



PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Patient-Centered Outcomes Research Institute

Cooperative Agreement Funding Announcement:
Improving Infrastructure for Conducting Patient-Centered
Outcomes Research

The National Patient-Centered Clinical Research Network:
Clinical Data Research Networks (CDRN)—Phase One

Released April 23, 2013



Action	Due Date
Release Date	Tuesday, April 23, 2013
PCORI Online System Opens	Wednesday, May 15, 2013
Pre-LOI Informational Webinar	3:00 PM (EST), Tuesday, June 4, 2013
Letter of Intent (LOI) Due*	5:00 PM (EST), Wednesday, June 19, 2013
Applicants Notified of LOI Approval Status	Wednesday, July 17, 2013
Application Deadline	5:00 PM (EST) Friday, September 27, 2013
Merit Review	October–November 2013
Awards Announced	December 2013

* A LOI is required to submit an application

Notes	Due Date
Coordinating Center Announcement	Summer 2013

I. Opportunity Snapshot

A group of clinical researchers at a healthcare delivery organization has been asked by clinician colleagues to investigate a question that compares one treatment to another and that, when answered, is believed will have a positive impact on the health outcomes of a large patient population. The idea of gathering data from real-world clinical experiences of patients within their system is very appealing to both the clinicians and the researchers. In spite of the strong skills of the researchers, the interest from clinicians and their patients, and the rich clinical data contained in the organization's electronic health record (EHR) and other clinical data, there are multiple barriers impeding the ability to conduct this research. For example, the available sample size of persons exposed to each treatment is often inadequate within a single system. Capture of many key outcomes can be incomplete if some patients obtain some of their care outside the system. Patient-reported outcomes, often important in comparative effectiveness research, are almost entirely missing. If the research question requires randomization, recruitment of patients is costly and inefficient, and obtaining informed consent is made cumbersome by an Institutional Review Board (IRB) that does not understand the low-risk nature of many studies, nor the adverse impact of excessive IRB requirements on study feasibility and validity. Eager to have an answer that could benefit so many individuals, all parties involved wonder if there are better ways to leverage existing electronic healthcare data within and across systems; other methods for collecting data and engaging patients, such as social media and modern digital technologies; and opportunities for interested, activated patients and clinicians to participate in and facilitate the efficient conduct of important comparative effectiveness research and the rapid clinical implementation of effective treatment strategies.

A. Purpose

Every day, patients and their caregivers are faced with crucial healthcare decisions while lacking key information that they need. The Patient-Centered Outcomes Research Institute (PCORI) was created to conduct research to provide information about the best available evidence to help patients and their providers make more informed decisions. PCORI's research is intended to give patients and their caregivers a better understanding of the prevention, treatment, and care options available and the science that supports those options. However, the nation's capacity to conduct patient-centered comparative effectiveness research (CER) quickly and efficiently remains extremely limited.

The goal of PCORI's National Patient-Centered Clinical Research Network Program is to improve the nation's capacity to conduct CER efficiently, by creating a large, highly representative, national patient-centered clinical research network for conducting clinical outcomes research. Specifically, this program will promote a more comprehensive, complete, longitudinal data infrastructure; broader participation of patients, clinicians, health systems, and payers in the research process; and improvements in analytic methods for both observational and experimental CER. The creation of a national patient-centered clinical research network could empower the United States to become a learning healthcare system, which would allow for large-scale research to be conducted with enhanced accuracy and efficiency. The core components of this network will be Clinical Data Research Networks (CDRNs), which are system-based networks (such as hospital systems) that have the potential to become an ideal electronic network, without



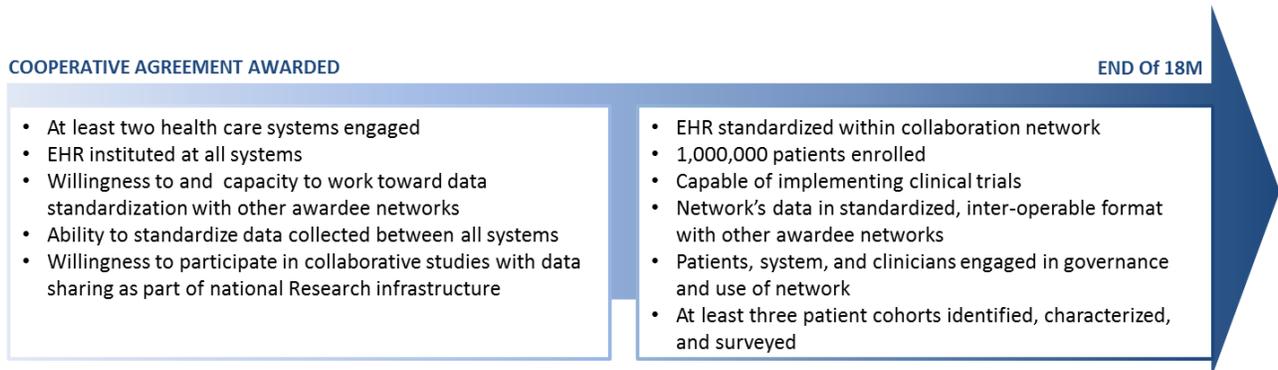
structural impediments, and Patient-Powered Research Networks (PPRNs), which are groups of patients interested in forming a research network and in participating in research.

