Cycle 2 2020 Funding Cycle

PCORI Funding Announcement:
Conducting Rare Disease Research Using PCORnet®
Published May 5, 2020

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes September 1, 2020, at 5 pm (ET). Submission Instructions, templates, and other resources are available at https://www.pcori.org/funding-opportunities/announcement/limited-competition-conducting-rare-disease-research-using-pcornet-cycle-2-2020.
About PCORI

The Patient-Centered Outcomes Research Institute (PCORI) was authorized by Congress in 2010 as a nonprofit, nongovernmental organization. PCORI’s purpose, as defined by our authorizing legislation, is to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders make better-informed health decisions by advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions 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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**Overview**

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<td>May 5, 2020</td>
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<td>Town Hall:</td>
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<td>June 2, 2020, by 5 pm (ET)</td>
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<td>June 2021</td>
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<tr>
<td><strong>Maximum Project Budget (Direct Costs)</strong></td>
<td>$3.5 million</td>
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<td>At the time of contract execution, PCORI sets aside all of the funds associated with an awarded project to be made available throughout the contract’s period of performance. The maximum budget includes all research- and peer review–related costs. This PFA does not consider exceptions to the budget. PCORI will not review submissions exceeding the stated maximum budget.</td>
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<td><strong>Maximum Research Project Period</strong></td>
<td>3 years</td>
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<td>This PFA does not consider exceptions to period-of-performance limits. PCORI will not review submissions exceeding the stated period of performance.</td>
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<td><strong>Funds Available Up To</strong></td>
<td>$25 million</td>
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<td><strong>Eligibility</strong></td>
<td>For this limited competition PFA, PCORI is soliciting applications from organizations that are currently funded to participate in PCORnet®, including Clinical Research Networks (CRNs)/ Health Plan Research Networks (HPRNs) or their partner organizations. More than one Letter of Intent (LOI) can be submitted by a PCORnet participating organization, as long as each application proposes different Principal Investigators.</td>
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| **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:** email (sciencequestions@pcori.org), phone (202-627-1884), or online (http://www.pcori.org/PFA/inquiry)  
**Administrative, Financial, or Technical Inquiries:** email (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 an LOI or application deadline. Applicants are asked to plan accordingly; it is the applicant’s responsibility to submit the application on or before the application deadline. |

PCORI Cycle 2 2020: Conducting Rare Disease Research Using PCORnet Funding Announcement
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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.

PCORI is seeking applications designed to provide information that can inform critical decisions facing patients and caregivers, clinicians, policy makers, and healthcare system leaders. These decisions must be consequential and occurring now, in the absence of sound evidence about the comparative effectiveness of alternative approaches. Substantial potential must exist for patients and caregivers to benefit from the new knowledge in ways that are important to them. The premise of the research should be that the new knowledge will inform critical choices of patients and stakeholders in health care. This knowledge should offer insight about the comparative benefits and harms of the options and should provide information on outcomes that are important to patients.

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 the way research is conducted. PCORI distinguishes itself by supporting research 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 research findings, and using the results to understand and address patient and other stakeholder needs.

**Summary of Program**

PCORnet®, the National Patient-Centered Clinical Research Network, is an initiative funded by PCORI to harness the power of rich clinical information contained in electronic health records (EHRs) and claims data, as well as other patient-generated data. This large, highly representative, national network offers a vehicle to learn from the healthcare experiences of millions of Americans by embedding research within the clinical care setting. PCORnet® currently includes nine Clinical Research Networks (CRNs), two Health Plan Research Networks (HPRNs), and a Coordinating Center. It is a network of networks that spans many partner healthcare organizations, including hospital systems; specialty clinics; primary care clinics, including federally qualified healthcare systems; and US health plans.

