

PCORnet: Building Evidence through Collaboration and Innovation

Next Generation Distributed Research

The Patient-Centered Outcomes Research Institute (PCORI) is a statutorily recognized body authorized to prioritize and fund comparative effectiveness research (CER) to develop the evidence needed to better understand patients' prevention, treatment and care options. PCORI recently awarded \$93 million to begin construction of the National Patient-Centered Clinical Research Network (PCORnet), an ambitious clinical research network focused on patient-centered priorities for CER.¹ PCORnet will represent the next generation of distributed research networks combining patient-generated data with clinical data collected in "real world" settings. It is hoped that as governance processes and policies become uniformly implemented across the network, PCORnet will usher in a new frontier of next generation, rapid-learning research. The expanded and improved capacity to conduct CER will reduce the time and effort needed to launch new research and develop innovative CER methodological approaches, such as observational studies and interventional trials, transforming health research from researcher-driven to patient-centered research.

As the first step in establishing a shared vision of PCORnet, the Engelberg Center on Health Care Reform at the Brookings Institution is hosting the **"PCORnet: Building Evidence through Innovation and Collaboration"** in Washington, DC January 21-22, 2014. There are a number of organizational, technical and cultural challenges that must be addressed in order for PCORnet to achieve its objectives. This will require engaging providers, patients, leaders of health system organizations, and a wide variety of other stakeholders to develop partnerships within PCORnet that are built on the principles of shared responsibility, mutual respect, trust, and inclusiveness.

Current Challenges and Motivation for PCORnet

Historically, clinical research used by the U.S. Food and Drug Administration (FDA) for regulatory approval for drugs, is conducted under "ideal conditions" (i.e. efficacy research) where results are population-oriented and not necessarily generalizable to any given individual or situation. Effectiveness research seeks to investigate how well a given health technology or intervention performs relative to other available treatment options. This requires gathering data from real-world clinical experiences of patients within the health care system. This data allows researchers to ask key questions that can be

¹ PCORI. PCORI Awards \$93.5 Million to Develop National Network to Support More Efficient Patient-Centered Research. Dec. 18, 2013. Available at: <http://www.pcori.org/2013/pcori-awards-93-5-million-to-develop-national-network-to-support-more-efficient-patient-centered-research>.

tailored to a similar cohort of individuals with a given set of circumstances. Results would yield important insights and help inform both clinician and patient on best available treatment options, facilitating shared-decision making and achieving the goals and priorities of the patient. Currently there are many, significant barriers that impede this type of research which include:²

- 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 can be costly and inefficient, and finally,
- Obtaining informed consent can be cumbersome and Institutional Review Boards (IRB) may not understand the low-risk nature of studies nor the adverse impact of excessive IRB requirements on study feasibility and validity.

To begin addressing some of these real, practical challenges, The Recovery Act of 2009 (Public Law 111-5) appropriated \$1.1 billion to support a national CER infrastructure. This initial investment seeded the establishment of PCORI and authorized the Federal Coordinating Council (FCC) for Comparative Effectiveness Research to prioritize and coordinate CER activities across Federal agencies. The Recovery Act also tasked the IOM with establishing a list of research questions and conditions that should be given the highest priority for CER studies.³ Building on this report, the FCC released a set of visionary recommendations to the U.S. President and Congress that established a common definition of CER, a strategic framework, and identified prioritization criteria for CER investments.^{4,5} Additionally, the FCC identified seven core needs for developing a national infrastructure to advance CER aims as depicted in Table 1 below. Collectively, these challenges hint at a fundamental and crosscutting issue that has hindered the research community: the lack of access to diverse data sources across large populations.

In addition to the challenges involved with developing the evidence, shortcomings in the nation's health information infrastructure have fragmented information flows and prevented collaborative environments to conduct research.⁶ Absent is an effective mechanism to standardize the collection,

² PCORI. CDRN-Funding-Announcement. April 23, 2013. Available at: <http://www.pcori.org/assets/PCORI-CDRN-Funding-Announcement-042313.pdf>

³ Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: National Academies Press; 2009. Available at: http://www.nap.edu/catalog.php?record_id=12648

⁴ Defined CER as the "conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."

⁵ US Department of Health and Human Services, Federal Coordinating Council for Comparative Effectiveness Research. Report to the president and the Congress. Washington, DC: 2009 Jun 30.

⁶ NCVHS, *Information for Health—A Strategy for Building the National Health Information Infrastructure*, 15 November 2002. Available at: <http://www.ncvhs.hhs.gov/nhiilayo.pdf>

aggregation and widespread transfer of information to the point of need. Digitizing the health system with electronic health records (EHRs) could provide a shared platform to reduce the cost and complexity of designing studies and facilitates access to the information needed to answer research questions that are meaningful to both practitioner and patient.

Table 1. CER infrastructure gaps identified by the Federal Coordinating Council for Comparative Effectiveness Research.

Coordination across the CER framework	<ul style="list-style-type: none"> • Substantial CER assets exist across the Federal Government, but coordination is necessary to capture their full value
Research	<ul style="list-style-type: none"> • Many comparative, patient-centered research questions remain unanswered.
Human and Scientific Capital	<ul style="list-style-type: none"> • CER methods development needed • Limited trained research for conducting CER
CER Data Infrastructure	<ul style="list-style-type: none"> • Fragmented data • Data sources limited in terms of clinical robustness of data and longitudinal data capture • Data capture and feedback loop at point of care often lacking
Dissemination and Translation of CER	<ul style="list-style-type: none"> • Suboptimal dissemination and translation of CER findings to patients and clinicians • Limited linkages between CER findings and directly improving patient outcomes
Priority Populations	<ul style="list-style-type: none"> • Limited information on many priority populations and sub-groups
Priority Interventions	<ul style="list-style-type: none"> • Less information on certain comparative interventions such as behavioral change, procedures, devices, delivery system strategies, and prevention

Source: Adapted from FCC for CER Report to the President and Congress, June 30, 2009

There is growing interest and support in moving to a health system that uses routine collection of electronic data to develop much better evidence from clinical practice - a learning health care system. A number of Federal initiatives have sought to support this goal, particularly the \$30 billion "meaningful use" incentive payment program for adopting certified EHRs contained in the Health Information Technology for Economic and Clinical Health Act (HITECH) as part of the Recovery Act.⁷ To support efficient, routine, large-scale comparative effectiveness research more progress is needed, but Federal initiatives alongside private efforts to adopt health information technologies are reducing historical data infrastructure barriers making rapid communication between providers and health systems a reality.⁸ PCORnet represents a significant step towards a rapid-learning health care system by utilizing a digital

⁷ The Medicare and Medicaid EHR Incentive Programs are jointly implemented by the Centers for Medicare & Medicaid Services and the Office of the National Coordinator for Health Information Technology. See: <http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html>.

⁸ The Care Connectivity Consortia is an example of private led efforts to use electronic health records to share health information between health systems. For more information see: <http://www.careconnectivity.org/about/details/>

health information infrastructure to enable new types of research yielding innovative solutions to existing challenges in the CER landscape.

Conceptualizing the National Patient-Centered Clinical Research Network

Building upon these substantial investments in CER and health information technologies, PCORnet is poised to deliver on the nation's call to action to fill existing infrastructure gaps and curate meaningful, patient-centered research. The following provides an overview of potential areas where PCORnet will add significant value and fill existing research needs.

Coordinating Research. There is a large body of CER evidence that currently exists and continues to grow. However, research activities across the Federal government and private sectors have not been well coordinated. CER resources and inputs are not being efficiently used in the absence of well-documented research efforts and without the capability to discover and connect similar research aims.⁹ PCORnet will fill this gap seeking to coordinate previously fragmented information sources for tracking populations and treatments.

Improving research methods. A common challenge in designing CER studies is the tradeoffs researchers must make between establishing internal validity of the study and the external validity of patient-centered outcomes. This tension has caused many important research questions to remain unanswered. PCORnet is set to pioneer innovative study design methods for CER as a result of having access to a large, highly representative network that will facilitate the collection of varied and comprehensive cohorts to enable enhanced observational and interventional studies. Innovations in study methodologies will bring pragmatic approaches so that researchers can use the full breadth of patient and clinical information collected from real world settings. This will lead to increases in the acceptance and adoption of CER results in clinical settings.

Engaging patients and integrating patient generated information. Greater involvement of stakeholders (e.g., patient advocates, health professionals, researchers, technology manufacturers, payers) in CER processes can help to achieve the goals of CER, including more informed priority setting, input on certain aspects of study design (e.g., identification of important subgroups and patient-centered outcomes), and identification of target audiences for CER and strategies to reach them. PCORnet will investigate challenges to engaging patients and providers together for the purposes of a comprehensive network model at all levels (e.g. governance, core technical capabilities, metrics, and engagement). Given the wide stakeholder solicitation and synthesis of PCORnet, it will work towards the balancing of research priorities and stakeholder needs. By requiring that health systems, clinicians, and patients who generate information be involved in all aspects of the governance and use of this information, PCORnet is shifting health research from researcher-driven to patient-centered research. Patient participation and buy-in will be key in facilitating patient reported outcomes (PROs) and other related measures of patient experience. Given the increasingly expanding and fragmented nature of the current PRO landscape, PCORnet will lead the development of pragmatic methods to accommodate patient generated information into research efforts.

⁹ US Department of Health and Human Services, Federal Coordinating Council for Comparative Effectiveness Research. Report to the president and the Congress. Washington, DC: 2009 Jun 30.

Guiding Principles for PCORnet

- **Trust and Transparency.** The success of PCORnet research will largely depend on the level of trust established by Partner networks. Trust can only be established through transparent and open processes to ensure equal representation on decision-making and prioritization.
- **Inclusiveness and Diverse Representation.** The hallmark of PCORnet will be patient engagement at all levels of CER, giving researchers decisive data and patients better outcomes. By including diverse sets of patients in research activities, PCORnet will be the first distributed research network to bring patient-centered outcomes research to national scale.
- **Distributed Governance.** PCORnet and its Partners will need to develop reproducible research by using uniform protocols and governance models to reduce organizational and cultural boundaries to network initiated research. Streamlining protocols for governance structures like institutional review boards (IRBs) and research contracts will be necessary in reducing the time from research proposal to the first patient enrolled in a study.
- **Continuous Learning.** Aggregation and dissemination of CER results will be critical to delivering this value to patient populations. Generating timely research results with real world applications and allowing patients to effectively inform themselves of these findings will be crucial.

PCORnet Organization and Structure

To implement a nationally representative patient-centered clinical research network that unites patients, researchers, and health care systems, three core components will be the fundamental building blocks of PCORnet's infrastructure: 1) Partner Networks, 2) an Executive Body, and 3) Coordinating Center. A visual depiction of these structures is provided in Figure 1.

Partner Networks

The core components of PCORnet are the partner networks. Each partner network has a Principal Investigator leading the PCORnet initiative for their individual network. A network may consist of multiple organizations that are partnering to satisfy eligibility requirements for participation identified in PCORI's Funding Announcement issued in 2013.¹⁰ Eligibility criteria were developed to identify two categories of data networks: Clinical Data Research Networks and Patient-Powered Research Networks.

CDRNs

Clinical Data Research Networks (CDRN) are system-based networks that originate in health care settings, such as hospitals, health plans, federally qualified health centers, or other practice-based networks, and securely collect health information during the routine course of patient care. CDRNs will strive to:

- stimulate broader participation of patients, clinicians, health systems, and payers in developing, governing, and using large databases of clinical information;

¹⁰ PCORI Funding Announcement. Available at: <http://www.pcori.org/assets/2013/07/PCORI-Coordinating-Center-RFP-Questions-Answers-070213.pdf>

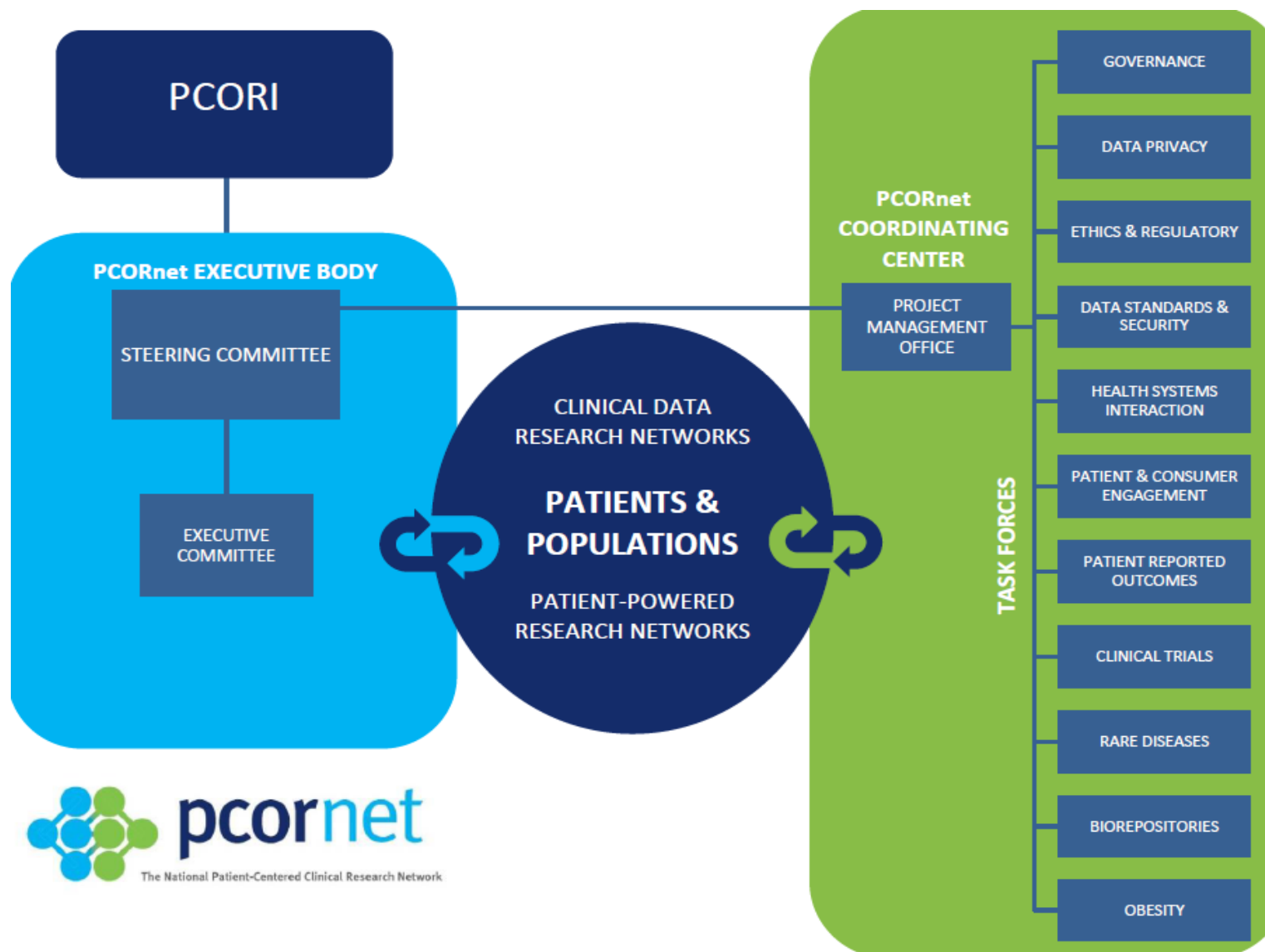


Figure 1. PCORnet Organizational Chart

- facilitate rapid, efficient conduct of both randomized trials and observational studies within care delivery systems using the network infrastructure; and
- promote and support greater collaboration and information sharing between networks based on standardized, interoperable data structures.¹¹