Through this funding announcement, PCORI seeks to support new or existing CDRNs that will develop the capacity to conduct randomized comparative effectiveness studies using data from clinical practice in a large, defined population (at least one million people by the end of Phase One for conditions other than rare diseases). PCORI has defined the characteristics of an ideal CDRN to include the following:

1. Coverage of large, diverse, defined populations unselected for a particular disease, condition, or procedure; ability to capture complete clinical information on this population over time, including longitudinal information on clinical care, changes in clinical characteristics and conditions, and the occurrence of clinical care or outcomes, within or outside the system.
2. Involvement of multiple (two or more) health systems, with data interoperability and data standardization to allow efficient, valid sharing of individual or aggregate data across systems for purposes of data analysis.
3. The ability to efficiently contact patients for the purposes of efficient recruitment; collecting patient-reported information; and maintaining consistently high levels of participation in research studies, including sustained randomization, participation, and follow-up over time.
4. Demonstrated ability to engage substantial patient populations with selected conditions, both within and outside their systems, for purposes of generating research questions, participating in network governance, or in appropriate research studies.
5. Involvement of the healthcare system leadership in governance and use of the network to enhance network efficiency, utility, and sustainability.
6. Willingness to serve as a national data infrastructure resource for the conduct of CER by researchers outside the network.
7. Capacity to support large-scale comparative effectiveness trials, as well as observational studies of multiple research questions, including prevention and treatment, at low marginal cost, with substantive patient involvement throughout, including formulation of research questions and essential study characteristics, study participation, and dissemination of study findings¹.
8. Capacity to embed research activity within functioning healthcare systems without disrupting the business of providing health care; alignment of human subjects oversight, IRB review and approval, and informed consent procedures with the level of risk in proposed comparative effectiveness studies, including plans to obtain buy-in from all organizations to accept review of specific projects under auspices of a central IRB.
9. Clear, proven policies to maintain data security, patient privacy, and confidentiality; ability to collect, store, retrieve, process, or ship biological specimens for research purposes, with appropriate consent, for use by qualified researchers.
10. Ability to streamline subcontracting processes for research involving multiple sites.

¹ PCORI Methodology Standards, PC-1, p. 4

Through this funding announcement, PCORI seeks to support up to eight new or existing research networks and their progression toward a reusable, scalable, and sustainable clinical data research network. PCORI recognizes that existing research networks currently differ widely with respect to how closely they come to achieving these features. Thus, applicants may propose to focus efforts on enhancing different aspects of their network, but in a collaborative effort with other awardees. The figure below articulates the minimal requirements of an applicant organization on the left, and, on the right, the expected minimal achievement of a funded applicant at the end of Phase One.



The CDRNs most likely to advance to Phase Two funding will be those that most thoroughly achieve all the listed features in the figure and list above, particularly requirements for interoperability with other networks; involvement of patients, clinicians, and health systems in governance and use of the resource; and willingness to fully participate in a national patient-centered research network.

B. Funds Available

We anticipate disbursing funding totaling up to \$56 million under this Cooperative Agreement, assuming receipt of a sufficient number of high-quality applications.

C. Budget and Project Periods

Total project costs are limited to a maximum of \$7 million (total costs, including indirect costs). The project period is 18 months and may not exceed 18 months to complete work. Applicants who wish to apply for a larger award must contact PCORI by or before the due date for the letter of intent to explain why a larger award could present extraordinary opportunities to build national a patient-centered clinical research network. All budget proposals will be scrutinized and scored for the efficient use of research resources as part of the merit review process, and all expenses must be clearly justified.

D. Organizational Eligibility

PCORI is interested in applications from each of the following broad types of clinical data networks, provided that the network has as a central goal of becoming part of a national infrastructure for the purpose of conducting research studies that promise to improve decision making and outcomes for patients. These types are meant to be illustrative, and this list may not be comprehensive.

Types of Organizations Eligible for this Announcement

Established or newly developed networks that involve two or more healthcare systems, with plans to function as an integrated research network, such as:

- Two integrated healthcare delivery systems
- A healthcare delivery system and one or more health plans
- A health plan and two or more delivery systems
- A practice-based research network and a health plan
- An accountable care organization and its affiliates

This is not an exhaustive list, and applicants representing other types of potential CDRNs are encouraged to apply. Applications may be submitted by any private sector organization, including non-profit and for-profit organizations; any public sector organization; universities; colleges; hospitals; laboratories; healthcare systems; and units of state and local governments. Only US-based organizations may apply as primary institutions. All primary applicants must be recognized by the US Internal Revenue Service. Individuals may not apply.

PCORI also has a special interest in supporting research for patients with rare diseases.



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For information about the PCORI Cooperative Agreement process, please go to the [application guidelines](#).

II. Cooperative Agreement Detail

A. Overview

Through this funding announcement, PCORI is soliciting proposals for Clinical Data Research Networks (CDRNs) that will develop the capacity to conduct randomized comparative effectiveness studies using data from clinical practice in a large, defined population (at least one million people by the end of Phase One for conditions other than rare diseases). In an effort to achieve a national patient-centered clinical research network, applicants are required to demonstrate a willingness and capacity to share individual-level data, by collaborating with at least one other system. These collaborations may be between two or more systems that serve entirely distinct patient populations or between systems (e.g., hospitals, primary care networks, health plans, specialty organizations with data registries) that together provide and/or administer complete medical care to a single, large population. Additionally, addressing and resolving issues of data standardization and interoperability both within the applicant networks and across all participating networks is a key part of the anticipated work.

The present Cooperative Agreement is not meant to fund CER scientific studies or clinical trials; however, demonstrated capacity to utilize this network to conduct research will be a requirement for subsequent funding in Phase Two.

B. Background

For the first time in the United States, the use of EHR has spread to include the majority of ambulatory and inpatient settings, thanks in substantial part to the initiatives and policies of the Department of Health and Human Services (HHS) through its Medicare and Medicaid EHR Incentive Programs. The policies set forth by HHS in the final rules for Meaningful Use Stage 2 represent a major step forward in advancing the secure exchange of information among clinicians and with patients to support better care across the nation. In support of Meaningful Use Stage 2, HHS adopted common standards and implementation specifications for the electronic exchange of information, including common transport standards and a common data set for the summary of care records, with an array of structured and coded data that can be formatted uniformly and sent securely to providers or patients during transitions of care or upon discharge. By 2014, clinicians will have to demonstrate, and vendors will have to support, the exchange of structured care summaries with other clinicians, including across vendor boundaries. Vendors and providers will also need to support the “Blue Button” initiative capabilities—direct patient access to and use of their own electronic health data—through the ability to view, download, and transmit (VDT) their coded clinical information to a third party. EHR technology will need to enable the Nationwide Health Information Network Direct Project for uniform transport and Consolidated Clinical Document Architecture (CCDA) for coded content, to support the VDT requirements.