Signaling that PCORI is giving special attention to the conduct of rare disease research, PCORI’s authorizing legislation mandated the establishment of a Rare Disease Advisory Panel (RDAP). Yet, the number of rare disease comparative effectiveness studies funded by PCORI to date has been modest. The small numbers affected by any given rare disease is one factor that contributes to the difficulty of conducting robust rare disease research. PCORnet’s scale, with records for 66 million patients available for observational studies, and 30 million accessible for clinical trials, provides a potentially rich resource for the conduct of rare disease research. To this end, PCORI intends to pursue this limited competition opportunity to fund the use of PCORnet infrastructure to conduct observational research studies that
will answer important research questions about the treatment and management of rare diseases. Rare disease research will be strengthened by building strong partnerships between researchers and the rare disease community, rapid cohort identification, and standardized queries against analysis-ready standardized data, which PCORnet infrastructure was built to facilitate. Ultimately, the research funded through this solicitation, by building partnerships, tools, and data linkages, is intended to enhance the capabilities of future rare disease comparative effectiveness research.

Research Topic Selection
As defined by the Rare Disease Act of 2002, a rare disease affects fewer than 200,000 people in the United States. There are over 7,000 known rare diseases afflicting an estimated 25–30 million Americans. Treating rare diseases presents many challenges: diagnoses are difficult, standards for treatment are often lacking, and care is often poorly coordinated between the few specialists with a deep knowledge of the disease and other providers. Conducting research on rare diseases is also challenging. Basic information on which treatments are being used and how the disease naturally progresses is often lacking. Phenotypic diversity and subsets are often present within a specific disease, adding to complexity of research. The small numbers of patients affected, and their wide geographic dispersion, often lead to suboptimal recruitment into clinical trials and necessitate collaboration and data sharing among many institutions.

Given these challenges, PCORI’s RDAP has long had an interest in the potential that PCORnet offers for rare disease observational research. This solicitation is in direct response to the rare disease community as reflected through its representation on our advisory panel.

Funding Announcement Objectives
PCORI seeks to fund new research that meets the following two primary objectives:

- Answer one or more important questions about the care of patients with rare disease through observational cohort studies utilizing PCORnet resources. Work to achieve this objective is expected to entail the following:
  - Identifying and refining one or more compelling question(s) about the treatment or management of patients with rare disease and their associated outcomes in close collaboration with the rare disease community
  - Testing the feasibility of identifying the target rare disease cohort across multiple CRNs/HPRNs by developing and validating or using existing algorithms
  - Exploring the utility and feasibility of data linkages using PCORnet’s Common Linkage Method (if available) to enhance the power of the observational cohort to address the research question(s)

- Identifying and recruiting a rare disease cohort across multiple CRNs/HPRNs following the ethical guidelines of review boards involved
- Conducting the observational research in close collaboration with rare disease partners

Enhance the capabilities for the conduct of multisite rare disease research by creating or strengthening partnerships, methods, tools, and data linkages. This will include the following:

- Establishing a partnership between two or more CRNs/HPRNs and one or more rare disease organizations, with attention to representing the diversity of the population affected by the target disease(s)
- Sharing tools and resources that may inform or facilitate future engagement, research, or research collaboration in rare disease through appropriate common repositories (e.g., PCORnet Resources Repository, PCORI Engagement Tool and Resources Repository)
- To the extent that a computable phenotype is developed, depositing it in an appropriate common repository (e.g., PheKB)
- Making data elements and documentation available for external users for reanalysis and reuse following PCORI’s Policy for Data Management and Data Sharing
- Participating in PCORnet reporting, communication, and dissemination efforts to facilitate network learning and improvement
- Disseminating information about the availability of this resource to stakeholders and the research community.

Developing External Partnerships

For this PFA, PCORI requires applicants to partner with one or more rare disease organizations. Applicants are encouraged to consider the suitability of having a rare disease organization serve in the capacity as a co-Principal Investigator (co-PI). Membership for the partner rare disease organizations should be representative of the full range of patients who are affected by the disease or applicants must address how they will ensure representation that reflects the diversity of the population affected by the disease. PCORI also expects applicants to identify and partner with rare disease clinical experts who are affiliated with networks and organizations participating in PCORnet. Applicants may also consider partnerships with industry and academic organizations that are not participating in PCORnet that can bring a broader range of perspectives and expertise to the research.