PPRNs

Patient-Powered Research Networks (PPRNs) are networks operated and governed by groups of patients and their partners. They are focused on a particular condition and interested in sharing health information and participating in research. PPRNs are intended to further explore patient---centered approaches to network governance; research topic selection; research recruitment and participation; inclusion of broad, diverse, activated patient communities; and interoperability with other elements in the national patient-centered clinical research network.²¹

Executive Body

The Executive Body (EB) is composed of a Steering Committee (SC) and Executive Committee (EC). The SC is responsible for implementing the PCORnet vision through strategic planning, prioritization, oversight and as an advisory group to PCORI leadership. The SC is comprised of a broad range of representatives including PCORI leadership, each partner network, federal and private agencies, and the Coordinating Center. The SC guides the development of PCORnet by initiating governance and policy recommendations on key issues such as methods for EHRs, privacy and ethical considerations involving research, and technical capabilities to facilitate distributed querying across networks. The SC will be the main venue to promote partnership and consensus among the network and engage health care system leadership to support national-scale effectiveness research. The EC will address tasks assigned to it by the full SC, which may include recommending policies, procedures, and working in concert with the Task Forces.

Coordinating Center

The Coordinating Center is charged with providing technical and logistical expertise and assistance to facilitate connections across CDRNs and PPRNs, implement SC recommendations, and ultimately to achieve PCORnet strategic goals. The CC is comprised of two components: the Project Management Office (PMO) and the Task Forces.

Project Management Office

The PMO oversees the core functions of Program Management, Technical Assistance, Cross Awardee Activities, Evaluation and Logistical Support. The PMO will support the implementation of recommendations from the SC and is responsible for overall coordination and implementation of distributed research through PCORnet.¹² The PMO will oversee, support and coordinate working groups called Task Forces, including providing the technical assistance and infrastructure for information sharing across CDRNs and PPRNs to identify and disseminate best practices and policies.

¹¹ National Patient---Centered Clinical Research Network: The Concept: www.pcori.org/assets/2013/12/PCORI-National-Patient-Centered-Clinical-Research-Network-Snapshot.pdf.

¹² The National Patient-Centered Clinical Research Network webpage: <http://pcornet.org>.

Task Forces

Task Forces are the workgroups that will address specific issues identified as key to building PCORnet's infrastructure: Governance, Data Privacy, Ethics & Regulatory, Data Standards and Security, health System Interaction, Patient & Consumer Engagement, Patient Generated Outcomes, Clinical Trials, Rare Diseases, Biorepositories and Obesity. Charters and work plans established by each Task Force will be used to guide these activities ensuring work is coordinated and purposed to meet the milestones and deliverables of each respective Task Force. Task Forces will be led by national subject matter experts with co-chairs and membership derived from PPRN and CDRN representatives.

Defining Success

Over the next 18-months, PCORI will be working with the PPRNs, CDRNs, Coordinating Center, and other stakeholders to refine the capabilities and capacity of partnering networks. The vision, structure and scale for collaboration among partnering networks makes PCORnet a once-in-a-generation opportunity to improve not only health care research but more broadly – health.

As is the case with all blueprints, the challenge lies with execution. To achieve PCORnet's aim, three overarching strategies will be critical: 1) Leveraging and building on insights gained from existing distributed network initiatives, 2) Creating a shared culture of trust, mutual respect and inclusiveness to shape a community trust fabric, and 3) Developing a governance infrastructure that promotes uniform practices and policies to reduce the cost and complexity of research. By the end of the initial 18-month funding period, PCORI expects a single functional multi-center distributed research network to be in place with the following characteristics:¹³

- Patients, providers and health system leaders will be highly engaged in various aspects of PCORnet, with diverse populations enrolled for studies and patient cohorts successfully identified, characterized and surveyed.
- Able to support multi-center observational and interventional CER studies as well as other types of research (drug safety, etiologic studies and surveillance of clinical practice, etc.). This entails successfully standardizing data within a Partner's network.
- Open and available to external research affiliates willing to participate in observational and interventional studies alongside the PCORI-funded.
- Patients, health systems, and clinicians are engaged in governance goals and use of the network.
- Capability for implementing CER studies and opportunity for Partners to use the resources created with PCORI's support for a wide range of activities supported by other organizations.

The next 18-months will be critical in setting a solid foundation for PCORnet and its long-term success. Success for PCORnet can be defined as a network that not only enhances CER opportunities for all network Partners but does so without compromising existing resources or efforts. This vision can only be reached through collaborative and active engagement in the network. With the inaugural kickoff event, "PCORnet: Building Evidence through Innovation and Collaboration" a course is now set for transformative change in how research can be designed and implemented to answer questions that are meaningful to patients and clinicians, improving both quality and the delivery of health care in the United States.

¹³ Appendix C details the specific objectives relevant to CDRNs and PPRNs.

Appendix A: Task Force Descriptions

Task Force	Description	Leads
BIOREPOSITORIES	Develop and implement systematic approaches that support a regulatory-compliant, comprehensive, and sustainable network-wide biorepository to serve the PCORI NCRN research endeavors.	Kristin Newby, Duke Clinical Research Institute
CLINICAL TRIALS	Provide guidance on methods, standards and quality by designing principles for clinical trials using PCORnet. The TF will develop the pathway for the first PCORnet interventional clinical trial.	Robert Califf, Duke Clinical Research Institute
DATA PRIVACY	The Task Force will work collectively with the CDRNs and PPRNs to develop a set of privacy policies to govern information sharing by PCORnet. The Task Force also will identify privacy issues raising particular challenges for the PCORnet participants and draft white papers highlighting promising or best practices for addressing them.	Deven McGraw, Center for Democracy & Technology
DATA STANDARDS, SECURITY, AND NETWORK INFRASTRUCTURE	Create the PCORI Distributed Research Network, a functional distributed research network that facilitates multi-site patient-centered research across the CDRNs, PPRNs, and other interested contributors. The distributed network will enable to conduct of observational research and clinical trials while allowing each participating organization to maintain physical and operational control over its data. Members of this Task Force will contribute to the establishment of this network, through which all CDRN and PPRN members will be able to receive and execute distributed programs and return results.	Jeffrey Brown, Harvard Pilgrim Health Care Institute Lesley Curtis, Duke Clinical Research Institute Ed Hammond, Duke Clinical Research Institute
ETHICS & REGULATORY	The primary goal of the Ethics and Regulatory Task Force is to assist PCORI in addressing the ethical and regulatory issues related to research that arise in its work. By doing so, the responsible stakeholders should be better positioned to meet their ethical obligations towards patients and research participants as well as being in compliance with regulatory requirements regarding health related research. The Task Force will also generate solutions to problems that may involve novel approaches within the network to increase efficiency while meeting ethical and regulatory	Jeremy Sugarman, Johns Hopkins Berman Institute of Bioethics Robert Califf, Duke Clinical Research Institute Joseph Ali, Johns Hopkins Berman Institute of Bioethics

	obligations.	
GOVERNANCE & COLLABORATION	<p>Assist the CDRNs/PPRNs with establishing a culture of trust and collaboration among their Partners, as well as with each other, and with other external parties who participate in PCORnet activities. This will require clear governance policies and procedures that articulate the goals and purposes of the networks, establish transparent processes, and emphasize a forward thinking approach to both infrastructure development and future research activities. The key governance topics include:</p> <ol style="list-style-type: none"> 1) Stakeholder/Patient Engagement; 2) Leadership; 3) Human Subjects Policies (regulatory and ethical oversight); 4) Data Use (includes: Data Use Agreements (DUAs), Business Associate Agreements (BAAs), Data Sharing, Data Security, and Data Safety and Monitoring Boards); 5) Conflict of Interest; 6) Intellectual Property; 7) Privacy of Personal Information; and 8) Reproducibility of Research 	<p>Richard Platt, Harvard Pilgrim Health Care Institute</p> <p>Erin Holve, AcademyHealth</p>
HEALTH SYSTEMS INTERACTIONS	<p>Creating a supportive environment and sense of community across CDRNs; establishing trust, common goals, and a safe forum for shared learning; promoting collaboration across Task Forces when issues overlap; and connecting CDRNs with resources both in and outside of the PCORnet Coordinating Center to help them succeed.</p> <p>The Health Systems Interactions Task Force will specifically seek to:</p> <ol style="list-style-type: none"> 1) Establish a common vision of health systems involvement and sustainability. 2) Create a safe, neutral forum to meet and share needs and solutions to common challenges. 3) Explore concerns about research involvement and information sharing common to health systems (e.g., patient trust, proprietary interests, provider burden; impacts on workflow). 4) Assist CDRNs in developing consensus strategies and resolving controversial issues. 5) Facilitate alignment and standardization of 	<p>Eric Larson, Group Health Research Institute</p> <p>Katherine Newton, Group Health Research Institute</p>

	<p>practices across CDRNs to optimize activities.</p> <p>6) Assess training needs, develop training materials, and contribute to training opportunities.</p> <p>7) Provide subject matter expert consultation.</p>	
OBESITY	Facilitate and coordinate the construction of the obesity cohort at each of the CDRNs, and to assess its feasibility, quality and interoperability within the CDRNs and the PPRNs	Matthew W. Gillman, Harvard Pilgrim Health Care Institute
PATIENT & CONSUMER ENGAGEMENT	Ensure active and effective engagement of patients and consumers in the design and implementation of all components of PCORnet by serving as a technical resource for innovative problem solving, cross-project communication and application of cutting edge methods.	Sean Tunis, Center for Medical Technology Policy
PATIENT-REPORTED OUTCOMES (PROS)	Focus on strategies, tools, and resources related to the measurement, collection, and analysis of patient-generated information, including patient-reported outcomes data. PCORnet aims to add the domain of patient-reported information and outcomes (broadly termed PROs) to existing research data resources, and facilitate their use in planned research.	Amy Abernethy, Duke Clinical Research Institute
RARE DISEASES	<p>Support CDRNs and PPRNs in identifying populations, developing research priorities, designing, and implementing studies for rare diseases</p> <ul style="list-style-type: none"> • Act as discussion and advocacy forum to identify and advocate for needs specific to rare disease research. • Serve as a resource for PCORI on matters related to patient-centered outcomes research in rare disorders in PCORnet. 	<p>Priya Kishnani, Duke Clinical Research Institute</p> <p>Rachel Richesson, Duke Clinical Research Institute</p>

Appendix B: CDRN and PPRN deliverables at end of 18-months.

CDRN Objectives	PPRN Objectives
Coverage of at least one million people, 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 regardless of the site at which care is delivered.	PPRNs will be comprised of patients linked by a common condition, and may also include interested caregivers or clinicians, enthusiastic about participating in patient-centered outcomes research, including the potential to contribute research ideas, share information, adhere to protocols, and participate in observational studies and randomized clinical trials.
Involvement of multiple health systems, with data interoperability and data standardization to allow efficient, valid sharing of both individual and aggregate information across the PCORnet DRN.	Ability to collect information from patients that is suitable for research from at least 50,000 patients (less for patients with rare disorders). Develop a governance structure and operating policies that ensure patient control, that can establish relationships with qualified researchers and that can generate research questions from the community's membership and accumulate relevant clinical and patient-reported outcomes data from at least 80% of its membership.
Participation in the PCORnet DRN, that conforms to uniform data standards and networking capability.	Plan for participation in the PCORnet DRN that conforms to uniform data standards and networking capability.
Willingness and ability to share clinical information and a commitment to develop appropriate data use agreements, business associate agreements, or similar contractual documents to enable the research to be conducted.	Develop strategies to enhance and report the diversity and the representativeness of the patient community as it expands.
Ability to efficiently identify and contact patients for the purposes of recruitment, randomization, participation, and follow-up, including collection of patient-reported information.	Active involvement in planning and conducting dissemination of research findings to patients and providers.
Demonstrated ability to engage substantial patient populations with selected conditions for purposes of generating research questions, participating in CDRN governance, or in appropriate research studies.	Ability to explore novel and efficient approaches for patient members to contribute their electronic clinical data to the PPRN.

CDRN Objectives	PPRN Objectives
Involvement of the health care system leadership in governance and use of the CDRN to enhance PCORnet’s efficiency, utility, and sustainability.	Ability to explore novel and efficient approaches for patient members to collect self-reported data, including use of remote monitoring devices, mobile apps, and self-reported observations of daily living.
Willingness to serve as a national data infrastructure resource for the conduct of comparative effectiveness research (CER) by researchers outside PCORnet.	Ability to streamline contracting processes for research involving multiple sites.
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 findings	Participation in the PCORnet Steering Committee.
Capacity to embed research activity within functioning health care systems without disrupting the business of providing health care.	
Alignment of human research participants’ oversight, IRB review and decision-making, 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.	
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.	
Ability to streamline contracting processes for research involving multiple sites.	
Participation in the PCORnet Steering Committee.	

Appendix C: Meet your Partners

The following table provides the names of the Principal Investigators for each PCORnet network Partner as well as their executive summaries from their original proposals. The executive summaries are located after the table below. This is intended to serve as tool to better acquaint yourself with your network Partners and learn more about their exciting prospective research.