While this capability may be executed in a number of ways, some EHR technology developers are using the guidelines released by the Office of the National Coordinator for Health Information Technology (ONC) for “Blue Button Plus,” which satisfy Meaningful Use Stage 2 requirements and allow patients to direct an ongoing stream of their clinical data to a destination of their choice—which could include a PPRN or a

specific research initiative. This could give researchers working with patients a convenient and predictable way to receive and aggregate current clinical information. From a PCOR perspective, these initiatives introduce a novel potential path to building a foundation of clinical information on an activated, engaged population of patients.

In July 2012, PCORI convened expert stakeholders in the health data infrastructure field to provide insights into opportunities for strengthening existing research infrastructure to support the conduct of high-quality patient-centered CER. During this workshop, CDRNs and PPRNs were discussed. CDRNs are based primarily on data derived from EHR and other electronic sources within a healthcare system, whereas PPRNs are built primarily by communities of motivated patients. Participants recognized that each type of network possesses certain advantages and agreed that an ideal infrastructure would combine the rich clinical data from large representative populations (the CDRN) with the motivation and interest in research that characterize a successful PPRN.

C. The Value of CDRNs

Multiple efforts exist to leverage and use clinical data research networks based on EHRs.

Noteworthy efforts include the HMO Research Network, which, through its Virtual Data Warehouse, has created a standardized data model across 15 integrated care delivery systems, and the FDA-sponsored Mini-Sentinel initiative, which is a collaboration of numerous health plans and care systems, based substantially on electronic claims information and covering more than 120 million patients. Mini-Sentinel has been used primarily for comparative safety studies to date. Recently, the initiatives and policies of the HHS through its Medicare and Medicaid EHR Incentive Programs² have greatly increased the use of EHRs in both ambulatory and inpatient settings, creating possibilities for extending the collection of rich clinical data to smaller and less integrated care delivery settings. More than 70 percent of ambulatory care settings and more than 80 percent of hospitals now employ an EHR system. In support of Meaningful Use Stage 2 (MU2), which takes effect in 2014, HHS has promoted and incited use of common standards and implementation specifications for the electronic exchange of information, including common transport standards and a common electronic structure for the summary of care records. These specifications begin to standardize the data across disparate healthcare settings and EHRs. An array of structured and coded data can be formatted uniformly across settings and sent securely to other providers; directly to patients; or, with appropriate permission, to a research database. For instance, in the MU2 standards, every EHR will be able to send lab results using LOINC, diagnoses using SNOMED CT, and medications using RxNorm. Additional standards for structuring the data content for patient care summaries provide a structured way of organizing and sharing data.

Structured data derived from patient reports (including behaviors, medical history, and patient-reported outcomes) remain sparse in most systems, and even when the data fields are present, completion rates are typically low. Increased capture of high-quality patient-reported information could greatly enhance the

² <https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html?redirect=/EHRIncentivePrograms/>

ability to conduct CER that is meaningful to the patient, but decisions to collect such data must weigh the utility of the information against the costs of collection. Longitudinal data capture—defined as the ability to observe patients’ clinical experience over time with confidence that the patients are still under observation and that clinical outcomes are completely captured—is essential to support CER, but is absent or incomplete in most inpatient and outpatient settings. Even many established practice-based research networks have not yet solved the challenge of complete, longitudinal data capture. Linkage of care delivery data with enrollment and outcomes data from insurers or possibly from governmental data sources may be needed in many systems to guarantee longitudinal coverage of a cohort of patients.

The ability to efficiently recruit patients to participate in specific studies, either randomized trials or observational studies, is of critical importance to CER. In many cases, local IRBs continue to apply policies and requirements that are excessive for studies in which research risks are minimal and often incompatible with conducting valid practice-based research. With multi-system networks, challenges are compounded by the need to work with multiple IRBs that may have varying requirements for both research oversight and protection of privacy and confidentiality. These challenges may impose burdens that make it impossible to conduct large, realistic comparative effectiveness studies within or across healthcare systems. Lastly, the active involvement of those who create and control the databases—patients, clinicians, and health system leaders—is often missing from the governance and management of these research networks. Their absence reduces the use, the utility, accuracy, and sustainability of the systems. All these factors described above create obstacles to the conduct of high-quality patient-centered CER. These problems are typically worse for vulnerable patient populations, such as the poor, underrepresented minorities, the frail and elderly, rural populations, and individuals with disabilities.

D. Definition of Patient-Centered Outcomes Research

PCORI has defined patient-centered outcomes research, posted the definition for public comment, and incorporated these comments into the revised [definition](#). Applications for research projects to PCORI should be aware of and aligned with this definition as they propose the data infrastructure and the involvement of patients and stakeholders in governance and use of the network resource.

E. Funds Available

We anticipate disbursing funding totaling up to \$56 million under this Cooperative Agreement, assuming receipt of a sufficient number of high-quality applications.

F. Budget and Project Periods

Total project costs to a maximum of \$7 million (total costs, including indirect costs). The project period is 18 months and may not exceed 18 months to complete work. Applicants who wish to apply for a larger award must contact PCORI by or before the due date for the letter of intent to explain why a larger award could present extraordinary opportunities to build a national patient-centered research network. All budget



proposals will be reviewed and scored for the efficient use of research resources as part of the merit review process, and all expenses must be clearly justified.

III. The Technical Proposal

The technical proposal should be carefully organized in the sections described below. In each section, the applicant should describe what the network proposes to do during the 18-month period to make progress toward the ideal network. Goals, milestones, and deliverables should be described. PCORI recognizes that not all applicant networks will be able to propose activities in every area. For example, new networks may find it difficult to store biospecimens. Others may not have an IRB to work with. If your organization does not envision meaningful opportunities to make progress in either of these two or other areas, state this clearly. Such applicants will not be penalized during review.

A. Technical Requirements and Review Criteria (RC)

1. Description of the network, its component systems, the available data from each system, and the network's potential for demonstrating coverage of a diverse, representative population of at least one million persons by the end of the 18-month award period.