Respondents to this PFA must demonstrate that patients, clinicians, and other relevant stakeholders were consulted to select the proposed research questions, and detail how the proposed research will meet their evidentiary and healthcare decision-making needs.

Characteristics and Objectives of Priority Research Questions

Target Population

Rare disease in the United States has been statutorily defined as any disease or condition that affects fewer than 200,000 persons in the United States (or fewer than 1/1,500 individuals). Inconsistencies across various rare disease compendia are not uncommon given differences in whether the designation

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is for the disease itself or for a syndrome, condition, or expression of disease. Applicants are encouraged to consult compendia maintained by NIH’s Office of Rare Disease Research,6 those listed in the European registry known as Orphanet,7 or ones that have been deemed as rare by the Food and Drug Administration,8 to further justify the selected disease as qualifying for this solicitation.

Research Questions

The proposed research questions can be CER or descriptive studies that can form the basis for a CER question (e.g., describing treatments or care management studies being used and outcomes). Examples of research topics of interest, independently developed and derived from recommendations made by members of the RDAP, are listed below. The RDAP expressed a particular interest in studies that examine common treatment or management concerns across groupings of rare diseases, such as treatments for shared symptoms (e.g., sleep disturbance, digestion and cognitive functioning) or cross-cutting strategies to improve management (e.g., transition from pediatric to adult care), rather than a focus on any one specific rare disease. In addition to the examples listed below, members of the RDAP expressed an interest in research on pediatric rare disease, which represents over half of all rare diseases.9 Research topics of interest include the following:

- Comparison of treatment modalities that have been used in practice or have demonstrated efficacy and serve as current treatment choices available for a specified rare disease, evaluating treatment benefits and harms as well as financial burden to patients; examples include the following:
  - Medications, including prescription of off-label drugs
  - Complementary treatments
  - Devices, including those with expedited approval
  - Medical procedures
  - Assistive technologies
  - Behavioral change interventions
- Comparison of treatments that address cross-cutting symptoms common among groups of rare diseases; examples include sleep disturbance, pruritis, and comorbid mental health diagnoses (e.g., anxiety and depression)
- Comparison of screening practices that detect complications frequently observed for a given rare disease (e.g., spirometry tests to detect lung function for patients with scleroderma)
- Comparison of treatment strategies that improve care delivery; examples include the following:
  - Case management models, including family-based care management models that reduce caregiver burden or stress

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7 Orphanet. portal for rare diseases and orphan drugs. https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN.
- Care coordination models that support transition of care, including (1) transition from pediatric to adult care and (2) transition to end-of-life care
- Case management and care coordination models that improve access to supportive care and specialty care, including telementoring and digital health tools
- Communication or dissemination, including decision aids that guide treatment choices being made by patients and providers.

**PCORnet Use and Optimization**

Having invested in the development of the PCORnet infrastructure, PCORI now intends to support the use and optimization of PCORnet to answer important research questions. The following are core elements of the network: streamlined, efficient processes for study establishment and startup; preexisting, standardized, curated, and research-ready clinical data on large numbers of people with specific clinical conditions and illnesses; actively engaged patients who join in governing the research uses of these data; access to and engagement from clinical experts with a wide range of specializations; distributed (rather than centralized) data 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 sources at the individual patient level to create complete, longitudinal data in a way that preserves privacy.

This PFA aims to fund research that will demonstrate the readiness of PCORnet CRNs and HPRNs to conduct multinetwork observational research that addresses important questions about the care of patients with rare disease. This will depend on an applicant’s ability to (1) leverage PCORnet’s administrative and governance processes to make maximal use of network resources and contribute to the learning network (e.g., Front Door, PCORnet Study Designation); (2) work collaboratively across two or more CRNs or HPRNs; (3) leverage the PCORnet Common Data Model and distributed research network to identify cohorts of patients across PCORnet, contact them to assess their interest in participating in a study, and execute the study; and (4) use the PCORnet Common Data Linkage method (if available) to link to other data sources to enhance the power of the observational cohort, as appropriate.