Network	Principal Investigator	Organization
<i>Accelerating Data Value Across a National Community Health Center Network (ADVANCE)</i>	Jennifer DeVoe	OCHIN
<i>ALD Connect</i>	Florian Eichler	Massachusetts General Hospital
<i>American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network (ABOUT Network)</i>	Rebecca Sutphen	University of South Florida Morsani College of Medicine
<i>Arthritis Patient Partnership with Comparative Effectiveness Researchers (AR-poWER PPRN)</i>	Seth Ginsberg	Global Healthy Living Foundation
<i>CCFA Partners Patient Powered Research Network</i>	R.Balfour Sartor	Crohn's and Colitis Foundation of America
<i>Chicago Area Patient Centered Outcomes Research Network (CAPriCORN)</i>	Terry Mazany	The Chicago Community Trust
<i>Community Engaged Network for All (CENA)</i>	Sharon Terry	Genetic Alliance
<i>Great Plains Collaborative (GPC)</i>	Lemuel Waitman	University of Kansas Medical Center
<i>ImproveCareNow: A Learning Health System for Children with Crohn's Disease or Ulcerative Colitis</i>	Peter Margolis	Cincinnati Children's Hospital Medical Center
<i>Kaiser Permanente & Strategic Partners Patient Outcomes Research to Advance Learning (PORTAL) Network</i>	Elizabeth McGlynn	Kaiser Permanente
<i>Louisiana CDRN (LACDRN)</i>	Anjum Khurshid	Louisiana Public Health Institute
<i>Mid-South CDRN</i>	Russell Rothman	Mid-South CDRN (Vanderbilt)
<i>Mood Patient-Powered Research Network</i>	Andrew Nierenberg	Massachusetts General Hospital
<i>Multiple Sclerosis Patient Powered Research Network</i>	Robert McBurney	Accelerated Cure Project for MS

Network	Principal Investigator	Organization
<i>National Pediatric Learning Health System (PEDSnet)</i>	Christopher Forrest	PEDSnet
<i>NephCure Kidney Network for Patients with Nephrotic Syndrome</i>	Bruce Robinson	Arbor Research Collaborative for Health
<i>New York City Clinical Data Research Network (NYC-CDRN)</i>	Rainu Kaushal	Weill Cornell Medical College
<i>P2aTH: Towards a Learning Health System in the Mid-Atlantic Region</i>	Rachel Hess	University of Pittsburgh and UPMC
<i>Patient Oriented Scalable National Network for Effectiveness Research (pSCANNER)</i>	Lucila Ohno-Machado	University of California San Diego
<i>Patient Research Connection: PI-Connect</i>	Kathleen Sullivan	Immune Deficiency Foundation/USIDNET
<i>Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium</i>	Laura Schanberg	Duke University Medical Center/PARTNERS
<i>Phelan-McDermid Syndrome Data Network</i>	Megan O'Boyle	Phelan-McDermid Syndrome Foundation
<i>Rare Epilepsy Network (REN)</i>	Janice Buelow	Epilepsy Foundation
<i>Scalable Collaborative Infrastructure for a Learning Health care System (SCILHS)</i>	Kenneth Mandl	Harvard Medical School
<i>Sleep-Apnea-Patient Centered OutcomesNetwork (SA-PCON)</i>	Susan Redline	Brigham and Women's Hospital
<i>The COPD Patient Powered Research Network</i>	Richard Mularski	Kaiser-The Center for Health Research & The COPD Foundation
<i>The DuchenneConnect Patient-Report Registry Infrastructure Project</i>	Holly Peay	Parent Project Muscular Dystrophy
<i>The Health eHeart Alliance</i>	Mark Pletcher	University of California, SF
<i>The Vasculitis Patient Powered Research Network</i>	Peter Merkel	University of Pennsylvania

Clinical Data Research Networks (CDRNS)

Scalable Collaborative Infrastructure for a Learning Health System (SCILHS)

Principal Investigator: Kenneth Mandl, MD, MPH

Fifteen years ago, we began our quest to develop informatics infrastructure and regulatory innovation that would convert the emerging electronic health record (EHR) into a research tool that could improve patient outcomes. First, we built Indivo, the first personally controlled health record, which gave patients their data, and apps to make that data useful. Then, i2b2 (Informatics for Integrating Biology and the Bedside), built an open source “sidecar” to the EHR, to fuse and analyze data produced by the delivery system, and identify research cohorts. The i2b2 flexible common data model readily accommodates all data types. Our next advance was SHRINE (Shared Health Research Information Network) a tool enabling investigators to query i2b2 sidecars across multiple sites simultaneously. i2b2-SHRINE has been successfully implemented at more than 100 sites across the US thereby enabling investigators to use delivery system data to identify patients with specific illnesses and clinical characteristics. At least three other CDRN applications are using i2b2 and SHRINE, attesting to their value and dissemination. Finally, we built SMART—a platform to enable any developer to contribute to an “App Store for Health and Research” compatible with i2b2-SHRINE instances or compliant EHR.

Although these informatics tools and regulatory advances have had the potential to be transformative, they have yet to substantially impact the health of our patients and those at risk. Until PCORI presented its focused challenge to the nation, we did not have sufficient vision or resources to address the critical collaborative patient-oriented questions that are necessary to improve human health. Nor had we fully partnered with our patients to define and continuously refine the nature of these questions and their outcomes. The opportunity to design a CDRN provided this vision but also catalyzed our interest, resolve, and commitment to focus our effort and resources on the objectives of PCORI. If funded, within 18 months, we will enable and share our informatics tools and join with our geographically and ethnically diverse PCORI network to partner with our patients and address the most important questions in pulmonary arterial hypertension, osteoarthritis, and obesity.

We will build, test, and deliver our Scalable Collaborative Infrastructure for a Learning Health System (SCILHS), which leverages the \$48 billion dollar federal investment in health IT to enable a common data model across 10 health systems covering more than 8 million patients, plugging universally into the point of care, generating evidence and discovery, and thereby enabling clinician and patient participation in research during the patient encounter. Central to the success of SCILHS is development of innovative “apps” to improve PCOR research methods and capacitate point of care functions such as consent, enrollment, randomization, and outreach for patient-reported outcomes. SCILHS adapts and extends an existing national research network formed on an advanced IT infrastructure built with open source, free, modular components. To achieve our goals and meet the metrics within this 18-month timeline, we have assembled a team of: clinical and patient stakeholders; internationally recognized medical computing and informatics experts; and leaders in the fields of PCOR, patient engagement, and regulatory innovation.

Our governance model includes patients, clinicians, health plan stakeholders and illness specific investigators who will ensure that we meet our goals and milestones. SCILHS will GENERATE research agendas, APPROVE studies, IDENTIFY participants from diverse populations, INFORM them about research, ENROLL them in trials, ENGAGE them, along with their families and providers, STUDY the cohort with ongoing bidirectional communication, and RETURN research results. Phase I addresses arthritis, pulmonary arterial hypertension and obesity, in pediatric and adult patients, at 10 diverse sites, including the major hospitals in Boston. We foster a virtuous cycle where shared information drives improved care and returns knowledge to participants, sustaining engagement and enabling all health care stakeholders to LEARN from every health care encounter.

SCILHS brings to PCORI the ability to leverage the federally mandated protocol (we lead with the White House design of “Blue Button” for data exchange among EHRs and patients) to promote data liquidity by interchanging data within SCILHS and sharing it with other CDRNs and PPRNs (10 PPRNs partner with us) as well as with NIH CTSAs and RMCI (Research Centers in Minority Institutions). We will deliver to PCORI, the CDRN network, and the

nation, the backbone for a “Learning Health care System.” Most importantly, SCILHS will ensure that the patient voice is “heard and listened to” and that our patients are our full partners in developing our studies, interpreting their outcomes, and prioritizing their impact on the health of the nation.

Mid-South Clinical Data Research Network

Principal Investigator: Russell Rothman, MD, MPA

The Southern United States has the highest rates of obesity, diabetes, cardiovascular disease, certain cancers, and other conditions, and significant rates of health disparities. We propose the development of a Mid-South Clinical Data Research Network (CDRN) centered at Vanderbilt University (VU). This Network will focus on health systems in the Southern United States that reach rural and urban populations, but will also include the capacity to reach a national population. Our proposed CDRN will encompass three large health systems: (1) the Vanderbilt Health System which currently includes electronic medical records for over 2 million patients, (2) the growing Vanderbilt Healthcare Affiliated Network (VHAN) which currently includes 32 hospitals, hundreds of ambulatory practices, and will cover over 3 million patients in the mid-South, and (3) a partnership with Greenway Medical Technologies and other national organizations to provide access to over 24 million patients across the country. These groups were deliberately assembled to provide synergy in constructing CER capabilities via diverse performance sites bringing different strengths.

Vanderbilt has developed a comprehensive electronic health record (EHR) system over nearly two decades, and is consistently ranked as one of the “Most Wired” health systems in the nation. The robust EHR includes all inpatient and outpatient clinical and administrative data, and is designed to interoperate with other health information technologies (HIT) and EHR systems. The EHR is implemented as a secure web-based system that can be rapidly customized as needed to store and integrate new forms of patient data through clinical templates or patient-facing surveys, and for new management interventions. A key advantage of using the Vanderbilt EHR system for this project is that it allows us the ability to control all aspects of how it is implemented, which will confer an agility to implement changes as new data and decisions are needed. Vanderbilt has also developed an array of complementary HIT tools that demonstrate our ability to produce a thriving CDRN including: 1) a web-based patient portal that currently includes 220,000 users, 2) validated algorithms that use claims data, clinical data, and natural language processing of text data to automatically identify patients with certain conditions and provide integrated clinical decision support, 3) patient-facing tools that allow for daily assessment of patient activities and patient reported outcomes, 4) the Synthetic Derivative, a tool that uses text processing and concept indexing to enable user-customized research on de-identified clinical data from all records in the EHR, and the Research Derivative tool for researching identifiable data, 5) Subject Locator tool for identifying patients with certain characteristics for study recruitment, 6) REDCap, our nationally adopted web-based data collection system, 7) BioVU, an integrated biologic repository with 175,000 DNA samples linked to de-identified patient data, and 8) ResearchMatch.org and CommunityResearchPartners.net, web-based tools for matching researchers, patients, and community organizations.

The proposed CDRN will allow us to: 1) expand our data network to include two other clinical data networks - the VHAN and Greenway systems, 2) develop data integration/interoperability between all sites across the 3 systems, 3) expand and optimize patient facing tools for collection of patient data, including research consent, behaviors, quality, adverse events, and outcomes; and, 4) improve our current tools for extracting and presenting data for research. This includes the integration of health information including genetic/epigenetic and biologic data, clinical data, claims data, birth/death certificate data, patient reported data, and other local and national data. We will also develop vital patient, provider and community engagement which will include active CDRN advisory boards, listening sessions to identify priorities and needs, and a more rigorous process for eliciting patient and provider input to specific research studies.

We will demonstrate CDRN capacity through identification, recruitment and data collection from three cohorts: 1) Sickle Cell Disease (SCD), 2) Coronary Heart Disease (CHD), and 3) Overweight/Obesity. Identification of the SCD Cohort will occur through our EHR and direct patient contact at our community based Comprehensive Sickle Cell Center (a joint effort of Vanderbilt and Meharry Medical College) which sees ~90% of the pediatric/young adult

SCD patients in middle TN. The CHD Cohort will be recruited from across the VHAN System and demonstrate our ability to robustly identify and extract data from our EHR, to reach patients through our patient web-portal, and to link to genomic and other clinical data. The Obesity Cohort will demonstrate our capacity to collaborate with Greenway to use health information technology tools to identify, recruit, and collect data on patients from across the country. By 18 months, we anticipate the CDRN will readily take on future projects in comparative effectiveness research, pragmatic clinical trials, and other key research areas. Our site would also have the capacity to share data and HIT nationally to advance research. The sustainability of the network will be supported by its efficient design, by our own health system, and by future externally funded research opportunities. Our vision is that this CDRN propels PCOR to advance health for all.

Patient-oriented SCALable National Network for Effectiveness Research (pSCANNER)

Principal Investigator: Lucila Ohno-Machado, MD, MBA, PhD

The patient-centered SCALable National Network for Effectiveness Research (pSCANNER) will contribute to PCORI's National Patient-Centered Clinical Research Network (NCRN) initiative as a clinical data research network (CDRN). pSCANNER will be a stakeholder-governed federated network that will utilize a distributed architecture to integrate data from three existing networks covering over 21 million patients : (1) the University of California Research eXchange (UC- ReX) network, with data from UC Davis, Irvine, Los Angeles, San Francisco, and San Diego; (2) VA Informatics and Computing Infrastructure (VINCI), with data from Veteran Health Administration's (VHA) 151 inpatient and 827 outpa- tient facilities supplemented with data on veterans and active-duty service members from 231 military treatment facilities worldwide; and (3) the SCALable National Network for Effectiveness Research (SCANNER), with data from UC San Di- ego (UCSD), the VA Tennessee Valley Healthcare System, and three ambulatory care systems in the Greater Los Angeles area supplemented with claims and health information exchange (HIE) data. All of the participating institutions have an extensive history of integrating translational research into clinical operations and organizational priorities for patient- centered care.

pSCANNER has strong foundational data capabilities to serve PCORI's CDRN. All systems have fully operational electronic health record (EHR) systems that are capable of facilitating randomized interventions. The existing data infra- structures have all been used for exploratory analysis in preparation for research; some are also in use for observational and randomized intervention studies. All participating systems have information and processes to recontact patients. The participants' clinical data warehouses (CDWs) routinely collect clinical data for multi-year longitudinal patient records. Security, privacy, and confidentiality of identified patient data in CDWs are maintained using the same standards as those required of EHR systems in HIPAA-compliant environments. The participating organizations have the proper infrastruc- ture for handling biospecimens and currently host several biorepositories. Streamlining of IRBs occurs through a "trust- and-rely" process among the UC sites. VHA has streamlined procedures for access to data, once IRB's approve a protocol. Finally, the patient population from pSCANNER institutions is highly diverse in terms of insurance coverage, socioeco- nomic status, demographics, and health conditions.

We will focus on three conditions: (1) Congestive heart failure, (2) Kawasaki Disease, and (3) Obesity. Patients, patient advocates, domain experts for these conditions, health services researchers, clinicians, and administrators from across the country have agreed to participate in pSCANNER's governance. In addition, we will use innovative user- friendly, online software to conduct a rigorously designed Delphi consensus process that engages 360 patients, clinicians, and researchers in the prioritization of research questions. All systems involved have agreed to allow pSCANNER users, as well as other CDRNs, to access their data using a privacy-preserving distributed computation model and research portal that was successfully piloted in SCANNER. This portal includes a study registry and per-site approval of specific analytic tools and protocols. Federal, state, and institutional policies are encoded in the registry to be easily configurable depend- ing on where the institution is located and which policies it utilizes. Patient and institutional privacy can be preserved with the use of new privacy technology algorithms. Analysis tools include methods that allow model fitting, causal inference, and hypothesis testing without the need for patient-level data to leave the institutions. This workflow allows for local con- trol and increases efficiency by

avoiding more complex IRB and data use agreements, though the network can handle data transfers where permissible.