Describe and document your research network's history and that of each component system, including network leadership, current annual funding for maintenance and expansion of the network, current size in terms of covered lives, data content (in general categories such as enrollment, diagnostic codes, prescription records), any current linkages with data sources outside of the network's component systems, and any affiliations (e.g., with research institutions, data vendors, local or national disease registries that originate outside of the applicant health system, or patient networks). If the network is currently comprised of two or more systems, describe each of the health systems, as well as relevant differences between systems.

Address known differences between component systems in organization and governance, in care delivery patterns and practices, enrollee retention patterns, and policies regarding patient privacy and patient/provider participation in research.

Describe the volume and types of research projects that have been conducted within the applicant network, with particular attention to longitudinal outcomes studies or randomized intervention studies that have been completed or are underway.

If available, provide tabular information on the size and demographic characteristics of the current patient population(s) (age, gender, race/ethnicity, and education level) and estimated prevalence of common chronic conditions, such as diabetes mellitus, hypertension, previous myocardial infarction, asthma, and depression. In general, greater variation in treatment practices provides richer opportunities for conducting relevant CER. Finally, address what is known about variation in treatment



practices within the system and the extent of use and adherence to clinical practice guidelines and formularies.

If the population does not currently exceed one million persons, describe what the network will do to expand the size of the covered population during the 18-month period.

RC1.

- a. The application presents a clear description of the current characteristics of the research network and its component healthcare systems. The application will come from at least two systems. These systems may cover distinct patient or member populations, or they may each cover aspects of care delivery to the same population.
 - b. The application describes the potential to create an unselected population of a least 1,000,000 persons by the end of the study period, including explicit plans to increase the number of observed patients to at least one million if the network currently captures fewer than one million members.
 - c. The application presents, in clear fashion, the demographic and clinical features of the covered population, including information on the potential variation in treatment patterns that may be observed within the population.
 - d. The application clearly states willingness to work with all other awardees toward semantic and syntactic interoperability and toward a data standardization model that will enable the ultimate goal of performing research across multiple CDRNs.
 - e. The application describes evidence of successful experiences in network-based research, if applicable, including information on the varieties of study design, conduct, data analysis, and management of such projects.
2. Current informatics standards, interoperability between systems, and plans for achieving data standardization and interoperability between systems within network and across CDRNs.

Although EHRs are now deployed across the majority of hospital and ambulatory care sites in the United States, the ways in which these records are implemented and the ways data are entered vary substantially. Much work remains to be done in terms of standardizing data capture and in aggregating and storing the data. Agreement on and use of specific informatics standards across all settings and systems is a part of the solution.

Describe the extent to which each component system uses national informatics standards for capture, storage, and exchange of clinical information. Describe differences/similarities in the standards used by the component systems within the proposed network. Describe any efforts to date to examine or enhance the interoperability of the databases and data exchange between component systems.

Describe proposed activities to enhance data standardization and interoperability within each system and between systems within the network, especially as the network works to increase comprehensiveness or completeness by incorporating data from new sources. Describe approaches that will be used during the 18-month period to validate aspects of data quality and comparability

across sources within the network. These approaches should ideally also be useful for evaluating data standards and interoperability across the several funded CDRNs.

If new relationships with other healthcare systems, registries, or patient networks are proposed, describe how issues such as data interoperability, data system structures, and data standardization will be addressed. Finally, provide thoughts on how CDRNs might work to enhance the standardization, exchange, and use of data across networks in a national clinical research infrastructure.

RC2.

- a. The application clearly describes the clinical and information technology systems at each of the healthcare systems participating in the network, including specific standards used for capture and storage of various clinical data elements (diagnoses, prescriptions, laboratory tests and results, radiologic images, progress notes). It also addresses issues of adherence to standards within systems.
- b. The application clearly describes standards in use for information exchange between systems. Interoperability gaps within and between systems are identified. Plans are presented for enhancing standardization and interoperability of data within and across the network's component systems during the award period.
- c. The application clearly describes the policies, procedures, tools, and methods already in place to ensure that data collected across these systems are comparable and valid for research purposes. Plans for further developing such policies, procedures, tools, and techniques during the 18-month award period are proposed.
- d. The applicant demonstrates an understanding of the intent of this project to work toward data standardization and interoperability across CDRNs and PPRNs and expresses willingness to work toward these ends.

3. Capture of complete, comprehensive clinical information over time.

A critical concern for comparative effectiveness research is the comprehensiveness and completeness of data capture over time within the population. Describe how well the network can currently follow individuals longitudinally for assessment of outcomes once treatments are noted. What are the year-over-year retention rates for members within the database? How certain is it that endpoints are currently captured in network data sources? This may present challenges to some networks, either because patients do not remain under observation (e.g., do not remain enrolled in the same system) for long periods or because not all clinical care is provided by the system.

CER, especially observational CER, is strengthened by having a comprehensive range of data available and is critically threatened by missing data. Applicants should describe in tabular form the content of their current database. All available categories of data available to the network should be shown. These may include enrollment data; ambulatory diagnoses; procedures; laboratory and imaging utilization and results; prescriptions and pharmacy dispensing; biophysiological data such as height, weight, blood pressure values, infusion data, clinical notes, referrals outside the covered system, ED utilization and

clinical information; hospital admissions and inpatient EHR data; self-reported data such as smoking status, symptom status, quality of life; and nursing home admission data.

Completeness refers to the probability that data on a specific clinical care event will be captured, given that type of data is assumed to be included in the database. Carefully explain the reasons for deficits in either comprehensiveness or completeness of data availability. It should be noted that incompleteness does not refer to system failures to perform given clinical actions.

Describe the proposed efforts that will be undertaken during the 18-month funding period to increase the ability to follow patients over time, to increase the comprehensiveness of available data, and to improve or validate data completeness. For example, improving comprehensiveness of the resource by incorporation of previously unused clinical data resources within systems is of interest. Linkages to new sources of data from outside the care system (e.g., hospital EHR data, linkage with personal health record information, data from the Center for Medicare and Medicaid Services or commercial health plans), or linkage with well-developed, independent disease registries, would be of great interest as approaches to ensuring the longitudinality of the database and its completeness. This is expected to be a major activity for most applicant networks. For each activity, describe the final goal, quantitatively when possible.