**Budget and Duration of Project**

Applicants may request up to $3.5 million in total direct costs for a research project period not to exceed three years (not including peer review). The maximum budget includes all research and peer review–related costs (refer to the Submission Instructions for further details). Applicants should submit a realistic budget and timeline reflective of the scope and requirements of the proposed study. PCORI expects that project budgets and duration will vary, depending on the rare disease cohort(s) selected, whether a validated phenotype for identifying the cohort exists, whether data linkage is required, whether a prospective or retrospective study is proposed, needs for recruitment and or primary data collection, length of follow-up, and analytic complexity. PCORI seeks efficient studies that use PCORnet resources to enhance contracting, Institutional Review Board (IRB) approval, recruitment, and data collection.

Total project funding is contingent on successful programmatic and budget performance. Awardees will
be expected to provide corroborating evidence to receive continual funding support. PCORI will conduct a programmatic assessment of the study’s progress to determine its viability and feasibility. Factors that will be considered in this assessment include the strength of the involvement of the rare disease community in refining one or more compelling research questions; ability to identify and recruit a validated study cohort of adequate size to answer the proposed question(s); completeness and accuracy of required analytic variables; viability of required data linkages, if needed; and strength of study governance and management. Only studies that are deemed satisfactory after this assessment will receive continual funding support. The timing of this review will depend on the nature of the study proposed.

II. General Requirements for PCORI-Funded Rare Disease 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 Letter of Intent and application submission, please consult the PCORI Submission Instructions.

Research Priorities

To be considered responsive, applications must do the following:

- **Describe the target rare disease population and plans and/or ability to identify and recruit cohorts of patients with the defined conditions.** We are particularly interested in those rare diseases that are not well represented in PCORI’s rare disease research portfolio. Identify in the application whether a mechanism to identify the cohort has already been validated for this disease or group of diseases and, if not, describe the plans for identifying and validating the cohort, following the ethical guidelines of the review boards involved. Describe how ethical concerns will be addressed.

- **Describe one or more compelling treatment or management questions that are comparative effectiveness research (e.g., that compare two or more alternatives, each of which is in common use or have established efficacy), or can form the basis of a future comparative effectiveness research question (e.g., that examine treatment patterns or care management strategies being used and associated outcomes).** Studies should assess the association of management or treatment options with benefits or harms to patients and caregivers. This PFA is not soliciting studies examining the natural history of disease or descriptive epidemiologic studies; the research question(s) should address a realistic clinical choice or decisional dilemma faced by patients or their caregivers. Recognizing that many comparators for rare disease studies may not have significant efficacy data, studies examining benefits or harms associated with interventions that have limited evidence of efficacy may be acceptable if the applicant can provide information supporting that they are in common use in the rare disease population being studied. More information is available by consulting PCORI’s Guidance on Research in Rare Disease.

- **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 the rare disease community 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, caregivers, and other stakeholders.

- **Describe how PCORnet infrastructure will be leveraged.** Identify and justify all participating research network entities (e.g., CRNs, HPRNs, affiliated partners, disease registries). A minimum of two CRNs/HPRNs must be participating in the research. Explain how the project will take advantage of the data standardization and interoperability of PCORnet’s Common Data Model to the fullest extent possible. Describe how the project will comply with PCORnet governance policies. Describe all PCORnet infrastructure resources used to conduct the study (e.g., coordinating center, streamlined IRBs, contracting, engagement and consenting processes, standardized data resources training). Applicants must describe a plan to query other CRNs that are not part of the proposed partnership to test their ability to identify the cohort. If addressing the proposed research question requires data linkage, explain how the project will accomplish this using the PCORnet Common Data Linkage Method (if available) and provide clear evidence of the data partners’ willingness and capacity to affect such linkages.

