Cycle 2 2021 Funding Cycle

PCORI Funding Announcement: Nonsurgical Options for Women with Urinary Incontinence

Published May 4, 2021

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes August 31, 2021, at 5 pm ET. Submission Instructions, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/nonsurgical-options-women-urinary-incontinence-cycle-2-2021.
About PCORI

PCORI was authorized by federal law in 2010 and reauthorized for an additional ten 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.

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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**

<table>
<thead>
<tr>
<th>Event</th>
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<tr>
<td>Online System Opens:</td>
<td>May 4, 2021</td>
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<tr>
<td>Town Hall:</td>
<td>May 10, 2021, 12 pm ET</td>
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<tr>
<td>Letter of Intent (LOI) Deadline:</td>
<td>June 1, 2021, by 5 pm (ET)</td>
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<td>LOI Status Notification:</td>
<td>June 29, 2021</td>
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<td>Application Deadline:</td>
<td>August 31, 2021, by 5 pm (ET)</td>
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<td>Merit Review:</td>
<td>December 2021</td>
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<tr>
<td>Awards Announced:</td>
<td>March 2022</td>
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<td>Earliest Project Start Date:</td>
<td>August 2022</td>
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**Maximum Project Budget (Direct Costs)**

- $5 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 Inquires:** 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
II. General Requirements for PCORI Research ................................................................. 6
    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 ............................................................................. 9
    Leveraging Existing Resources, Including PCORnet .......................................................... 9
    Patient and Stakeholder Engagement ............................................................................. 10
    Populations Studied and Recruited .................................................................................. 11
    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 ............................................................................................................. 17
    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 ...................................................................... 19
    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 (CER) 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 high-quality, comparative effectiveness research projects that focus on efficacious interventions for nonpregnant women with stress, urge, or mixed urinary incontinence (UI), addressing high-priority patient- and stakeholder-guided research questions.

Although the efficacy of many nonsurgical interventions for UI are soundly substantiated, evidence gaps remain, particularly related to direct comparisons of the options. The full range of women affected by UI should be considered, although each application does not need to include all affected populations. If proposed studies include participants with more than one type of UI (stress, urge, or mixed), such studies should be adequately powered to detect differences by type. Study populations should include appropriate racial and ethnic diversity as well as those individuals for whom access to care is a challenge.

PCORI will accept applications that propose rigorous randomized controlled trials or observational, prospective cohort studies. Applicants can propose to compare two or more of the nonsurgical treatment options for UI, including pharmacological, behavioral, lifestyle, and other nonpharmacological options. Alternative models of care delivery and coordination approaches that address some of the barriers and dissatisfaction around the various options previously described are also welcomed. Submitted proposals should evaluate both patient-centered functional and adverse outcomes and may take place in various care settings where women receive treatment for UI.

Applicants may request up to $5 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**

A common problem among women, urinary incontinence (UI), or loss of bladder control, has a
significant impact on women’s lives beyond just the symptoms themselves. In addition to basic interference in daily activities, strong associations have been found between UI and decreased quality of life (QOL), social isolation, depression, falls/fractures, and nursing home admission. Prevalence estimates for UI vary widely: conservative estimates claim that 17 percent of US women have UI, but many other estimates indicate that number is much higher. For instance, the National Health and Nutrition Examination Survey results indicate that more than half of US women have some type of UI. It is well accepted that the prevalence is higher—at least 30 percent—in women age 60 and older.

The main types of UI are stress UI, urge UI, and mixed UI (i.e., symptoms of both urge and stress UI). Stress UI is most common in women of reproductive age, while the incidence of urge UI increases with age and mixed UI is prevalent among older women.

Extensive stakeholder interest and perceived evidence gaps in the UI field led PCORI to conceptualize and fund an update to the Agency for Healthcare Research and Quality’s (AHRQ’s) 2012 systematic review on nonsurgical treatments for UI in women. In 2016, PCORI hosted a multi-stakeholder workshop for discussion to inform the update, and the proceedings were published with support by PCORI through a research partnership with AHRQ in 2018. To make the findings more accessible to clinicians and women with UI, PCORI created for each of these audiences Evidence Updates, which distill evidence from the updated report in concise and comprehensible formats. PCORI then worked with stakeholder organizations and coalitions, including the American Urological Association, National...
Association for Continence, and Bladder Health Alliance to disseminate these findings to their audiences. A PCORI-funded evidence map also grew out of the systematic review update effort.