RC3.

- a. The application clearly describes the current state of the network's database in terms of its comprehensiveness, completeness for data elements currently captured, and ability to reliably follow patients and observe clinical care and events over time. It demonstrates an appreciation of the potential categories of data needed to conduct CER and the critical importance of longitudinal follow-up.
 - b. Current gaps in the comprehensiveness, completeness, or longitudinality of data capture are recognized and clearly described.
 - c. The application clearly describes steps that will be taken to improve the network capacity to acquire complete longitudinal data on covered members. The status of the network database by the end of the 18-month period is well described and a convincing case is made that, by that time, longitudinal capture of relevant data on network members will be substantially complete.
4. Demonstrated ability to engage and mobilize patients and clinicians to participate in network governance and use, including generation of research questions.

An innovative aspect of this funding announcement is PCORI's requirement that applicant networks actively involve patients as well as clinicians in network governance and in use of the data resource. PCORI believes that patient-centered CER is best accomplished when end users of the data are engaged in planning and conducting the research. Involvement of clinicians and health system leadership is critically important. Clinicians are responsible for inputting much of the data that ultimately create the resource. Because much of the burden falls on them, it is essential that they share in potential benefits. Their involvement and appreciation of the potential uses of the information beyond patient care may encourage more careful or complete recording of data.

Efforts to inform the patient and clinician populations of the existence and work of the network should be described, as should efforts to engage each group in generating research questions, and in helping to govern the development and uses of the network and its database. Proposed structural and policy details of how engagement will be accomplished should be described.

Applicants may propose to carry out this work solely within the three distinct patient communities described in requirement 6 below, or with the broader patient or enrollee population.

RC4.

- a. The application describes how the network plans to engage patients in the governance of the CDRN and in generating research questions and in participating in research studies.
 - b. The application describes how the network plans to engage clinicians in all relevant sectors, in the governance of the CDRN, in generating research questions, and in participating in research studies.
 - c. The proposed infrastructure and strategies for communicating with and inviting participation from patients and clinicians must be substantial, feasible, and promising.
5. Involvement of systems leadership in the application and in plans for governance and use of the resource.

A second innovative aspect of this announcement is PCORI's requirement for involvement of the healthcare system, its administrative and clinical leadership, in governance and use of the network. PCORI sees this involvement as critically important to the efficiency, utility, and sustainability of a network. Involvement and support of system leadership is essential for authorizing and facilitating access to clinical data; for allowing contact with members of the covered population; and for approving proposals to conduct research within clinical settings, including randomized assignments to treatments. PCORI will expect to see a strong expression by organizational leadership of interest in and understanding of the goals and promise of the network.

Applicants should present evidence that the leaders of the system(s) are fully aware of and supportive of the concept of building a national patient-centered research network for randomized studies, and of becoming a national resource for collaborative research with other, non-system-based researchers. Ideally, applicants should be able to demonstrate the intent of system leadership to use the infrastructure for asking and answering comparative questions of interest to the healthcare system, for performance measurement and quality improvement projects.

Specifically, applicants should describe plans for further engaging system leadership in ongoing governance of the network, including decision making regarding expansion, collaboration with other healthcare systems and researchers, selection and approval of specific research questions, and implementation of study findings into clinical practice.

RC5.

- a. The application documents that the health systems' leadership, including clinical and executive leadership, are aware of and support the proposed project, that they will be engaged in the project during the funding period, and that they would consider using the infrastructure for performance measurement and/or for asking and answering comparative questions of interest to the healthcare system. Organizational commitment should be documented in the form of a detailed letter(s) from appropriate systems leaders.
- b. The application presents a clear and appropriate plan for engaging system leadership in governing the network, including decision making regarding expansion, collaboration with other healthcare systems and researchers, selection and approval of specific research questions, and implementation of study findings into clinical practice.
- c. Evidence of past support or indications of present support from the systems, such as in grants management, personnel management, space allocation, access to data, procurement, and equipment, as well as general support of research activity, is particularly welcome.

6. Plans and/or ability to identify and recruit cohorts of patients with defined conditions.

A critical requirement of a data infrastructure for CER is the ability to identify and follow highly representative, unselected cohorts of patients with specific illnesses or conditions. During the 18-month funding period, each awardee must identify, characterize, and recruit at least three patient cohorts with defined conditions or symptoms (e.g., chronic pain) using available electronic data. The first cohort must be a clinical population with a relatively high prevalence disorder of the network's own choosing (with at least 10,000 identified persons). Applicants are encouraged to select a condition for which they have expertise and to carefully describe their ascertainment and validation methods. The second cohort must be of patients with one or more rare disorders (defined by a prevalence of less than one per 1,500 persons in the United States). Again, prior experience and detailed specifications of ascertainment plans are important. The third patient cohort, patients who are overweight or obese, is to be pursued by all awardees. The presence of diabetes or pre-diabetes should also be identified in these patients. All funded networks will work together on this third cohort.

For each cohort, applicants should describe their approach to defining membership and characterizing cohort members. Applicants should describe the data elements that will be used and the implications of these choices for identifying the entire cohort without bias in the covered population. For the rare condition, applicants are encouraged to reach out to and collaborate with the appropriate rare disease organization(s) to identify and include additional individuals with the condition. Applicants might identify an organization that is applying to be a PPRN. Others might define how they would collaborate with the appropriate rare disease organization after funding is obtained. Applicants will be expected to work with other funded networks to insure that methods of cohort construction use data standards that support interoperability and construction of similar cohorts elsewhere.

Each of the three cohorts must be contacted and recruited to participate in the cohort and in a brief baseline survey. The survey must assess the patient's level of interest in participating in research related to the condition being studied, including interest in participating in randomized trials should an appropriate one be launched; interest in participating in network development and governance; and

interest in communicating with other patients about possible uses of the network. A high response rate to the survey is desirable, and a variety of approaches to conducting the survey may be proposed, including traditional mail or phone surveys or surveys using e-mail, social media, or mobile devices.