**Categories of Nonresponsiveness**

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

- Instrument development, such as new surveys, scales, and so on
- Studies that develop, test, or validate new decision aids and tools, or clinical prognostication tools
- Pilot studies not intended to inform larger efforts
- Studies that compare patient characteristics rather than clinical strategy options

Consistent with its authorizing law, PCORI does not fund research whose findings will include the following:

- Coverage recommendations
- Payment or policy recommendations
- Creation of clinical practice guidelines or clinical pathways
- Establishment of efficacy for a new clinical strategy
- Pharmacodynamics

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• Study of the natural history of disease
• Basic science or the study of biological mechanisms

**Studies of Cost-Effectiveness**

PCORI will consider an application nonresponsive if the proposed research does any of 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

Proposals that include studies of these issues may measure and report utilization of any or all health services, but may not employ direct measurements of care costs. For further information, please reference our cost-effectiveness analysis FAQs.

PCORI does have an interest, however, in studies addressing questions about conditions that lead to high costs to the individual or to society. This interest is reflected in our review criterion on the condition’s impact on the health of individuals and populations. Thus, 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.

**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. If planned outcome measures have not been validated in the study population, as is often the case with rare
disease, investigators should provide evidence of their validation in a related population and credible justification for use in the population being studied. We encourage investigators to consider those measures described in the Patient-Reported Outcomes Measurement Information System.\textsuperscript{11} (PROMIS). We also encourage investigators to consider ongoing work in defining core outcome sets for rare diseases, such as that being done by the Food and Drug Administration in collaboration with the Critical Path Institute and National Organization for Rare Disorders and the International Rare Diseases Research Consortium, or other relevant core outcome sets developed by groups such as the Comet Initiative. PCORI’s RDAP has identified the following core outcome domains as important for pediatric rare disease research: health-related quality of life, treatment side effects, and cognitive function. Applicants should consider the relevance of these domains for the proposed study. As caregiver burden is often a concern in rare disease, we encourage the assessment of validated caregiver outcomes.

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. Engagement approaches and practices vary from project to project based on the patient population, the setting, and the needs of a study. PCORI encourages study teams to be creative in their methods for engaging with research partners. Effective involvement of patients and other stakeholders requires a well-thought-out engagement plan that includes the goals for engagement and information on who will be involved, what preparation will be provided, points and intensity of involvement, and the decision-making process.

Populations Studied and Recruited

PCORI seeks to fund research that includes diverse populations regarding 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 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.

- Racial and ethnic minority groups
- Low-income groups
- Women

\textsuperscript{11} Available at https://commonfund.nih.gov/promis/index
- Children (0–17 years of age)
- Older adults (65 years of age and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Patients with low health literacy or numeracy, 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 Policy for the Protection of Human Subjects (45 CFR part 46), including the Common Rule. For more detailed information, please see Section 5, “Human Subjects Research Policy,” in the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports, which is issued by the US Department of Health and Human Services (HHS). In referencing the HHS Supplemental Grant Application Instructions, note that PCORI does not require that applicants comply with sections of the 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 IRB or international equivalent that has jurisdiction over 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.  

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**III. LOI Review**

Applying for funding from PCORI 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 responses to the LOI questions
- The investigators’ prior relevant experience, and strength of the proposed rare disease and other partnerships
- Strength of proposed CRN/HPRN participation and use of the PCORnet infrastructure
- 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 the portfolio with certain characteristics, including disease category, topics, priority population, 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 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.

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• 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., nonresponsiveness). An application may be administratively withdrawn if it is incomplete; submitted past the stated due date and time; or does not meet the formatting criteria outlined in the 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.

