication policies, which will be shared with awardees within the research contract.

**Standards for Privacy of Individually Identifiable Health Information**

On August 14, 2002, the Department of Health and Human Services issued a final modification to the Standards for Privacy of Individually Identifiable Health Information, the “Privacy Rule.” The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information and is administered and enforced by the Department of HHS Office for Civil Rights.

Decisions about the applicability and implementation of the Privacy Rule reside with the researcher and his or her institution. The [Office for Civil Rights](http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools related to “Am I a covered entity?” Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding and progress monitoring of grants, cooperative agreements, and research contracts is available from [NIH](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html).

**Data Management and Data-Sharing Plan**

PCORI is committed to publishing and disseminating all information and materials developed using PCORI funding, in accordance with its authorizing legislation. All recipients of PCORI contracts must agree to these principles and take steps to facilitate data availability.

PCORI encourages openness in research and making research data available for purposes of replication and reproducibility. As such, if an award is made, the awardee will be expected to adhere to PCORI’s

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31 Available at [https://prsinfo.clinicaltrials.gov/](https://prsinfo.clinicaltrials.gov/).
32 Available at [http://www.crd.york.ac.uk/prospero/](http://www.crd.york.ac.uk/prospero/).
33 Available at [http://www.hhs.gov/ocr/](http://www.hhs.gov/ocr/).
Policy for Data Management and Data Sharing. The Policy articulates PCORI’s requirement that certain awardees make the underlying data and data documentation (e.g., study protocol, metadata, and analytic code) from their PCORI-funded research projects available to third-party requestors.

A full data management and data sharing plan is not required at the time of application. If an award is made -- specifically for the Pragmatic Clinical Studies (PCS) and the targeted PFA studies -- the awardee is required to develop and maintain such a plan, which is described in detail in the PCORI Methodology Standards for Data Integrity and Rigorous Analyses, specifically Standard IR-7. This plan must be appropriate for the nature of the research project and the types of research project data, and consistent with applicable privacy, confidentiality, and other legal requirements. The Policy includes details about what data certain awardees will be expected to deposit into a PCORI-designated data repository and when that data would be available for third-party requests.

For research awards funded under Broad funding announcement (Assessment of Options, Improving Healthcare Systems, Addressing Disparities, Communication and Dissemination Research, Improving Methods), the Policy calls for awardees to maintain the Full Data Package for seven (7) years. PCORI may, in selective cases, notify the researcher of its intent to provide funds for the deposition of the Full Data Package in a PCORI-designated repository in circumstances where PCORI requests such deposition.

The information here is meant for informational purposes only and does not attempt to be an exhaustive representation of the Policy for Data Management and Data Sharing. Please refer to the Policy in its entirety for additional information.

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.

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. After awardee institutions have responded to reviewers’ comments to PCORI’s satisfaction, the report will be accepted and considered final. PCORI will then prepare two 500-word standardized abstracts summarizing the study results (as detailed below), which the awardee institution will review and approve.

No later than 90 days after the draft final research report is accepted, PCORI will post the following materials on its website: (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.