RC6.

- a. The application demonstrates a deep understanding of the clinical and epidemiologic characteristics of the two applicant-selected patient cohorts and demonstrates experience and knowledge of the issues related to building each of the three cohorts.
 - b. The application demonstrates that the network has the ability to rigorously identify members of these cohorts and that the cohorts will be of sufficient size and composition to contribute to meaningful studies.
 - c. A plausible plan for engagement with a rare disease community is described.
 - d. The application demonstrates willingness and ability to work with other awardees to build the capacity to consistently and comparably query clinical data to build a cohort across systems in a standards-based fashion.
7. Willingness to serve as a national data infrastructure resource for the conduct of CER by researchers outside, as well as within, the network.

PCORI's intention is to build a national resource for conducting CER. PCORI does not intend to limit future use of the resource infrastructure to researchers associated with building the infrastructure. That is, applicants must understand the rationale and embrace the necessity for sharing data in either aggregate or de-identified form and for collaborating actively with qualified researchers from outside the network in using this resource. While this Phase One agreement does not fund research projects, PCORI requires the awardees to work together through the steering committee to define and implement a plan for data sharing for the national patient-centered research network by the end of award period. The proprietary interests of the parent organizations should always be taken into account in considering individual studies, but they are not a reason to impede access in most instances. Understanding and willingness to participate in this arrangement must be clearly demonstrated by the parent organizations as well. The steering committee and the coordinating center will play important roles in enabling these collaborations. Applicants should plan for an important time commitment to work with the steering committee and the coordinating center throughout the process, including biweekly telephone calls and up to five face-to-face meetings during the 18-month period. Budgets should include travel for these meetings.

Applicants should describe the activities they currently have in place and those they will undertake to build capacity to support inquiries from outside researchers regarding preparation of applications, to facilitate contracting and IRB review for successful researchers, and to provide ongoing collaborative support of studies once launched. This may include building web portals; providing meta-data and data dictionaries; and development and publication of policies, procedures, and processes for making multi-site data available, for coordinating analyses and publication of collaborative work multiple studies. The capacity and willingness to efficiently and effectively archive data from completed studies to make these data resources available for secondary data analysis by researchers internal to and external to the

CDRN is also expected.

RC7.

- a. The application indicates clear intent and plans for participating in an infrastructure that is a national resource. This includes clear recognition of the commitment by the healthcare systems providing the data.
 - b. The application clearly describes availability or plans for developing policies, procedures, and processes to make network data available for analysis as aggregate data or through federated access (distributed data network) or possibly through pooling of de-identified data for pre-specified analyses; to support timely and coordinated analysis and publication of multiple studies; and to efficiently and effectively archive data from completed studies to make the data resource available for secondary analysis by researchers internal to and external to the CDRN.
8. The ability to efficiently contact patients within the covered population for the purposes of collecting patient-reported information and for efficient recruitment to clinical trials.

A particular concern for PCORI is the network's ability to contact patients within the covered population for research purposes. CER studies require patient-reported information on behaviors, risk factors, and outcomes from members of the covered population. Both the efforts initiated by delivery systems to incorporate routine collection of patient-reported information into the EHR and efforts by researchers or systems to collect patient-reported information by other means (e.g., surveys, mobile health applications) are of interest. Proposed activities under this award to expand either the comprehensiveness or the completeness of patient-reported data should be carefully described.

Rapid identification and contact of eligible patients for recruitment to clinical trial participation is also of great interest. New methods for alerting eligible patients to the opportunity to participate in a clinical trial, including new contact methods such as use of e-mail or mobile health strategies, will be needed, and their development and evaluation are of great interest. Applicants should describe efforts that are planned in this area, including development of agreements with healthcare systems or their institutional review boards to allow various new approaches to contacting or communicating with patients, and development of new IT tools or mobile health applications.

RC8.

- a. The application clearly describes the current capacity of the network to collect data from patients on patient-reported outcomes, behaviors, comorbidities, symptoms or functional status, either by virtue of system-initiated data collection via the EHR or other means, or through network-initiated data collection efforts. Plans for enhancing these capabilities are described.
- b. The application describes proposed innovations for the efficient identification and contact of patients for recruitment into prospective studies, including, but not limited to, enhanced use of electronic medical records data, patient surveys, patient portals and mobile health devices, engagement with patient networks, and development of policies and practices that facilitate health provider and patient contact for research purposes.

9. Capacity to support large-scale comparative effectiveness randomized trials, and to embed research activity within functioning healthcare systems without disrupting the business of providing health care, coupled with evidence of support for these activities from administrative and executive leadership.

Many CER studies will require randomized assignment of treatments to achieve the validity required to satisfy patients, clinicians, and policy makers. Broadly representative patient populations and conduct in clinical settings as similar as possible to usual clinical care are key requirements of CER trials.

Describe any previous accomplishments of the network in this regard. It is PCORI's expectation that all awardees will have achieved capacity to conduct or participate in such trials by the end of the 18-month period. Ideally, both individual and group (cluster) randomization should be feasible. This capacity will depend heavily on the involvement and support of the sponsoring healthcare system(s) in which the covered population receives care.

Discuss the current potential and the challenges to mounting randomized trials within the applicant network, and then describe the proposed activities efforts to be undertaken during the 18-month funding period to enhance this potential. Agreements with clinician networks or healthcare systems to allow and to participate in practice-based trials (with randomization at the individual level or at the level of clusters, such as practitioners, clinical units, facilities employer units, or geographical areas) are of high value. Applicants should focus on those approaches with the greatest potential for improvement, taking into account their networks' and health systems' unique circumstances.

RC9.

- a. The application clearly describes the current capacity of the network to enroll patients and to conduct or participate in prospective randomized studies, including examples of past or current randomized studies where this capacity has been utilized.
- b. The application clearly describes how this capacity will be improved over the course of the project and describes examples of the kinds of studies that could be supported with this enhanced capacity.
- c. The understanding and support of the healthcare system, especially of clinical leadership, is demonstrated.