We have developed two modes for network operation: (1) synchronous mode—pre-approved types of computation on the data are immediately allowed to run at local sites; and (2) asynchronous mode—a human inspects the results of all computations before approving their delivery to the requesting hub. Our distributed system will allow the construction and evaluation of multivariate models that can be used for statistical process control, data safety monitoring in clinical trials, adjustment for confounders, propensity score matching, risk prediction, and other methods employed in patient-centered outcomes research. For studies that require pooling of data, the hub will store the data in a HIPAA-compliant private cloud. Programming interfaces to the PCORI NCRN will be developed to ensure pSCANNER's interoperability. pSCANNER will adopt the Observational Model for Outcomes Partnership (OMOP) specification as its data model. Mappings from CDW data to OMOP are already in place in SCANNER sites and will be developed as part of this project for the other sites.

Greater Plains Collaborative

Principal Investigator: Lemuel Waitman, PhD

The Greater Plains Collaborative (GPC) is a new network of 10 leading medical centers in 7 states committed to a shared vision of improving healthcare delivery through ongoing learning, adoption of evidence-based practices, and active research dissemination. Partners by state are: KS, the University of Kansas Medical Center (KUMC); MO, Children's Mercy Hospital; IA, University of Iowa Healthcare; WI, the University of Wisconsin-Madison, the Medical College of Wisconsin, and Marshfield Clinic; MN, the University of Minnesota Academic Health Center; NE, the University of Nebraska Medical Center; and TX, the University of Texas Health Sciences Center at San Antonio and the University of Texas Southwestern Medical Center. The GPC builds on strong research programs at our sites, existing community engagement and informatics infrastructures and data warehouses developed through the NIH Clinical and Translational Science Award (CTSA) initiative at most of our sites, extensive expertise with commercial EHR systems and terminology standardization, and strong working relationships between investigators and healthcare system information technology departments.

Our network brings together a diverse population of 6 million people across 1300 miles covering 7 states with a combined area of 679,159 square miles, and that includes patients in underserved minority and rural areas (RC1). We complement considerable investments in electronic health records by our healthcare systems with existing NIH-funded open source technology (e.g., i2b2, REDCap) to provide a cost-effective common data model that promotes data transparency and interoperability (RC2, RC3). In addition to our data repositories and their accompanying data security and de-identification methods (RC11), the GPC builds on other existing CTSA and research investments for: (a) patient and community engagement (RC4) which will be extended to provide patient and clinician voices and participation in all GPC activities; (b) biostatistics and epidemiologic expertise to inform research designs and informatics methods for research participant identification, recruitment (RC6) and collection of patient reported outcomes (RC8); (d) human subjects protection, IRB, and contract approvals (RC10) that span institutional boundaries and cross state lines; and (e) mature biospecimen management and unique resources at several of our institutions (RC12). The GPC also has an innovative research methods core that will complement and inform our informatics team. Across our 10 sites, our informatics team has expertise in commercial EHR development and project management (RC13), clinical decision support, and standard terminology development. We will tailor our existing EHR research modules and patient portals and, where needed, will integrate existing clinical research systems in order to support comparative effectiveness randomized trials within the clinical workflow (RC9) and to increase robust collection of patient reported outcome measures.

Using input from community members and community advisory groups across our network, we selected Breast Cancer as our high-prevalence disorder. In 2013 alone it is estimated that 232,340 women will be diagnosed with breast cancer. Not only was breast cancer the top choice of the community members polled, but focusing on breast cancer will allow us to capitalize on our existing relations with NCI Centers at GPC sites for engaging investigators and patients. Our network also has considerable strengths in neuromuscular rare diseases. After conferring with clinicians treating neuromuscular rare diseases in our GPC network and the leadership of a

neurological patient advocacy group, we selected Amyotrophic Lateral Sclerosis (ALS) as the rare disease for which we could readily access all patients across our network. ALS has an estimated prevalence of 40-60 cases per 1,000,000 and an incidence of 0.4 to 1.8 per 100,000. As detailed in RC6, all ALS patients residing around our GPC sites are seen in the specialty clinics of our GPC neuromuscular rare disease specialists and thus we will have complete access to this population in our broad geographic region.

Fulfilling the PCORI vision of an engaged network of patients, investigators, and providers is fundamentally built on trust earned from successful relationships. Not only do we have strong community engagement programs across our sites on which we can build patient and community trust in the GPC, but GPC members also have strong regional collaborations between academic and health system informatics departments that are complemented by healthcare system and university governance (RC5). We are eager to participate in the national network. Modeled after existing national health care system collaborations (UHC), our low cost infrastructure (RC14) and current regional policies to maintain patient and clinician privacy and confidentiality will align with community-based practices and address organizational privacy sensitivities so that the GPC will allow for data sharing nationally, both within and outside of the network (RC7).

While the GPC is a new network, proven technologies based on two common EHR systems (Epic and Cerner) used at our sites, shared open source software, strong research infrastructures (e.g., CTSA programs, NCI-funded Cancer Centers), and experience with PCOR and CER at each site will enable implementation and ensure sustainability of the GPC network. Most notably, the GPC will provide a blueprint for creating de novo highly functional research data networks to conduct pragmatic PCOR and CER trials required for a national learning healthcare system.

Patient Outcomes Research To Advance Learning (PORTAL)

Principal Investigator: Elizabeth A. McGlynn, PhD

Patient Outcomes Research To Advance Learning (PORTAL) is a new network that brings together four leading health care delivery systems: Kaiser Permanente, Group Health Cooperative, HealthPartners, and Denver Health. The 11 research centers affiliated with these systems will collaborate with patients, clinicians, and operational leaders to develop the infrastructure necessary to create a highly functioning clinical data research network. The senior leaders of the four health systems have provided their enthusiastic support for this proposal, as shown in the letters of support. The PORTAL network has nearly 11 million members enrolled in its delivery systems in 9 states and the District of Columbia, has at least one site in each of the four major Census regions, and offers a diverse patient population that reflects the characteristics of US residents. The delivery systems that form PORTAL are integrated, have mature electronic health records systems, and demonstrate sufficient variation in practice patterns to enable observational comparative effectiveness studies. The PORTAL sites are actively engaged in designing, conducting, and participating in clinical trials and are eager to expand their capacity to conduct pragmatic trials that produce information for patients and doctors that more closely reflects outcomes of how care is provided in the real world.

The PORTAL network proposes to create Cohorts of: (1) patients with a diagnosis of colorectal cancer (CRC); (2) adolescents and adults with severe congenital heart disease (CHD); and (3) adults who are overweight or obese, including those who have pre-diabetes or diabetes. The cohort development activity will demonstrate that the PORTAL network is able to meet the 10 criteria for a clinical data research network specified in the PCORI funding announcement. Further, PORTAL will offer a scientifically sound set of Cohorts on which to conduct comparative effectiveness research and a foundation on which to build future cohorts.

The organization of the PORTAL network emphasizes the central role of engaged patients, clinicians, and operational leaders in the governance of the network, including participating in key decisions about Cohort construction. We have created three interlocking Councils (Patient Engagement, Clinician Engagement, and Operational Engagement) that together constitute the PORTAL Advisory Committee. A plan for how these groups will be actively and meaningfully involved throughout the project is described in the proposal and representatives of each of these groups were engaged in developing the proposal. By engaging broadly with Fight Colorectal

Cancer, the Adult Congenital Heart Disease Association, Smart Patients, and our members, we will build considerable enthusiasm and excitement for pursuing high priority research questions related to our Cohorts.

The data systems available to the PORTAL network are comprehensive, mature, and have demonstrated their utility in previous collaborative networks and projects. Interoperability among the sites is achieved through the use of a Common Data Model, which is built on a foundation established by the HMO Research Network, and has been expanded through Kaiser Permanente's investments in developing additional content areas. Data security, patient privacy, and confidentiality are assured through the use of established mechanisms that have been successful across multiple combinations of networks, sites, and types of projects.

We believe the PCORI funding will enable the PORTAL sites to efficiently develop subsequent cohorts over time and apply the approaches developed for PORTAL to existing or novel cohorts. We expect to be a contributing member of a national network of networks and look forward to helping to advance the nation's ability to answer questions that are important to patients about what works best for whom under what circumstances. We believe that the organizational structure that we establish through PORTAL will substantially increase opportunities to translate research findings back into improvements in the delivery of health care.

Louisiana Clinical Data Research Network (LACDRN)

Principal Investigator: Anium Khurshid

The Louisiana Clinical Data Research Network (LACDRN) is based on a partnership between a fully operational Greater New Orleans Health Information Exchange (GNOHIE) run by Louisiana Public Health Institute (LPHI), Pennington Biomedical Research Center's (PBRC) HarmonIQ data warehouse, and Tulane University clinical researchers. GNOHIE maintains and continuously updates a centralized clinical data repository that stores all information passing through the health information exchange, a data sharing infrastructure to facilitate care coordination across community-based clinics and currently one hospital system. The HarmonIQ data warehouse draws data from two major EMR/EHR systems used within the LSU Health System. Both the GNOHIE and HarmonIQ accept, standardize, and validate health information from a multitude of electronic health records systems and have vast experience in sharing data across networks. In total, these systems currently have approximately 382,000 unique patients with full demographic and clinical information, approximately 210,000 in the GNOHIE and approximately 172,000 in HarmonIQ. Both systems have expansion strategies to collectively increase this number to approximately 1,000,000 unique patients in 18 months.

Louisiana has some of the worst health outcomes (and disparities) in the country and has a high prevalence of diabetes and obesity. LPHI and its partners have a rich background in translational research and clinical trials related to these conditions (and others). Pennington has extensive experience in designing and conducting various types of research studies, including analyses of retrospective data, prospective quasi-experimental designs, and prospective randomized clinical trials. Tulane University has conducted retrospective CER studies utilizing a diverse assortment of data sources, including Veterans Affairs electronic medical records, commercial insurance claims, prospective observational databases, and randomized clinical trials. This three-way partnership will develop the capacity to serve as a national resource jointly with other CDRNs throughout the country. The LACDRN provides a unique opportunity to study and test health system improvements and conduct comparative effectiveness research in an underserved, safety-net population that faces significant environmental, socioeconomic, and health challenges.

The proposed network will advance the capacity to conduct efficient clinical research on two highly prevalent health conditions (obesity and diabetes), multiple associated comorbidities, sickle cell disease, and a group of ten rare cancers. By conducting on-going, broad recruitment across the partner health systems to build cohorts of patients with these diagnoses, the LACDRN will improve access to these particular patients for prospective studies and rich clinical and patient-reported data on these specific health conditions to facilitate efficient and robust clinical research.

The LACDRN will be a significant socio-technical advancement in CER. The project will provide a large volume of comprehensive, longitudinal, and up-to-date clinical data on a diverse, state-wide patient population. The project will also employ innovative technologies in the routine collection of patient-reported data both within and outside the clinical setting. The availability of this innovative data resource will enhance the efficiency and effectiveness of clinical research that will ultimately improve healthcare delivery and health outcomes within and beyond the network's patient population. By actively and continuously engaging patients, clinicians and health systems leadership in the LACDRN governance, design and implementation, the network will be a patient-centered, community-based resource that prioritizes and facilitates clinical research that reflects and addresses patients' needs and is conducted congruously with healthcare delivery.

National Pediatric Learning Health System (PEDSNet)

Principal Investigator: Christopher B. Forrest, MD, PhD

We propose to create a national, pediatric-specific learning health system (LHS) composed of a newly formed multi-institutional CDRN (called PEDSNet), three condition-specific PPRNs focusing on pediatric inflammatory bowel syndrome, hypoplastic left heart syndrome, and childhood obesity, and two national data partners. A LHS is organized around communities of patients, families, clinicians, and researchers who work together to purposefully integrate knowledge generation (research) with knowledge dissemination and implementation at the point-of-care (quality improvement).¹⁻⁶ Its goal is to provide information about available, reasonable alternatives that will allow patients and families to make informed, shared decisions with their healthcare team in ways that lead to improvements in outcomes.

The PEDSNet-CDRN includes 8 of the nation's largest children's hospital health systems—Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Children's Hospital Colorado, Nemours Children's Health System, Nationwide Children's Hospital, St. Louis Children's Hospital, Seattle Children's Hospital, and Boston Children's Hospital. These institutions provide services to 2.1 million children per year (2.8% of the nation's children), providing a large and diverse population for conducting pediatric research. The PPRNs include two established networks—ImproveCareNow (16,000 pediatric inflammatory bowel disease patients), and the National Pediatric Cardiology Quality Improvement Collaborative (1,000 hypoplastic left heart syndrome patients)—and a newly established network for childhood obesity. The national data partners are Express Scripts (a pharmacy benefit management company) and IMS Health (a data analytics company).

The goal of the proposed project is to transform pediatric healthcare and children's health in the nation by developing an extensible and efficient infrastructure that enables all participants to collaborate in the work of producing new knowledge and improving health and care delivery. Our specific aims are to: (1) engage patients/families, clinicians, researchers, and system executives in the creation of the pediatric LHS; (2) form governance structures that provide operational and strategic oversight of the LHS; (3) establish an interoperable digital infrastructure to support learning (research, dissemination, and implementation), recruitment, and engagement of stakeholders; (4) create a recruitment infrastructure to support prospective research studies; and, (5) develop policies and procedures (e.g., a central IRB) that facilitate collaboration.

Our application benefits from robust pre-existing resources and a unique history of collaboration by children's hospitals that has fundamentally reshaped outcomes for previously fatal diseases, such as cystic fibrosis and many childhood cancers. Building on this history, we created with AHRQ and NIH sponsorship an operational prototype of the LHS for pediatric inflammatory bowel disease, which over the past four years has increased rates of remission (no disease activity) from 55% to 77% of patients in the network.^{7, 8} The pediatric institutions participating in the newly formed CDRN have already collaborated on EHR-based data sharing studies.⁹ With NIH funding, we have launched a national Pediatric Terminology Project, which is harmonizing clinical concepts across conditions and specialties.¹⁰

These successes demonstrate both the will and capacity of participating institutions to develop a national pediatric LHS that addresses fundamental questions of clinical effectiveness for children and their families, particularly for individuals affected by serious, and generally rare, illness that persists into adulthood. The individuals and

organizations collaborating in this effort have the expertise needed to address questions of interoperability, patient engagement, governance, and other factors critical to developing a capable national infrastructure that will: enable learning across pediatric conditions and stakeholders; harness the motivation and expertise of engaged participants to contribute to advancing knowledge and improving child health; embed research within healthcare delivery; and, efficiently implement and disseminate new approaches to care based on research results, ultimately leading to transformations in children's health outcomes.