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

<table>
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<tr>
<th>Crosswalk of PCORI Merit Review Criteria with NIH Criteria</th>
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<td>SIGNIFICANCE</td>
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<td>1. Potential for the study to fill critical gaps in evidence</td>
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<td>2. Potential for the study findings to be adopted into</td>
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<td>APPROACH</td>
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<td>3. Scientific merit (research design, analysis, and</td>
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<td>4. Investigator(s) and environment</td>
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<tr>
<td>PCORI-Only Merit Review Criteria</td>
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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 them?
- 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 clear plan to provide documentation for their methods for external users, share tools and resources through common repositories, and provide a plan for disseminating information about the availability of this resource for stakeholders/the research community 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
that 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?

• If a comparative effectiveness study is proposed, are each of the comparators (e.g., active intervention arm, 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? If a descriptive study is proposed, has a strong case been made for its potential to lay the foundation for future comparative effectiveness research? Has the potential for the answers to the descriptive question to improve outcomes been well motivated?

• Are the sample sizes and power estimates appropriate (if relevant)? Is the observational cohort design 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?

• Does the application adequately describe the use of PCORnet infrastructure resources (e.g., Coordinating Center, Common Data Model, streamlined IRBs, contracting, engagement and consenting processes)? Have they proposed to query a large number of CRNs outside of the proposed partnership to test their ability to identify the rare disease cohort?

• Does the application clearly describe data linkages using the PCORnet Common Data Linkage Method (if available and relevant) between the required data sources (i.e., patient data, EHR data, claims data, and disease-specific registry data) to facilitate the conduct of the proposed study?

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

This criterion should assess the appropriateness (e.g., qualifications, experience) of the investigator(s)/team, the environment’s capacity (e.g., resources, facilities, equipment) to support the proposed project, and plans to use PCORnet resources. It should not be an assessment of the institution’s quality.

The application should also address the following questions:

• How well qualified are the PIs, collaborators, and other researchers to conduct the proposed activities? Is there evidence of sufficient rare disease, clinical, or statistical expertise (if applicable)?
Does the investigator or co-investigator have demonstrated experience conducting projects of a similar size, scope, and complexity?

If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate for the project?
  - (Dual-PI Option Only) Does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?

Is the level of effort for each team member appropriate for successfully conducting the proposed work?

Does the application describe adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research?

Is the institutional support appropriate for the proposed research?

**Criterion 5. Patient-centeredness**

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

The application should also address the following questions:

- Does the application include a thorough description about which outcomes (both benefits and harms) are important to patients, and are those outcomes included in the study plan?
- Does the application provide information indicating that closing the evidence gap is important to patients and other stakeholders?
- If a CER study, 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 should be evaluated based on scope, form, and frequency of patient and stakeholder involvement throughout the research process.

- Does the application describe a strong partnership with one or more rare disease organizations within the rare disease community, and have they addressed how they will ensure this partnership reflects the diversity of the population affected by the target disease(s)?
- 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, training institutions) to ensure that the projects will be carried out successfully?

- Does the application show evidence of active engagement among rare disease and other relevant scientists, patients, caregivers, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, implementing)? Is the frequency and level of patient and stakeholder involvement sufficient to support the study goals?
- Is the proposed Engagement Plan appropriate and tailored to the study and target population?
- 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 further clarify the merits of the proposed research. They also identify areas for improvement. Each application is re-scored based on the content of discussion. The panel chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review according to the standards outlined in the PFA.

Post-Panel Review

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

- In-person panel discussion notes
- Final average overall score
- Preliminary reviewer critiques
- Application quartile, to help applicants understand how they performed 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 2021.

**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 database16 (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.17 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.

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16 Available at https://prsinfo.clinicaltrials.gov/.
17 Available at http://www.crd.york.ac.uk/prospero/.
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 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 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.

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, 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 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 repository and when those data would be available for third-party requests. The Policy also addresses requirements relating to research awards that are conducted using PCORnet.

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 adopted the Process for Peer Review of

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18 Available at http://www.hhs.gov/ocr/.  
Primary Research and Public Release of Research Findings.\textsuperscript{20}

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.