10. Alignment of human subjects oversight, IRB review and approval, and informed consent procedures with the level of risk in proposed comparative effectiveness studies.

The ability to conduct research embedded within healthcare delivery settings requires streamlined, unobtrusive approaches to recruiting patient participants and obtaining informed consent. Complex consenting requirements can slow clinical care, raise undue concern on the part of patients, interfere with clinician-patient relationships, and render CER impossible to conduct or to be fatally biased. Human subjects protection policies, including those for informed consent, that have been designed to protect subjects in trials of unapproved therapies (including drugs, devices, or procedures) may present insuperable barriers to the conduct of CER. Most CER studies present few, if any, risks beyond those of seeking clinical care, because they are studies of currently used approaches. Thus, a reduction in the complexity of oversight and of the complexity of informed consent requirements is appropriate as well

as essential. At the same time, systematic oversight of individual studies remains necessary to identify true potential risks, if any, and to ensure that oversight requirements are commensurate with risks.

Multi-system studies pose further opportunities to streamline oversight through agreements by participating systems to rely on a single, central institutional review board. Requirements of cluster randomized trials, where individual informed consent would be impossible, are not well delineated or standardized yet.

Applicants should describe efforts that will be made during the period of funding to streamline any aspects of oversight or consenting practices and, more broadly, to strengthen the appropriate engagement of the health system and of IRBs in considering the role of randomization in CER activities. Efforts to establish and refine policies for patient recruitment and for centralizing IRB functions for multi-system studies are of interest. Efforts to engage system leadership in deliberations regarding the acceptability of randomization, of engaging the patient membership or population about the role and necessity of randomization, are of great interest. Development of novel, more efficient and convenient approaches or new IT tools for obtaining informed consent from patients are also of interest

RC10.

- a. The application clearly describes the current organizational structure, policies, and procedures of the IRB(s) that oversee network activities, especially in regard to the timely review, approval and oversight of large and complex research projects that involve multiple sites, and of RCTs embedded in practice settings.
 - b. Examples of successful innovations within the system or network to support patient recruitment and participation in clinical research based in practice settings are welcome.
 - c. The application clearly describes proposed efforts to improve and streamline the patient consent process and the IRB approval and oversight process during the award period.
11. Clear, thoroughly described and proven policies to maintain data security, patient privacy, and confidentiality, as well as organizational privacy.

The vision of a national patient-centered clinical research network for conducting CER relies on the support and trust of individual patients, of the clinicians and healthcare systems participating in and providing data to the network, and of the public. The applicant should describe current practices, with respect to data acquisition, linkage, storage, analysis, and transmission that are directed toward protecting the security and confidentiality of individual-level clinical data.

Describe efforts that will be undertaken during the 18-month period to further enhance data security, including development of written policies and practices, the testing of methods for de-identifying data, and development of new approaches to secure data sharing and de-identification of data sharing across systems. Efforts to inform patients and clinicians of these policies and research activities and to enlist their support are of great interest. Comply with all federal (eg., HIPAA), state, and health system requirements regarding patient privacy and health system data protection issues is expected and should be discussed. Any current deficiencies addressed.

RC11.

- a. The application describes current policies and practices to ensure data security, including those required to adhere to federal, state, and health system requirements.
- b. The application clearly describes any capacities and resources that will be developed by the project to ensure that data security is preserved as the addition of new health systems to the network, sharing of data with other networks, acquisition of new types of data (e.g., biospecimens, patient reported outcomes), and sharing of data with external researchers occur.

12. Ability to collect, store, retrieve, process and/or ship biological specimens for research purposes.

Some healthcare systems have begun to archive stored biospecimens, either from material remaining after clinical tests are performed or via special specimen collection efforts. Archived biospecimens present major opportunities to conduct certain types of CER studies, particularly those that focus on identifying potential differences in treatment responsiveness and comparative effectiveness as a function of biomarkers or genotypic traits.

Describe efforts already underway within the network or new efforts that will be expanded or initiated with funding during this 18-month work period to collect and store biospecimens. Provide estimates of the target numbers and types of specimens (e.g., DNA, serum, whole blood, sputum, pathology specimens) anticipated by the end of the work period. Describe plans for developing appropriate annotation and storage documentation to support future research as part of the resource. Describe carefully the approach to obtaining informed consent and to human subjects protection that will be developed to ensure that specimens may be used in future research with the full consent of the patients involved. If a biorepository already exists within the network, or if the network contributes biospecimens to other national biorepositories, describe these activities, including any research uses to which the specimen data have contributed.

RC12.

- a. The application clearly describes the current capacity, if any, of the network to acquire, store, archive, annotate, and make biospecimens available for research, including the type of biospecimens collected, facilities for quality control and storage, IT and informatics systems for inventory control and sharing, policies and procedures for informed consent, and protection of patient privacy.
- b. The application demonstrates a full appreciation of the human subjects issues related to obtaining consent for future use of stored biospecimens.
- c. The application clearly describes proposed steps for expanding the size, scope, and quality of this resource and indicates the type of research studies that such an enhanced resource could support.
- d. For those institutions without the capacity to store and share banked biospecimens at their facilities, or that wish to consider working with a biospecimen repository, such as RD-HUB or a similar repository, knowledge of the policies and practices of the biorepository is demonstrated

and plans for contributing are presented, including estimates of the potential numbers and types of biospecimens.

13. Centralized monitoring for review of progress with ongoing studies to identify and address unanticipated problems or issues.

Monitoring of progress throughout the 18-month period will be conducted by PCORI, with the assistance of the coordinating center, and under the oversight of the steering committee. PCORI reserves the right to discontinue funding of a network at the nine-to-12 month point within the funding period, if it becomes clear that an awardee will be unwilling or unable to realize the intended aims of the cooperative agreement.

Applicants should identify key milestones for their proposed activities under each technical requirement at six, 12, and 18 months.

RC13.

- a. The application includes a description of key milestones for each proposed activity. Some milestones may be the result of work on two or more of the proposal's technical requirements.
- b. The application demonstrates a clear organizational chart for the network and adequate capacity and procedures at the network level to monitor and report its progress periodically, to ensure the quality of work, and adherence to stated project aims and milestones.