New York City Clinical Data Research Network

Principal Investigator: Rainu Kaushal, MD, MPH

The New York City Clinical Data Research Network (NYC-CDRN) will bring together a total of 22 organizations across 7 systems in the nation's most populous and diverse region. These organizations are already pursuing data sharing and patient-centered clinical research, individually and collaboratively. The NYC-CDRN will be a network building on the strengths of and support from each participating organization, sharing capabilities across organizations, and facilitating coordinated and patient-centered clinical research within and across CDRNs. The NYC-CDRN will include complete, comprehensive, and longitudinal data for at least 2.5 million patients and potentially as many as 6 million patients. The NYC-CDRN has several distinguishing features, including prominent leadership roles for patients, expertise in community engagement, a setting in the most diverse city in the nation, support from state government, participating clinical organizations with decades of research experience including patient-centered comparative effectiveness research, newer partners with innovative technologies, strong informatics expertise, existing clinical information exchange and interoperability, privacy and security expertise, and membership organizations that can effectively convene multiple stakeholders.

The NYC-CDRN will build on the 6 existing Clinical and Translational Science Award Centers at the medical schools and universities in New York City (Weill Cornell Medical College, College of Physicians and Surgeons at Columbia University, Icahn School of Medicine at Mount Sinai, NYU School of Medicine, Albert Einstein College of Medicine, and Rockefeller University), which are already pursuing collaborative research, data sharing, and patient engagement. The NYC-CDRN will also include the 4 associated medical centers (New York-Presbyterian Hospital, Mount Sinai Health System, NYU Langone Medical Center, and Montefiore Medical Center), 5 organizations for patient engagement (Center for Medical Consumers, Consumer Reports, American Diabetes Association, New York Academy of Medicine's DASH initiative for obesity, and Cystic Fibrosis Foundation), 1 practice-based research network of Federally Qualified Health Centers (Clinical Directors Network), 1 genome center (New York Genome Center), 1 research support organization (Biomedical Research Alliance of New York), and the new Cornell Tech Campus (which includes a focus on developing new technologies to capture patient health information). The NYC-CDRN has strong support from the New York State Department of Health and builds on infrastructure established by 2 New York State-supported health information exchanges (Healthix and the Bronx RHIO).

The NYC-CDRN will include clinical, patient-reported, patient-generated, bio-specimen, claims, registry, and study-specific data on an unselected population of patients, approximating 100% of the patients who receive health care at the participating institutions and reflecting the full diversity of people living in the New York City region. The NYC-CDRN will develop three cohorts for patients with diabetes, obesity, and cystic fibrosis as well as fully partner with patients and clinicians through disease-specific community workgroups. The involved personnel have expertise in informatics, comparative effectiveness research, patient recruitment and engagement, human subjects protection, ethics, privacy and security, randomization techniques, and bio-banking. Strong health system leadership support for data sharing is in place, including from clinical leaders committed to developing learning healthcare systems by embedding research activities into the provision of health care. The early and ongoing involvement of patients and patient organizations is key to the success of the NYC-CDRN, and our past experiences with successfully partnering with patients foreshadow similar successes to come. Finally, this project enjoys the strong support of the New York State Department of Health, which has invested over \$400 million in health information technology infrastructure for the state with goals that include facilitating data sharing for clinical purposes and fostering patient-centered clinical research.

Chicago Area Patient Centered Clinical Outcomes Research Network (CAPriCORN)

Principal Investigator: Terry Mazany, MA, MBA

Chicago is the third most populous city in the U.S. and, together with its metropolitan area, includes about 9.5 million residents. Chicago suffers from significant health disparities due to variable access to high quality care and differences in socioeconomic resources across its metropolitan area. With the support of city, county, and state-level governments (see letters of support), we have proposed an unprecedented collaboration across a diverse group of healthcare institutions, including private, county, state hospitals and health systems, a consortium of Federally Qualified Health Centers, two Veterans Administration Hospitals, and other partners to develop the Chicago Area Patient Centered Clinical Outcomes Research Network (CAPriCORN).

Over the course of the 18-month project period, the CAPriCORN clinical data research network (CDRN) will have captured complete longitudinal clinical information in >1 million patients (~50% non-white); developed the capacity to efficiently conduct CER trials and observational studies, including a fully operational central IRB; established procedures for clinical data standardization and inter-operability across the national patient-centered research network of CDRNs and patient-powered research networks (PPRNs); engaged patients, clinicians, and health system leaderships in governance and use of CAPriCORN resources; and recruited and surveyed five cohorts (2 cohorts representing common conditions; 2 cohorts representing rare conditions; and an obese/overweight cohort). These cohorts were selected on the basis of nationally prominent research expertise among the member institutions and because several of them are especially representative of conditions noted for health disparities.

With coordination by the Chicago Community Trust and the Illinois Medical District Commission and a participatory and nimble governance structure, CAPriCORN will seek to model how healthcare institutions in complex urban settings can overcome barriers of competition, care fragmentation, and limited resources to develop, test and implement strategies to improve care for diverse populations and reduce health disparities. The diverse healthcare settings and populations within CAPriCORN will also serve as a natural laboratory in which we can examine and learn to address the heterogeneity of treatment effects.

Our overall strategy is to build upon the strengths of our participating institutions and existing collaborations, to develop a cross-cutting infrastructure for sustainable, population-wide and patient-centered CER in Chicago. In preparation for this proposal, we successfully pooled EHR data across 7 of the 9 CAPriCORN institutions to identify over 5 million unique patients and potential study patients for all 5 study cohorts as part of our ongoing Chicago Health Atlas project. Five of the CAPriCORN institutions already collaborate with the Chicago-based University HealthSystem Consortium (UHC), an alliance of 119 nonprofit academic medical centers, over 300 affiliated hospitals, and nearly 100 faculty practice plans. UHC will expand its role to serve as a data aggregator for all CAPriCORN sites. This partnership with UHC greatly enhances CAPriCORN's ability to develop a CDRN within the project period and to serve as part of a sustainable national model for PCORI, while creating a model that could later add other UHC institutions. Several of the member institutions in CAPriCORN have also participated in local and national research collaboratives, including the NIH NCATS Clinical and Translational Science Centers, AHRQ/NHLBI CONCERT, AHRQ-funded comparative Centers for Education and Research in Therapeutics (CERTs) and effectiveness trial in asthma (BELT study), and the NIH and CMMI-funded LEARN demonstration project. We have also established strategies to involve patients and clinicians at every stage of the research process, from soliciting research topics and prioritization, to assisting in the design and execution of CER studies, and dissemination of study results (e.g., PCORI-funded PaTNER and PELICAN trials). CAPriCORN stands ready to improve the nation's capacity to conduct CER efficiently and contribute to the national patient-centered research network.

Accelerating Data Value Across a National Community Health Center Network (ADVANCE)

Principal Investigator: Jennifer DeVoe, DPhil, MD

The proposed Accelerating Data Value Across a National Community Health Center Network (ADVANCE) Clinical Data Research Network (CDRN) will be led by the OCHIN Community Health Information Network in partnership with Health Choice Network and Fenway Health. Together, we have outpatient clinical data from 97 Federally-Qualified Health Center (FQHC) health systems with 744 clinics serving safety net patients, many of whom are uninsured or publicly insured – a population often underrepresented in research. The ADVANCE CDRN will greatly accelerate our efforts to build a “community laboratory” of FQHCs in which to conduct Patient Centered Outcomes Research (PCOR). We currently have electronic longitudinal outpatient clinical data on >1.6 million patients seen in the past two years (7/1/2011 – 6/30/2013) and a cumulative total of nearly 4.5 million patients ever seen within these systems. We will add inpatient data to this repository by strategically partnering with health plans and hospitals caring for the same patients; we will also add community-level and patient-reported data for these FQHC patient populations. Our community-based CDRN will have significant stakeholder engagement and a nimble yet robust infrastructure, and will offer unique opportunities for those wishing to partner with us. We have a demonstrated ability to participate in such collaborations; the ADVANCE CDRN will greatly expand our ability to do so. Our primary aims are to:

1. Integrate outpatient, hospital, and community-level data into a single data management system;
2. Expand our efforts to engage patients and clinicians who contribute to the design, implementation, and interpretation of comparative effectiveness research;
3. Develop electronic systems for recruiting study participants and collecting patient-reported data;
4. Strengthen the infrastructure of our community-academic partnerships to support PCOR, and support FQHCs to become learning health systems; and
5. Build the capacity of our FQHC networks to meet research regulatory requirements.

Project Pillars: The ADVANCE CDRN’s three project “pillars” will provide the core infrastructure and expertise for accomplishing these aims. The pillars will be operationalized by workgroups of patient investigators, community investigators, and academic investigators collaborating to meet project goals.

Data Pillar: This team will normalize, validate, and expand our clinical data repository. We have an integrated “horizontal” database of outpatient data from FQHC patients in 22 states, into which we will “vertically” integrate data from hospitals and health plans that serve the same patients in this population. We will also incorporate neighborhood-level data from the communities in which these patients live. **Cohort Pillar:** This team will engage and recruit patient participants for three cohorts.

- A. Common Disease Cohort: we have 91,668 adult patients in our CDRN population with diabetes.
- B. Rare Disease Cohort: we have 2,617 adult patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in our CDRN patient population.
- C. Obesity Cohort: we have >264,000 obese adult patients (BMI) > 30), of whom 21% have been diagnosed with diabetes, and another 7% have pre-diabetes or metabolic syndrome. **Regulatory Pillar:** Building on OCHIN’s existing policies, and working closely with our compliance officer and data stewardship committee, this work group will streamline our existing policies for data security, privacy and confidentiality, identify one central Institutional Review Board (IRB) for our CDRN, and ensure that all partners have a Federal Wide Assurance (FWA) that designates oversight to that IRB.

The Data, Cohort, and Regulatory Pillar Workgroups will coordinate efforts with oversight by the ADVANCE Advisory Council. Each workgroup will dedicate members to liaise with the national coordinating center to ensure that our CDRN activities are well coordinated and synergistic with national efforts, and that the national network of CDRNs is able to include vulnerable and diverse FQHC patient populations in PCOR.

P2aTH network

Principal Investigator: Rachel Hess, MD, MS

The P2aTH network has all 10 features of an ideal CDRN and will expand these capabilities during the project period:

- 1) Population Coverage. More than 2.5 million patients in diverse communities spanning Appalachia to major cities across 7 mid-Atlantic states currently receive care and participate in clinical research at our P2aTH CDRN sites:

- University of Pittsburgh/UPMC and UPMC Health Plan (western PA, OH, WV)
- Penn State College of Medicine/Hershey Medical Center (central PA)
- Temple University School of Medicine/Temple Health (eastern PA, DE, NJ)
- Johns Hopkins University/Johns Hopkins Health System and Johns Hopkins Health Care (MD, VA, DC)

All sites use mature electronic medical records (EMRs) with 3 to 25 years of searchable clinical data, and all have active biorepository programs that can be linked with EMR data. Our network includes 2 larger insurers, which will allow us to track patient visits and outcomes outside the network health systems.

- 2) Data standardization & interoperability. All P2aTH partners currently share EMR data collected with collaborators and national networks, and they will each apply their prior experience to the PCORI program. The CDRN will use an open-source data-sharing tool, i2b2 (Informatics for Integrating Biology and the Beside), to enhance data sharing using international data standards, centrally defined data elements, and the integration of data from any source.
- 3) Patient contact. Each site can and currently does identify and recruit patients in clinical settings and via online health networks. All sites have expertise in comparative effectiveness research (CER), including many PCORI-funded studies. Each site has years of experience collecting patient-reported outcome measures (PROMs) as part of a routine clinical visit, with some partners doing so as part of their EMR. Each site has experience from scores of clinical studies that confirm, through their publication in medical journals, their ability to meet recruitment goals, minimize patient drop out and missing data, and conduct rigorous follow-up. Each site has Community/Patient Advisory Boards and Community Engagement Research Cores and involves clinicians in planning and conducting clinical studies.
- 4) Patient engagement. P2aTH partners use diverse methods for outreach and recruitment: clinic intake questionnaires (some embedded in the EMR), clinical alerts, online personal health records, direct mail (surface and electronic), and social, print, and broadcast media. P2aTH will specifically identify and engage patients with: Atrial Fibrillation, the most common arrhythmia, affecting ~2.2 million people in the US¹, which has a myriad of management options; Idiopathic Pulmonary Fibrosis, a rare, chronic, progressive, lung disease with an unknown cause and no standard, approved treatment;² and Obesity, which is at epidemic rates in the US.³ Throughout this proposal, we use examples from patients with these conditions to describe our network and provide patient-centered context for our vision.
- 5) System leadership in network governance. Leadership at each site recognize the importance of CER and PROMs in improving the quality and efficiency of care in their health system. Each contributed to the development of P2aTH (and remain involved in governance), provided strong letters of support, and will institutionalize network initiatives.
- 6) National resource. Separately and together, we have the capacity to serve as a national data infrastructure resource as evidenced by the participation of P2aTH partner sites in the national research consortium formed by the Clinical and Translational Science Awards and the National Cancer Institute Cancer Biomedical Informatics Grid.
- 7) Large-scale CER. Each P2aTH site currently designs studies, pools and integrates data, and disseminates datasets and tools through their participation in collaborative, large-scale CER as well as pragmatic, cluster-randomized, and observational studies of multiple research questions on a regional and national scale.
- 8) Embed research activity. P2aTH partners, recognizing the critical need to conduct research to improve the quality and efficiency of care, have embedded all aspects of the research process within their clinical workflow. Each site has clinical workforce for whom integrating research with patient care is second nature

and EMR systems to support data collection, abstraction, pooling, and sharing at a system-wide level. P2aTH will conduct joint pre-review of IRB protocols for CDRN projects, followed by rapid approval at each participating site.

- 9) Data security. Each institution adheres to HIPAA rules for data security, which are divided into administrative, physical and technical safeguards. The data center follows not only HIPAA standards but also the Federal Information
- 10) Streamlined subcontracting. P2aTH will use established subcontracting methods in place at each site and Federal Demonstration Project templates for subawards, which can be easily adapted for use in PCORI projects.