In 2019, PCORI proposed to AHRQ further work to disseminate and promote the uptake of findings on effective strategies from the systematic review update. PCORI and AHRQ jointly convened another group of stakeholders to gather input on strategies to improve care for women with UI. This effort culminated in two complementary funding announcements focusing on implementation of effective UI treatment approaches: (1) AHRQ’s recent issue of a Dissemination and Implementation Funding Announcement on this topic, and (2) PCORI’s addition of this topic, beginning Cycle 2 2021, to its ongoing open competition Implementation of Findings from Major Research Investments Funding Announcement.

Evidence Gaps

The updated systematic review concluded that behavioral (e.g., pelvic floor muscle training) and lifestyle interventions (such as weight loss for women with obesity) have been shown to be effective for many women with UI. For example, one study showed that more than 70 percent of women with urge UI who used behavioral therapy achieved at least 75 percent reduction in frequency of incontinence episodes. However, stakeholders have emphasized the challenges associated with these interventions. Behavioral and lifestyle interventions can be too slow for some women’s preferences. They can be difficult to do correctly and to integrate into daily life. Also, some clinicians may not have the expertise and/or the time to describe these options adequately to patients. Further, these interventions may not allow patients to achieve adequate treatment success.

Though surgery is an option for some women with stress UI, women with all types of UI often turn to nonsurgical options. Commonly used FDA-approved pharmaceutical options for urge UI include anticholinergics, Botox, and the beta-adrenergic agonist mirabegron. Alpha agonists can also be used for stress UI. Other nonsurgical options include neuromodulation (including device implantation), intravesical pressure release, and periurethral bulking. Last, the serotonin-norepinephrine reuptake inhibitor duloxetine is also prescribed off-label for stress UI.

Despite the compelling evidence for the efficacy of behavioral and lifestyle options, stakeholders have emphasized that there are frequently barriers and dissatisfaction with the various behavioral and lifestyle options compared with pharmacological interventions, indicating comparative analyses could further shed light on the tradeoffs among the many options. Furthermore, the updated systematic review showed that we currently lack head-to-head comparisons of almost all the nonsurgical options to inform patient and provider decision making, a key evidence gap. Last, a new treatment alternative has also emerged with the December 2020 FDA approval of another beta agonist, vibegron.

Recent discussions with stakeholders have emphasized that many of these UI treatment options,  

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17 U.S. Food and Drug Administration. (2021, Jan 19). Drug Approval Package: GEMTESA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213006Orig1s000TOC.cfm
especially the anticholinergics, have unpleasant side effects that lead many women to discontinue use within a few months. Other treatments such as mirabegron and Botox may have more favorable side-effect profiles but are expensive, and insurance often will not cover them until two other options have failed. Since the publication of the updated systematic review, evidence from prior studies suggesting a link between anticholinergics and dementia was strengthened by the publication of a large study in 2019 that found a strong association between anticholinergics commonly prescribed for UI and later dementia development.\textsuperscript{18} Such matters are also in need of PCOR.

**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 nonsurgical interventions for adult women with UI?

Proposed interventions should represent important, relevant choices currently encountered by the target patient population, caregivers, and healthcare providers. Applicants must provide a justification for the appropriateness of the interventions within the proposed population as well as a description of the decisional dilemma that justifies the proposed comparison of interventions. PCORI is interested in the comparison of interventions that have demonstrated evidence of efficacy for UI-related outcomes and/or that they are in common use. Applicants must provide evidence to substantiate the efficacy and common use of interventions. Evidence of efficacy may be documented by systematic reviews, prior empirical investigations, guideline development, or previous research prioritization.

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

- **Population:** The target population is adult, nonpregnant women with stress, urge, or mixed UI. A well-justified description of the proposed sample size and power should be provided to demonstrate adequacy for producing robust study results. Applicants should clearly articulate the hypothesized effect size and the relevant citations to support these assumptions. Further, reasonable estimates of participant attrition should be accounted for in the proposed sample size. If more than one type of UI is included, the proposed study should be adequately powered to detect differences by UI type (stress, urge, or mixed).

  The full range of women who experience UI should be considered for inclusion in proposed studies, although each application does not need to include all affected populations. Examples of populations of interest include healthy women in the community; older women with and without other chronic conditions; and women with mild cognitive impairment. Plans to ensure racial and ethnic diversity that reflect the population of women affected by UI are encouraged as well as inclusion of those patients for whom access to care is a challenge.

- **Interventions:** Proposed interventions may include pharmacological, behavioral, lifestyle, other nonpharmacological, or any of these interventions combined. In general, intervention types considered as “nonsurgical” in the updated systematic review can be included; if an intervention

is too new to have been included in the review, then it should be similarly noninvasive. Alternative models of care delivery and coordination approaches that address some of the barriers and dissatisfaction around the various options previously described are also welcomed. Surgical interventions are not included as an option for this announcement.