14. Clear description of the efficient use of human and other resources to accomplish the work.

PCORI envisions that a mature national patient-centered clinical research network will be a lean, efficient, and potentially sustainable endeavor. PCORI evaluates all applications in terms of the efficiency with which resources are proposed to be used. Budget items must be clearly linked to proposed activities within each requirement and in a budget justification. Efficiency is expected not only during the funding period, but as a key strategy for sustainability into the future.

Describe how the budget requested aligns with project plans and how it reflects efficiency within the network. Describe any aspects of the project's organization or financing that may help to sustain the network after the growth and expansion accomplished with PCORI funding. Plans for making the ongoing maintenance of the infrastructure affordable, including the identification of multiple uses of the data both within and outside of the system, or of other funding streams within or outside the network, are of particular interest.

RC14.

- a. The application provides a clear and well organized explanation of the human, technical, and organizational resources that will be required and the tasks for which the resources are being requested throughout the 18 months of the project.
- b. All items in the proposed budget are justified in terms of resources and activities associated with the work tasks described.
- c. The application describes attention to future efficiency and value in the operation of the network and its participation in a national patient-centered clinical research network.

- d. The application demonstrates adequate administrative, statistical, and data organizational management facilities.
- e. The application describes institutional assurance to provide support to the study in such areas as fiscal administration, personnel management, space allocation, procurement, planning, and budgeting.

B. Review and Selection Process

PCORI conducts rigorous merit reviews of all applications for all PCORI Funding Announcements (PFAs). In order to promote quality scientific research, while ensuring patient-centeredness, the PCORI merit review is distinguished by the full participation of scientists, patients and their caregivers, and other stakeholders in the process. The review process includes online review, in-person merit review, and post-panel assessment. You can learn more about the PCORI standard review process [here](#).

PCORI's merit review panels are composed of scientific reviewers, patients, and other stakeholders. At least 30 percent of review panel members are non-scientists. Moreover, not all scientists will be specialized in the topic of your research. Therefore, applicants are strongly advised to write their applications as clearly as possible without losing scientific meaning. Although applications will not be directly scored on the clarity of writing, clearly written proposals will have an advantage. Particular attention should be paid to the clarity of the lay abstract and to discussions of patient-centeredness and the engagement of patients and other stakeholders on the research team.

A summary of the general review process is as follows:

1. Full proposals receive an internal review by PCORI staff.
2. Online external review: reviewers provide qualitative critiques and quantitative scores for the applications. Each application will be reviewed by two external scientists, one patient, and one stakeholder.
3. In-person merit review: final review and discussion by external reviewers.
4. PCORI scientific staff makes preliminary funding recommendation to PCORI selection committee. *
5. PCORI selection committee makes final funding recommendation to PCORI Board of Governors (BoG).
6. PCORI BoG makes final decision.
7. PCORI staff conducts a business review to evaluate and possibly negotiate aspects of the budget.

* PCORI selection committee includes PCORI Board of Governors members, PCORI executive leader, and PCORI scientific personnel.

You should carefully read and thoroughly understand the PCORI review criteria as listed in the description of each technical requirement. Participants in the merit review process will be asked to use these criteria in evaluating and scoring applications.



IV. Application and Submission Guidelines

Please refer to the Application and Submission Guidelines document [here](#) for detailed instructions of how to submit your LOI and full application via PCORI Online System.

A. Letters of Intent

PCORI recognizes that the range of applicants to this announcement may be broad and diverse and that not all potential applicants may be a good fit at this point. To reduce excessive work on the part of applicants and to reduce the time and resource requirements for technical review, prospective applicants for Phase One must submit a letter of intent (LOI) via PCORI Online System. Applicants are also encouraged to contact PCORI staff before and after submission of the LOI to ensure production of optimally responsive applications. LOIs will be reviewed based on the fit of the applicant network with the goals of the PFA and feasibility to complete work within budget and project period proposed. Applicants are encouraged to submit the LOI as early as feasible, rather than waiting for the submission deadline for LOIs. We emphasize again that new networks are encouraged to apply.

B. Funding and Project Period Limits

Total project costs are limited to a maximum of \$7 million, and projects must take no longer than 18 months to complete. Total awards include indirect costs calculated as 40 percent of direct costs. Applicants who wish to apply for a larger award must contact PCORI prior to the due date for the LOI to explain why a larger award could present extraordinary opportunities to build a national patient-centered clinical research network. PCORI does not guarantee that permission will be granted. Efficient use of research resources is a criterion that will be considered by merit reviewers, and proposed budgets will be reviewed by PCORI staff.

Efficient use of research resources is a criterion that will be considered by merit reviewers and will also be reviewed by PCORI staff. The total amount awarded and the number of awards will depend on the quality, duration, and costs of the applications received.

PCORI also reserves the right to discontinue funding for awardees that fail to meet the mutually agreed upon milestones at any time during the award. In addition, a go/no-go decision will occur after six months of the award. Proposed milestones should be presented in the application, but final milestones will be negotiated in the post-award period prior to the beginning of the funding period. Details of this policy will be outlined in the contract of these awards.

About PCORI

The Patient-Centered Outcomes Research Institute (PCORI) is an independent organization created to help people make informed healthcare decisions and improve healthcare delivery. PCORI will commission research that is guided by patients, caregivers, and the broader healthcare community and will produce high integrity, evidence-based information.

PCORI is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI will use a variety of forums and public comment periods to obtain public input throughout its work.

Our Mission: PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.

Our History: PCORI was created by the Patient Protection and Affordable Care Act of 2010 as a non-profit, nongovernmental organization. PCORI’s purpose, as defined by the law, is to help patients, clinicians, purchasers, and policy makers make better informed health decisions by “advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions.”

The statutory language defining PCORI is broad and authorizes research that will support a strong patient-centered orientation, inform better choices among alternative treatment and prevention strategies, and direct attention to individual and system differences that may influence strategies and outcomes. PCORI was designed to produce knowledge through the analysis and synthesis of existing research or the support of new research.