Patient-Powered Research Networks (PPRNs)

The Health eHeart Alliance

Principal Investigator: Mark Pletcher, MD, MPH

Our current team is led by researchers from the University of California, San Francisco who have recently launched an internet-based cardiovascular cohort study called the Health eHeart Study (HeH). HeH, with help from the American Heart Association (AHA), Practice Fusion, and three patient-advocacy groups, will form the core of a transformative new patient-powered research network (PPRN). Our team can already claim:

1. A large group of patients who have provided informed consent to participate in research and provided extensive self-reported cardiovascular health information
2. Established vehicles for additional recruitment via commitments from AHA, Practice Fusion, StopAfib.org, Mended Hearts, and the Sudden Arrhythmia Death Syndrome (SADS) Foundation
3. All data collection features of an ideal PPRN, including online surveys (many standard instruments), remote monitoring devices (sensors), mobile/online apps, electronic health records (EHR), and a state-of-the-art data system ready to scale up for collection and analysis of “big data”
4. Partnership with an innovative EHR provider (Practice Fusion) that can provide communication channels to providers as well as patients and a direct means of delivering interventions for comparative effectiveness research trials, quality improvement programs, and dissemination of research findings
5. An infrastructure for conducting very inexpensive trials and observations studies within HeH that can be used by investigators anywhere

Phase I funding: An ideal PPRN focused on cardiovascular health

Funding from PCORI will support creation of a new PPRN – The Health eHeart Alliance. The Health eHeart Alliance will work hand-in-hand with the Health eHeart Study to generate and test new patient-designed interventions for improving cardiovascular health. With the help of our partners, we have engaged a set of highly motivated patient-leaders, named and described in this application, who will form an Interim Steering Committee for the Alliance. We have committed a large portion of Phase I funding to resource this committee and support a deliberate “design process”, with the goal of delivering:

- A conference designed to galvanize enthusiasm for crowd-sourcing cardiovascular research ideas
- A new PPRN organization with a mission statement, defined governance structure, and key policies
- Five specific crowd-sourced and PPRN-prioritized trial protocols ready for implementation within HeH Our funding will support the following additional aims designed to accomplish transition to an ideal PPRN:
- Recruitment of 100,000 patient-participants representing diverse demography and heart-related condition
- Capacity for “Blue Button” EHR data consumption, an IRB-approved online HIPAA authorization system, and a pilot natural language processing algorithm that adjudicates hospitalization events
- Demonstration of DNA collection capability and willingness of participants to contribute specimens
- Integration with a CDRN and 2 other PPRNs and collaboration with the NCRN Coordinating Center

Our vision for contributing to the National Clinical Research Network (NCRN): The Health eHeart Alliance will be the hub for cardiovascular health research in the NCRN. Patients with cardiovascular conditions of any type will be welcomed and find a vibrant community and opportunities to contribute by participating in research studies, by joining research idea brainstorming sessions with other patients, and by getting involved in PPRN leadership. As a fully functioning research-grade IRB-approved cohort study that is highly engaging to patients, HeH will provide other PPRNs and CDRNs with a mechanism to collect rich and varied types of data including core cardiovascular measurements on their own patients through co-enrollment and data sharing. And as an inexpensive platform for testing interventions that will be available for use by outside investigator/collaborators, the Alliance will be a powerful engine for producing, testing and disseminating innovative patient-centered interventions that improve cardiovascular health.

ImproveCareNow (ICN) Network

Principal Investigator: Peter Margolis, MD, PhD

The ImproveCareNow (ICN) Network is poised to become a reusable, scalable, and sustainable peer production Learning Health System (LHS) in which patients and clinicians collaborate to learn from every interaction, conduct patient-centered outcomes research, and implement the findings. ICN has developed and piloted programs to fully engage patients, clinicians, and researchers as equal partners, but these programs are not yet at scale. ICN has extensive, standardized clinical data, but has not yet collected patient-reported outcomes (PROs) from the vast majority of patients. To complete ICN's transformation, we propose to: 1) implement a full-scale peer-production system that engages patients, families, clinicians, and researchers working together to conduct research and improve health and healthcare, and 2) develop the infrastructure to assemble a comprehensive set of longitudinal patient-centered data.

ICN's mission is to transform the health, care, and costs for children and adolescents with Crohn's disease and ulcerative colitis -- inflammatory bowel disease (IBD). As a network that engages patients, families, and clinicians in research and improving outcomes, ICN has achieved remarkable success. Since 2007, the proportion of patients in remission (with inactive disease) has increased from 55% to 77% and 95% of patients approached have consented for research. ICN has grown to 56 sites that provide care for 17,000 patients in 30 states; about 1/3 of all children with IBD in the US.

With support from an NIH Transformative Research grant (R01 DK085719), ICN has partnered with the C3N Project to develop and test interventions to transform itself into a peer-production system to improve health and healthcare. In a peer production model, the production of new knowledge and know-how is distributed among all participants. Wikipedia, the best-known example of peer production, stands in contrast to the firm-produced (and defunct) Microsoft Encarta. Applying peer production to the LHS model means that patients, parents, clinicians, and researchers collaborate as peers to produce information (e.g., clinical data, patient reported outcomes), knowledge (informal insights and formal research), and know-how (about how to change care) to improve healthcare and health outcomes. With PCORI funding, we propose to implement the peer production model at scale, dramatically expanding and enhancing patient and family participation in governance, research, and dissemination and implementation activities.

With support from an Agency of Healthcare Quality and Research (AHRQ) Enhanced Registries grant (R01 HS20024), we built on open-source software to enhance the ICN registry to enable clinicians to collect data once using the electronic health record (EHR), and to re-use the data to automate chronic care processes, quality improvement (QI), and comparative effectiveness (CE) research. Through continuation funding (AHRQ R01 HS22974), we are extending this infrastructure to capture laboratory and pharmacy data. With PCORI funding, we propose to broaden the range of data collected to include PROs and claims data, and work with other PPRNs and CDRNs to implement data standards for interoperability and exchange of data.

ICN has benefited from substantial federal investment; with PCORI funding, we propose to complete the transformation to a full-scale peer production LHS. As an exemplar PPRN, we are fully committed to accelerating other PPRN's transformation and in participating in the national patient-centered clinical research infrastructure in

collaboration with the Coordinating Center. As well, this proposal is one of a federation of 2 pediatric PPRNs (ICN and the National Pediatric Cardiology Quality Improvement Collaborative) and a pediatric CDRN (PEDSNet) that proposes to create a national pediatric LHS.

Crohn's and Colitis Foundation of America

Principal Investigator: R. Balfour Sartor, MD

Crohn's disease (CD) and ulcerative colitis (UC) are chronic Inflammatory Bowel Diseases (IBDs) that affect approximately 1.2 million individuals in the United States¹, cost over \$6 billion annually², and cause substantial patient morbidity^{3, 4}, missed work⁵ and school⁶, and diminished quality of life.^{7, 8} Fortunately, we have entered an era of rapid discovery of the genetic and microbiome-related factors involved in disease pathogenesis, and are now at the forefront of "personalized medicine". To translate these advances in basic science research into improved patient-centered care and outcomes, emerging genomic and microbiome data must be coupled with comparative effectiveness (and safety) research. Ultimately, this will enable patients and physicians to make collaborative choices about when, in whom, and how to use current and future therapeutic options (i.e. medications, surgery, diet, fecal transplant, etc). For this reason, comparative effectiveness research in IBD is recognized by the Institute of Medicine as a top national priority.⁹

Yet, the infrastructure required to conduct high quality, multidisciplinary, patient-centered outcomes research in IBD has, to date, been lacking. This is largely because the fields of IBD genetics, microbiome research, clinical research, and outcomes research have evolved in a parallel, rather than in an integrated fashion, hindering the much needed cross-cutting research. Fortunately, a number of technological advances and changes in health policy have recently converged, enabling the collection and seamless integration of disparate, yet complementary, sources of data (i.e. patient reported data, biometric data, health records, genetic data, and other biomarkers) in a way that has never before been possible—by putting patients in control.

The Health Information Technology for Economic and Clinical Health (HITECH) Act and the resulting Meaningful Use Stage 2 Final Rule have empowered patients to View, Download, and Transmit (VDT) their own health records. The proliferation of mobile health (mHealth) apps and devices now allows patients to record and track their health related activities (fitness, sleep, diet, etc.) and physiological/biometric responses—as often as they choose. The internet provides a means to efficiently conduct patient surveys, making the recruitment and long-term follow up of patient cohorts relatively cost effective. Social media now provides easy access for patients to create disease-oriented communities in which they can learn about their disease, share insights with others, and contribute to research. Widespread and low-cost genetic sequencing has turned this and other previously labor-intensive resources into a commodity. Finally, novel bioinformatics approaches have paved the way for the seamless integration of these data.

The Crohn's and Colitis Foundation of America Partners (CCFA Partners) study is a novel and highly successful internet cohort of over 12,500 patients with IBD (~1% of US IBD population), focusing on patient-reported exposures, health behaviors, and outcomes. In this application, we propose to radically transform CCFA Partners into a full-scale Patient Powered Research Network (PPRN). We have developed a partnership with Crohnology, the leading social network for patients with this condition, and have identified best-in-class vendors to assist us in integrating data from mHealth apps and devices and electronic health records. Together, we will accomplish the following specific objectives: 1) Enhance network growth, diversity, and retention; 2) Build a robust network community, including patient governance structures that allow greater involvement of patients in research 3) Expand the network database to include electronic health records, data from mHealth apps and devices, and biological samples, 4) Develop a customized, yet scalable and adaptable, distributed data network (i.e. virtual database) by repurposing NASA-built technology, 5) Develop and test patient and provider-focused tools that utilize individual patient data to improve health behaviors, healthcare decisions, and, ultimately, outcomes, 5) Further engage the scientific community through open collaboration and data sharing, and 6) Rapidly disseminate new knowledge to patients, enabling them to improve their health.

Our team is uniquely positioned to develop this IBD-focused PPRN. The sponsor of this proposal, the CCFA, is the leading, non-profit IBD patient organization, founded in 1967 to “cure CD and UC and improve the quality of life of those affected”. We have identified a highly engaged Patient Governance Committee and assembled an internationally recognized, multidisciplinary scientific team, representing disciplines of IBD basic science, epidemiology, computational mathematics, qualitative methods, patient-reported outcomes, health behavior design, computer programming, and bioinformatics. Finally, as IBD is model for other complex, chronic illnesses, we look forward to working collaboratively with other PPRN and CDRN awardees, through the Steering Committee, to assist in the development of a national patient- centered clinical research infrastructure.

Arthritis Patient Partnership With comparative Effectiveness Researchers (ARPoWER)

Principal Investigator: Seth Ginsberg, BS

Rheumatoid arthritis (RA) is a chronic, systemic, often disabling, autoimmune disease affecting 1% of adults and 2-3% of older individuals (1-4). A companion inflammatory arthritis, spondyloarthritis (SpA) has a similar prevalence and includes subtypes such as psoriatic arthritis, inflammatory bowel-related arthritis, and ankylosing spondylitis. These debilitating types of arthritis typically strike younger people (median age 30s and 40s), in the prime of work and family productivity, and are usually lifelong. There are genetic and environmental factors associated with their onset, but there is no known cure. According to the Center for Disease Control, arthritis is the leading cause of disability in the U.S. (5). New biologic medications that target specific components of the immune system have proved effective for most patients, with major improvements in quality of life (6). However, their high cost (~\$3,000 per month) and requirement for ongoing use, along with many unresolved safety questions, makes inflammatory arthritis a key disease focus for comparative effectiveness research. Indeed, the Institute of Medicine put the need to conduct new comparative effectiveness studies of these medications for RA and SpA in the highest tier (first quartile) of importance (7).

In recognition of the importance of filling evidence gaps in inflammatory arthritis-related research, our established CreakyJoints (CJ) arthritis patient network, part of the Global Healthy Living Foundation (GHLF) (<http://www.ghlf.org>), proposes the Arthritis Patient Partnership With comparative Effectiveness Researchers (ARPoWER) PPRN. CJ was established in 1999 as a 501(c) (3) non-profit organization based in New York, with the mission to improve the quality of life for people with arthritis. CJ, as part of the GHLF, accomplishes this by advocating nationally for improved access to care and by educating the community about the importance of diagnosis, early and innovative medical intervention, long-term lifestyle improvement, and therapeutic compliance with arthritis treatments. Co-founded in 1999 by arthritis patient and patient advocate Seth Ginsberg, CJ is a network of approximately 55,000 arthritis patients and caregivers in all 50 U.S. states. The CJ focus is on the most dominant disease in our network, RA, with an additional large patient base of SpA. Other diseases represented by the GHLF include osteoporosis (CreakyBones.org, ~5,000 patients) and psoriasis (RedPatch.org, ~5,000 patients) and systemic lupus erythematosus. For more than 10 years, CJ has provided in-person education, advocacy, and grassroots patient mobilization that occurs through live community programs and partnerships with provider networks, other patient organizations, and professional societies. We also include vibrant online communities with an active presence on Facebook, Twitter, YouTube, and other social media tools. Annually, we have more than 20,000 one-on-one interactions with patients through community-based education and advocacy events; partner with more than 100 other patient groups in the U.S.; have an Internet presence with 19 million unique website hits; 100 million “impressions” from traditional media; >250,000 YouTube views; and relationships with numerous U.S. Congress and State legislatures for patient advocacy. The CreakyJoints Facebook page (www.facebook.com/creakyjoints) is the most popular arthritis page in the world, with between 10,000 and 30,000 “conversations” per week.

The AR-PoWER PPRN is vital to translating our high-impact patient advocacy and education-focused organization into an equally high-impact patient-centered network able to conduct research. This PCORI proposal builds on an established track record of collaboration between CJ and comparative effectiveness researchers and informatics experts who are part of the Agency for Healthcare Research & Quality (AHRQ)-funded UAB Center for Education

and Research and Therapeutics (CERTs) of Musculoskeletal Diseases. Our relationship with UAB is well established, with multiple projects ongoing or under review (8, 9). Our other partners include a CDRN (DISCOVER), the American College of Rheumatology (ACR), CORRONA [a doctor-led arthritis research network], and IMS Health, a healthcare network representing 23 million patients, 88 health plans, and 40,000 physicians.