- **Outcomes:** Applicants should propose well-supported patient-centered outcomes. Study outcomes should include well-validated patient assessment measures, functional outcomes, safety, adverse events, and other key clinical outcomes, as appropriate. PCORI encourages applicants to consider the inclusion of outcomes in multiple domains that have been previously prioritized, including daily life function, mental health, social health, and physical health.\(^{19}\)

Once the awards for this PFA are announced, PCORI may deem it advantageous for awardees from this funding announcement to establish some consistent outcomes across studies. Applicants are expected to work with PCORI to adjust or add additional outcomes.

- **Timing:** Patient follow-up time should be determined based on appropriateness for the intervention/design. Long-term patient adherence to interventions should be a consideration in deciding on the appropriate length of follow-up time.

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

### Funds Available and Duration of Studies

PCORI has allotted up to $40 million under this PFA to fund high-quality CER studies that respond to the research question of interest. The proposed budget for studies under this initiative may be up to $5 million in direct costs, as appropriate.

Even though the maximum allowable project period is five years (60 months), most studies should not require five years to complete. 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.

PCORI seeks efficient studies, such as those that take advantage of large populations already under observation; registries; research cooperatives; and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of intervention-related costs.

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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,20 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

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.

20 Available at http://www.pcori.org/sites/default/files/PCORI_Authorizing_Legislation.pdf/.

PCORI Cycle 2 2021 Nonsurgical Options for Women with Urinary Incontinence Funding Announcement
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.

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

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\(^{21}\) (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/](http://www.comet-initiative.org/).

**Leveraging Existing Resources, Including PCORnet**

PCORI is interested in new research that derives data from a wide variety of sources and that uses study designs appropriate for the goals of the proposed project. PCORI encourages investigators to propose studies that leverage existing resources, such as adding Patient-Centered Outcomes Research (PCOR) to an existing large clinical trial or analyzing existing large databases that contain valuable, relevant information that may be used to answer important CER questions. Another possible resource is established patient outcomes registries, especially when such registries can be linked to electronic medical record (EMR) data from healthcare delivery systems or administrative claims data from public or commercial insurers. In circumstances where randomized control trials are not practical or ethically acceptable, studies leveraging established patient outcomes registries can have meaningful and complementary roles in evaluating patient outcomes. PCORI does not intend for this PFA to support the development of new data networks or patient registries, but rather to support the effective utilization of existing data resources for proposed new CER studies.

For some proposed projects, the data resources of PCORnet\(^{\text{®}}\), the National Patient-Centered Clinical Research Network, may be particularly appropriate. Over the last seven years, PCORI has made a major commitment to create the infrastructure of PCORnet, which was designed to improve the nation’s capacity to conduct efficient large-scale clinical research and to learn from the healthcare experiences of millions of Americans. This large clinical research network represents patients, clinicians, health systems, and health plans across the country and supports research that will improve health care and health outcomes. The network currently includes nine Clinical Research Networks (CRNs), representing more than 60 health systems, two Health Pan Research Networks (HPRNs) and a Coordinating Center. PCORnet Networks provide access to large longitudinal datasets that enhance the capture of relevant outcomes and provide more detail on specific procedures or treatments, disease severity, and the presence of comorbid illness.

The following elements are central features to PCORnet as a resource:

- Preexisting, standardized, curated, and research-ready clinical data on large numbers of persons with specific clinical conditions and illnesses;
- Actively engaged patients who join in governing the research uses of these data;

\(^{21}\) Available at [http://www.nihpromis.org/](http://www.nihpromis.org/).
• Distributed (rather than centralized) data platforms that maximize the security and local control of all data;
• A readiness among network members to collaborate and a willingness to share data in pursuit of worthy research aims; and
• The capacity to link data across data sources at the individual patient level.

Applicants are encouraged to consider whether using the PCORnet infrastructure might assist in one or more aspects of their proposed research study. Examples include, but are not limited to, the following:

• Background to the research question or feasibility of study
• Document the importance of the research question
• Estimating the size of the potentially eligible population
• Determining the range of current treatment practices and sequencing
• Assessing the duration of continuous treatment and care

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.22 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. 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 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

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• 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.

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?
  - (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 March 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-XXXXX). Clinical trials must be registered before enrollment of the first patient. All trials that meet the definition on the NIH database27 (see Data Element Definitions) are required to register, if funded.

Funded clinical trials or observational outcomes studies must be registered at ClinicalTrials.gov.

Funded evidence-synthesis studies must be registered at PROSPERO.28 Funded patient registries must be registered at 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 Rights29 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

27 Available at https://prsinfo.clinicaltrials.gov/.
28 Available at http://www.crd.york.ac.uk/prospero/.
29 Available at http://www.hhs.gov/ocr/.
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.30

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 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.31

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.