We will satisfy and exceed all PPRN milestones and: 1) develop sophisticated information technology tools to securely capture our patients' data; 2) collect informed consent from our membership; 3) map our data to a common data model, and exchange encrypted information with other CDRNs and PPRNs, as well as 3 additional external data sources; 4) establish an expanded governance structure to ensure patient privacy and transparency about research activities, involving data security, privacy and Institutional Review Board experts. Our novel and timely PPRN will augment our already appreciable education and advocacy efforts with a greatly expanded research capacity to conduct comparative effectiveness studies in a key area deemed of major public health importance by the IOM. Additionally, CJ has a well-established mechanism to allow CER results to be disseminated directly from their source to our expansive patient base, as well as through more traditional sources like the peer-reviewed scientific literature. Our patient network, led by arthritis patients and supported with substantial expertise from our federally-funded research experienced collaborators, and effectively leveraging an existing ARHQ-funded infrastructure, allows us to have tremendous effectiveness to support PCORI's mission to provide timely information on risks and benefits of treatments directly to arthritis patients in making real-world decisions.

Sleep Apnea-Patient Centered Outcomes Network (SA-PCON)

Principal Investigator: Susan Redline, MD, MPH

Breathing and sleep are both essential to life. Unfortunately, millions of adults and children suffer from sleep apnea, which causes nightly, recurrent interruptions of breathing during sleep due to collapse of the tissues in the throat.¹ Sleep apnea deprives individuals of oxygen during sleep, and results in sympathetic nervous system over-activity, profound blood pressure surges, and sleep disruption. The immediate sequelae of Sleep Apnea and hypoxemia cascade into life threatening health problems with major public health impact. The consequences range from sleepiness, depression and impaired quality of life to hypertension, myocardial infarction, stroke, diabetes and early mortality.²⁻⁹ Sleep apnea affects 17% of adults and 1-4% of children,¹⁰ with rates increasing in association with the obesity epidemic.¹¹ Sleep apnea aggregates in families;¹² affects all age groups; and disproportionately affects minorities¹³ and those from poor neighborhoods.¹⁴

Though much has been learned about the epidemiology and pathophysiology of sleep apnea, management of the disease is disjointed and often suboptimal. Minority and disadvantaged groups are at increased risk for sleep apnea,¹³ yet are less likely to receive effective treatment.¹⁵ Use of diagnostic tests (home or lab-based sleep studies) is more often influenced by the patient's insurance than by clinical factors. Treatments include positive airway pressure (PAP), mandibular advancement devices, various surgeries, and behavioral interventions. However, there are little data to inform which treatments, or combinations of treatments, work best in given patients.¹⁶ Treatment strategies often reflect which specialist (e.g., pulmonologist, ENT, etc.) the patient sees rather than his or her clinical presentation or preferences. Traditionally, treatment has focused on improving a number- the Apnea Hypopnea Index- rather than improving patient-centered outcomes such as quality of life. Achieving optimal adherence to treatments such as PAP is a challenge.¹⁷ Efforts heretofore to develop strategies for improving adherence have not involved the patient; furthermore, minimizing treatment burden is not routinely considered. Behavioral approaches including modifying diet, physical exercise, and sleep position are not often systematically addressed. The sleep apnea patient is left to his or her own devices to find relief, which is particularly troubling for poor and minority patients with fewer resources. Thus, the Sleep Apnea-Patient Centered Outcomes Network (SAPCON) proposes to address the dual need to conduct critically important comparative effectiveness research while actively engaging patients and other key stakeholders in every aspect of research and implementation by participating as a PCORI Patient Powered Research Network (PPRN). Patients (including children via caregivers), particularly minorities and the medically underserved, will be given a voice in directing Sleep Apnea research that focuses on outcomes that matter to them.

The SAPCON represents an exciting collaboration of the American Sleep Apnea Association (ASAA), the nation's sole sleep apnea patient-centric organization, which serves as an information clearinghouse and support network for people who suffer with sleep apnea and their loved ones, with major research and clinical partners that include Harvard's Brigham and Women's Hospital and Informatics for Integrating Biology & the Bedside (i2b2) / Shared Health Research Informatics Network (SHRINE) and the Centers for Translational Science Award (CTSA) Sleep Research Network (SRN). Already, novel collaborations have been initiated with other PPRN and CDRN applicants, with plans for co-development of informatics tools and infrastructure and for co-enrollment. The team has the talent and resources needed to efficiently build a PPRN of actively engaged patients and to collect and share health information needed to support critically needed research. Over an 18 month period, 50,000 patients will be recruited from a pool of over 10 million patients, using a broad strategy including social media and targeted clinic-based recruitment. A patient friendly web-portal will be built using open-source and robust tools that will provide each patient a "dashboard" for contributing health information, coupled with powerful visualization and aggregation tools for viewing and monitoring data. "Blue button" technology under development by our partners (national leaders in health exchange information) will be leveraged to rapidly deploy a standardized, interoperable and scalable network model using the same standards of clinical data exchange already required by Federal regulation to support patients in gaining access to and controlling flows of their health information.

The COPD Patient Powered Research Network

Principal Investigator: Richard Mularski, MD, MS

The Chronic Obstructive Pulmonary Disease (COPD) Foundation, in collaboration with the CONCERT and COPDgene research networks proposes to develop and host the COPD Foundation Patient Powered Research Network (PPRN). The collaboration brings together a patient developed and governed patient education, advocacy and support group with the research expertise of two federally funded research networks to establish the COPD Foundation PPRN. The COPD Foundation PPRN will enroll 100,000 people with COPD, approximately 0.5% of the U.S. COPD population, into a registry with scalable data hub for the sole purpose of supporting patient-driven, patient centered outcomes research (PCOR). Enrolled patients will represent the spectrum of COPD disease severity—most with multiple morbidities, across diverse geographic regions, broad age and socio-economic ranges, both gender, and all racial and ethnic groups.

Chronic obstructive pulmonary disease (COPD) is a critical part of U.S. health care affecting 12–24 million individuals in the nation, is responsible for 800,000 hospitalizations per year, and recently became America's 3rd leading cause of death.¹⁻⁷ COPD related health expenditures are estimated to be as high as \$50 billion per year, driven primarily by costs of hospitalization and a 25% hospital 30 day readmission rate.⁸⁻¹² Healthcare expenditures for re-hospitalizations in patients with COPD exacerbations rank as the third highest among Medicare beneficiaries; provisions in the 2010 Affordable Care Act specifically list re-hospitalizations within 30 days after COPD exacerbations as a target for potential financial penalties by the Centers for Medicare & Medicaid Services (CMS).^{13,14} In recognition of the substantial and increasing impact of COPD on the health of the U.S. population, the U.S. Centers for Disease Control, the National Heart, Lung, and Blood Institute (NHLBI), and others have recently collaborated in the development of public and health professionals awareness campaigns to increase disease understanding, reduce stigma, and foster the use of evidence-based treatment and prevention approaches for COPD. The continuing lag between clinical practice and treatment options described by efficacy studies to improve the quality of life, functional status, and survival in patients with COPD, make COPD ripe for patient-centered outcomes research.^{1-9,15-24}

The COPD Foundation is a national not-for-profit organization established by patients in 2004 solely dedicated to representing individuals with chronic obstructive pulmonary disease in the United States. The mission of the COPD Foundation is to improve the quality of life for those affected by COPD. The Foundation's activities span research, education, and public health/policy related programs and services to patients, caregivers and healthcare providers. The collaboration with the two large, federally funded research networks (CONCERT and COPDgene) will both expand services and capacities of the Foundation as a PPRN and enhance the ability of CONCERT, COPDgene, and others within the PCORI infrastructure to conduct PCOR empowered by patients with COPD. The COPD Foundation

will lead an effort to expand its current network with registrants to its PPRN willing to share clinical information, patient-reported outcomes (PRO), and participate in PCOR. Active outreach for enrollment will include the 228,701 patients with linked administrative and clinical data of the CONCERT network as well as another 10,300 with patient reported outcomes and genetic data of the COPDgene network. COPD patients currently enrolled in the existing research studies will have the benefit of outreach and participation in the other Foundation's activities including Peer Health coaching and extensive educational material maintained by the COPD Foundation. Amongst the participants in the CONCERT data hub, outreach can take advantage of existing demographic data across its diverse health care delivery sites and regions to target under-represented groups including those defined in terms of race/ethnicity, socioeconomic status, geographic location, clinical severity, and multi-morbidity. From this large pool of patients with currently available data and the members across the COPD Foundation and affiliates networks, we are confident we can enroll at least 100,000 patients who will provide PRO and demographic information and sign comprehensive consent and data sharing agreements to allow common shared data use for the COPD Foundation PPRN and across PCORI networks.

Multiple Sclerosis Patient-Powered Research Network

Principal Investigator: Robert McBurney, BSc, PhD

Accelerated Cure Project for Multiple Sclerosis (ACP) is a patient-founded, patient advocacy organization, highly successful in engaging patients to create resources that catalyze innovative collaborative research. In 2006, ACP launched a patient network centered on an open-access biosample and data repository for use in investigating causes and mechanisms of multiple sclerosis (MS). Today, our network has an enthusiastic base of 3,200 participants (patients and control subjects), clinician-researchers at MS specialty clinics located across the USA, strong relationships with over 60 research teams in academia and industry, and an invaluable collection of tens of thousands of biological samples (DNA, RNA, serum, plasma, and white blood cells) linked with extensive medical data and patient-reported information that, to date, has supported 77 research studies worldwide.

In partnership with the Computational Sciences & Informatics of Complex Adaptive Systems at Arizona State University and Feinstein Kean Healthcare, ACP proposes to expand the repository network to an MS Patient-Powered Research Network (MS-PPRN), so that a large number of MS patients across the USA can participate in ACP's mission and in the National Patient-Centered Clinical Research Network (NPCCRN). The MS-PPRN will be supported by an integrated IT and communications platform featuring a patient-driven and controlled portal (iConquerMS) that can be accessed regardless of geographical location and healthcare provider. This portal will give patients the opportunity to provide health-related, demographic, and electronic health record (EHR) information that can be shared in a de-identified fashion with researchers who are investigating topics that are important to patients, such as comparative effectiveness of therapeutic agents. Patients will also have the option of contributing biosamples through home-based collection or local laboratories to support biomarker research in MS. To catalyze research using MS-PPRN biosamples and data, ACP will mobilize the scientists who have already used ACP Repository resources and will also leverage its MS Discovery Forum website to reach a wider audience of investigators.

ACP's 18-month goal for enrollment in the MS-PPRN is 20,000 people with MS (5% of the estimated population of MS in the USA), beginning with the 3,200 participants in the current ACP Repository network. Outreach will be made through ACP's existing participant and supporter base, its network of top-tier MS clinics, other MS clinics and community neurologists, MS advocacy organizations who have agreed to bring our invitation to their members, and social media and other communications channels. In addition to increasing the size of the network, an equally important goal is to enroll participants that reflect the full diversity of the population of Americans with MS. Programs will be put in place to ensure that people in underrepresented groups learn about the opportunity to join the network, perceive the benefits of the network for themselves and for the MS community in general, and feel welcomed and valued as participants.

ACP's top-level direction is set by people with MS and family members, and ACP includes patients and other stakeholders in research decisions and operations. For the MS-PPRN, a patient-centered governance structure will be established that includes a Governing Board, and Research, Membership, and Communications Committees, all

chaired by MS patients. Network participants will be invited to fill open governance positions and continually encouraged to participate in research topic generation, priority setting and decision-making by providing input via the portal. Educational content about the nature and practice of research, information about the participant cohort and studies supported by the MS-PPRN, and direct communications with researchers will be provided via the portal to give participants an enhanced level of knowledge about MS research and greater motivation to not only learn more but also contribute their own opinions and ideas.

The iConquerMS portal will be constructed in a modular fashion, composed of well-vetted, open-source components. Portal technology and data collection instruments will be standards-based whenever possible to enable seamless integration with other NPCCRN components and streamlined research across networks to facilitate investigations spanning multiple organizations and disease areas. The MS-PPRN team will be eager and active participants in the data standards and policies development activities of the NPCCRN.

American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network (ABOUT)

Principal Investigator: Rebecca Sutphen, MD

The ABOUT Network is a national patient-powered research network (American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network) focused on hereditary breast and ovarian cancer (HBOC) that will be expanded in significant ways through the proposed funding and is well positioned to participate in and contribute to the planned U.S. patient-centered network for comparative effectiveness research. Most HBOC is due to inherited mutations in two genes, BRCA1 and BRCA2 (BRCA) that put women and men at very high risk for breast, ovarian, and other cancers and are associated with aggressive and earlier onset cancers and multiple primary cancers in the same individual and family members, including men.

The ABOUT Network is the product of a nine-year collaboration between the leading national nonprofit advocacy organization for individuals and families impacted by HBOC: Facing Our Risk of Cancer Empowered, Inc. (FORCE) and a team of HBOC researchers based at the University of South Florida (USF). Both partners—led by patient advocates—have combined their strengths in advocacy, research, and engaging community participation to pursue better information, services and outcomes for the patient community to which they belong and conduct collaborative research that extends beyond academia to research powered by patients being cared for in communities across the country. Patient governance is fundamental to the ABOUT Network. The leaders of both partner organizations (Co-PIs in this application) are premenopausal breast cancer survivors (a clinical red flag for HBOC) and most of the other members of the ABOUT Network team have been personally impacted by HBOC.

The proposed efforts build on extensive, scalable research infrastructure, including a secure web-based data system and electronic interfaces developed by an experienced USF team that currently supports 1) enrollment and longitudinal follow-up, 2) patient-reported data collection, 3) real-time data sharing across the network, and 4) automated data transfer, including with health plans (for participant medical claims data) and genetic testing labs (for participant genetic test results). The work builds on a novel strategy for broad recruitment of individuals with HBOC in partnership with health plans, and a successful proof-of-concept project with Aetna that successfully enrolled 4000 individuals with HBOC over a single year, including consent for: longitudinal engagement and recontact, use of the data in future research, obtaining participant medical claims data, genetic test results and leftover DNA samples; which has expanded to recruit an additional 5000 newly diagnosed breast cancer patients over the next three years.

The proposed funding will be used to expand recruitment beyond current targeted efforts to all individuals with HBOC in the U.S., increase community engagement in research by operationalizing patient governance of the network and incorporating community input to direct research priorities, promote HBOC research opportunities, and optimize enrollment into HBOC-specific studies, as well as report back new research findings to the community. This will be accomplished by 1) enhancing the ABOUT data system to enable anyone with HBOC to easily establish a secure account that automatically generates an individualized dashboard for longitudinal

interactive engagement and VDT capabilities, 2) partnering with related advocacy organizations across the country to expand HBOC patient engagement, governance and representativeness in ABOUT, to set a patient-powered framework for research collaborations 3) partnering with the MI Department of Community Health Cancer Genomics Program in a method and model to engage and coordinate efforts between all relevant stakeholders (i.e., patients, providers, health plans, Medicaid, Medicare, military, public health officials and other policy makers), 4) expanding data collection in multiple ways (i.e., incorporate EHR data, integrate participant data of all types, implement questionnaires for additional relevant patient subgroups (i.e., beyond current high- risk women without cancer, women with breast cancer and men, to include ovarian cancer patients, women with metastatic disease, linked family members) and 5) implementing a biospecimen banking and automated tracking system. The ABOUT Network is committed to growing our capabilities, sharing our experience, best practices, and resources and fully participating in the national patient-centered network for comparative effectiveness research.

Mood Patient-Powered Research Network The mood disorders, Major Depressive Disorder (MDD) and Bipolar Disorder (BP), are highly prevalent and are among the top 10 causes of disability worldwide¹. The lifetime risk for MDD is about 17% with 12% for men and 25% for women; BP is about 2-4% for men and women²⁻⁴. With yearly costs of about \$100 billion and \$151 respectively^{5,6}, MDD and BP are associated with decreased earnings⁷, increased health care utilization for medical conditions and premature death with up to 25 years of lost life^{8,9}. After multiple, sequential interventions, about 50% of MDD patients¹⁰ and 30% of BP patients¹¹ achieve remission. Nevertheless, 90% can experience relapses within 6 months and recurrences thereafter¹²⁻¹⁴. Inter-episodic subsyndromal symptoms including cognitive dysfunction also persist and render many patients incapable of functioning, or holding a job¹⁵. Furthermore, while neuroscience has determined that mood disorders result from dysregulated brain circuits¹⁶, people with mood disorders continue to experience stigma even from physicians who provide their primary medical care¹⁷. Therefore, many patients with mood disorders feel disenfranchised and would welcome the opportunity to become more active and engaged in research collaborations to improve their lives. PCORI's funding of a PPRN that focuses around patients with psychiatric disorders will empower a patient group that often feels marginalized and unheard.

Mood disorders are complex conditions^{3, 4}, and effective treatments can make substantial differences on the trajectory of these illnesses but we are currently unable to match patients to treatments . Therefore, we propose to establish a Mood PPRN that will not only provide opportunities for patients to participate in comparative effectiveness research, but will engage them in all stages of research – from setting priority questions, to governance and oversight of studies, to dissemination of results with the ultimate goal of enhancing their sense of empowerment and agency through unprecedented collaboration with the research community. This Mood PPRN proposal centers on patients as collaborators to form a new patient-researcher- clinician community.

The ultimate goal of the Mood PPRN is to improve the lives of patients with mood disorders through prospective comparative effectiveness trials embedded within routine care¹⁸ and through patient reported outcomes as well as outcome data from electronic medical records (EMR)¹⁹. Clinicians who care for people with mood disorders frequently encounter uncertainty when making treatment decisions. Currently, no clinical or biological data can robustly guide clinicians to match patients with treatments. Instead, when faced with competing treatments, patients and clinicians must decide what course to take in the absence of adequate comparative effectiveness data. Even under optimal conditions when shared decision making occurs, those decisions are made under conditions of uncertainty. Thus, the Mood PPRN can be used to determine the best interventions for mood disorders that lead to the best patient-defined relevant outcomes.

The main aim of the Mood PPRN is to bring together at least 50,000 patients with mood disorders who will be willing and able to participate in prospective comparative effectiveness studies and provide longitudinal data through their EMR¹⁹ and patient recorded outcomes. Our main strategy to achieve this extraordinary aim within 18 months will be to collaborate with multiple mood disorder advocacy groups with their broad reach through their membership and websites to provide opportunities for patients to volunteer. From the very start, patients will be true partners in this initiative and will be instrumental in determining priorities. Key members of the team include the Medical Director of the National Alliance on Mental Illness (NAMI), the President of the Depression Bipolar Support Alliance (DBSA), the President of the International Bipolar Foundation, and most important, the

members of these patient advocacy groups as well as patients who receive care from a wide network of clinicians. In collaboration with the Partners Healthcare System, we will also have the expertise to aggregate data from multiple EMRs20-22 and integrate patient reported outcome data into a comprehensive database as well as setting up the infrastructure to obtain and process biosamples that will form a foundation to advance our understanding of the biology of mood disorders for personalized care.

Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium

Principal Investigator: Laura Schanberg, MD

The CARRA Registry and PR-COIN have enrolled almost 9,000 patients with pediatric rheumatic disease – a significant proportion of children in the U.S. with this uncommon condition – into next- generation registries at 62 pediatric centers. We use this achievement as a starting point to invert the current model to a patient-centric, patient-powered network. PCORI offers us the extraordinary opportunity to make patients and their families full collaborators in research and governance of a PPRN—the Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium—bringing together children with the most prevalent pediatric rheumatic diseases, Juvenile Idiopathic Arthritis (JIA) and childhood-onset Systemic Lupus Erythematosus (cSLE), which share overlapping biological, clinical, therapeutic, and psychosocial features. PARTNERS formally links patients, family members, and other stakeholders including healthcare providers, 3 advocacy groups (Arthritis Foundation [AF]; Friends of CARRA [FoC]; Lupus Foundation of America [LFA]), a clinical research network (Childhood Arthritis & Rheumatology Research Alliance [CARRA]) and a quality improvement learning network (Pediatric Rheumatology Care & Outcomes Improvement Network [PR-COIN]).

PARTNERS will drive forward research based on patient-centered scientific priorities and integrate patient input into all aspects of research, from study design to analyses, creating a patient-centered learning health system. Complementary perspectives, infrastructure and expertise empower patients, clinicians, and researchers to learn together from every patient interaction by conducting patient-centered outcomes research, and implementing the findings in a virtuous cycle (see Fig 1). Patient engagement is the core—patients connect, participate in the governance structure, and contribute to comparative effectiveness research through data collected at clinical visits and on electronic devices. We will leverage existing outreach and technology capabilities of PARTNERS community building organizations, the AF, FoC and LFA, to reach out to patients affected with JIA and cSLE and optimize capture of diverse patient perspectives, focusing on engagement of underserved populations. These organizations will anchor PARTNERS in the JIA/cSLE community, raising awareness around the importance and opportunities of patient engagement for research purposes. LFA will extend its online patient registry to enhance cSLE enrollment and electronically link to the CARRA Registry. AF and FoC will partner with PR-COIN to expand current JIA patient engagement to reach a wider community. This approach will increase patient enrollment to support health care innovations. Registry (CARRA 6170 JIA patients, 921 SLE, 62 sites) (PR-COIN 1100 JIA patients, 11 sites) informatics infrastructure will connect physicians and researchers to patients.

PARTNERS governance structure links both strategic approaches. Patient groups learn from community building initiatives and build bridges with physicians developing technology driven health care innovations. Patients in the Project and Community Teams, will test innovations, provide feedback, and use AF, FoC and LFA patient networks to encourage other patients to adopt the technology and submit their own data. During the award period, we focus on: 1) establishment of a shared governance model, in which patients and advocates fully partner with clinician-scientists in network leadership; 2) implementation of consortium-wide strategies and metrics for enhanced patient engagement and adoption of patient-directed research priorities; and, 3) coordination and standardization of data collection and sharing across the consortium, extending existing online platforms for patient reported outcomes (PROs) and direct data transfer from electronic health record (EHR) to PARTNERS databases. These innovations eliminate duplicate collection of data and vastly increase the feasibility of widespread participation and promote integration of QI and research in a learning health system. PARTNERS will share open source tools and technical innovations (including i2b2) with other PPRNs and CDRNs, thus expanding the reach and scope of our accomplishments.

ALD Connect

Principal Investigator: Florian Eichler, MD

The ALD Connect consortium empowers patients, caregivers and their affinity groups to move beyond conventional research participation, advocacy, and fundraising efforts to improve care for and ultimately eradicate the debilitating single-gene disorder, X-linked Adrenoleukodystrophy (ALD). Through direct participation in decisions on research and drug development, patients will influence research priorities and directions. The ALD Connect collaborative network will introduce a novel all-inclusive model to improve care and drug discovery for well-defined single-gene disorders. Towards this end, we will accomplish two goals within the 18-month period:

- 1) Conduct an inventory of existing resources, design common data elements and collect information from resources around the world (patient registries, advocacy groups, electronic health records, academic databases, brain and tissue banks). Data will be captured, harmonized and aggregated in the NeuroBANK™ platform through a partnership of the ALD/AMN Global Alliance, the largest patient advocacy group for ALD, and the Neurological Clinical Research Institute at Massachusetts General Hospital.
- 2) Create a social network platform that allows for dynamic engagement of the patient community through two-way communication between patients and researchers. Examples include ALD Knowledge Portal, where patients vote on research projects, track their disease progression, and report outcomes, as well as ALD Patient Learning Academies, where patients learn about clinical research and therapy development and become ambassadors for ALD clinical research and champions of the latest methods, treatments and recommendations in clinical care.

An enormous advantage of utilizing the NeuroBANK™ platform and Global Unique Patient ID (GUID) technology is that patient-reported information will be aggregated along with the clinicians' and researchers' captured data. This approach alone will validate and enhance patient-reported outcomes within the overall repository.

Three innovative pilot projects will supplement the two stated goals. These patient-centered pilot projects will (a) evaluate new drugs through the ALD Treatment Pipeline, (b) assess devices to provide mobility training for ALD Patients, and (c) test remote data collection in ALD patients.

Unique to our efforts is the transformative collaboration between patients, patients advocacy groups and academic centers that will allow for data comparison and validation, patient feedback on research directions, and more rapid trial development because of an educated and engaged patient community. Social network maps and analytics will assess the level of activity in our network and directly measure and improve its success.

Phelan-McDermid Syndrome Data Network (PMS_DN)

Principal Investigator: Megan O'Boyle, BA

Objective: To collect all available patient data from Phelan-McDermid Syndrome (PMS) patients to make meaningful, well-annotated clinical data available to researchers and to share insights with members of the PCORI network.

PMS is an orphan genetic condition caused by deletions of 22q13 or mutations of the SHANK3 gene. The syndrome presents with an array of characteristics, but the manifestations are profound, and parents and caregivers must advocate for PMS patients throughout the life's course. The PMS Foundation (PMSF) is a parent-driven non-profit 501(c)3 organization, founded in 2002 by families of children diagnosed with PMS. The mission of PMSF is to provide family support and to accelerate research for individuals with PMS. PMSF parents recognized a need to compile health records in a meaningful fashion to further research, and together with researchers and advisors, they launched an international patient registry, the PMSIR, that is directed, governed and implemented by patient families. IRB approval was obtained in 2011 there are currently 546 active participants, 49.6% of the world's known patients.

PMSF has pioneered the concept of the patient-driven registry within a population of patients with a rare condition, through the perseverance of devoted parents. PMSIR provides a solid foundation upon which to build a network that can create new information in the form of meaningful data for researchers. Founded by parents, PMSIR is driven by parents, governed by parents, and will be transformed by parents who are stakeholders in the success of a standardized research data network. This network empowers both researchers and parents to address issues fundamental to the quality of a PMS patient's life. PMS parents have proven they are willing and able to collaborate with the medical community, researchers, clinicians, and consultants to bring a concept to fruition, evidenced by the current capacity of PMSIR and collaborations with researchers noted in this proposal. Because PMSIR is well established and parent constituents are committed to the mission, PMSF is uniquely positioned to expand the existing parent network through building transformative infrastructure to become a model Patient-Powered network as defined by the PCORI vision. The proposed PMS Data Network (PMS_DN) will continue to encourage active participation and leadership of PMS families, and enhance organizational structure and capacity to further develop PMSIR into a comprehensive data network. An existing Parent Advisory Committee (PAC) is charged with ensuring PMSIR meets the needs of families and is in alignment with the community's goals. Outreach to PMS families is an important strategy for increasing participation.

The real value in biomedical research lies not in the scale of any single source of data, but in the ability to integrate and interrogate multiple, complementary datasets simultaneously. Combining data across different scales and resolutions such that reliable results can be generated to address important questions is non-trivial. Thus the principal challenge is not a lack of data, but how best to make sense of it. This project will build a dedicated PMS_DN to enable scientists to have access to all available knowledge from PMS patients. Multiple data feeds will be established to extract and link data from well-characterized patient and population cohorts into the backbone informatics architecture provided by the open source, i2b2 based, transSMART platform. Such datasets must meet the needs of researchers (including support for diverse scientific collaborations with CDRNs or outside PCORI) while simultaneously preserving security and maintaining appropriate privacy and ethical safeguards. PMSF is excited to participate in the PCORI program-wide steering committee to share insights with the constituency of the PCORI network. PMSF is willing to share insights with other PPRNs who are just starting to build a patient network. PMSF believes that not only should patients be at the center of research, those that are doing it well have a commitment to the greater community to share best practices.

PI Patient Research Connection: PI-CONNECT

Principal Investigator: Kathleen Sullivan, MD, PhD

Primary Immunodeficiency (PI) represents a group of more than 185 related, rare genetic diseases with a diagnosed population prevalence of about 1:1200, although the prevalence for each specific diagnosis varies from 1:1000 to less than 1:1,000,000.^{1,2} The challenges for the study of these rare diseases are the geographic spread of patients making single center studies impossible except for the most common diseases, a lack of integrated effort by clinicians with research experience and the patients who are invested in specific answerable questions, and the infrastructure challenges of broad-based recruitment of patients for studies. This proposal describes a unique fusion of efforts to address those challenges, leveraging new technologies to answer important questions regarding the care of patients with PI.

Currently, a curated, data-validated, longitudinal registry of patient data exists, however, patient recruitment depends on physician entry and the cohort is strongly skewed towards academic centers. A second data set, produced to give patients a unified home for their medical information, has been developed. Our goal is to meld these two data sets to maximize the breadth of data and to promote improvements in patient care. Importantly, the melding of the data sets will also bring together the major groups invested in improving patient care: researcher/physicians and patients. Once the investment in technology infrastructure has been completed and the collaborations with like-minded groups established, we view this effort as self-sustaining.

Founded in 1980, the Immune Deficiency Foundation (IDF), the national nonprofit patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with PI, believes that advances in the medical care of patients with PI will require partnerships between patients and researchers. IDF developed the eHealthRecord, an electronic personal health record (ePHR) designed specifically for the PI community. This simplifies tracking healthcare information and activities by PI patients and caregivers. A backend database allows de-identified aggregate data to be analyzed for educational and research purposes. IDF also administers the United States Immunodeficiency Network (USIDNET), overseen by a steering committee of the leading clinical immunologists in the United States. USIDNET developed and maintains a patient-consented registry of U.S. and Canadian patients with the goals of providing a comprehensive clinical picture of each disorder and to serve as a resource for clinical and laboratory research.

In order to blend the personal patient information with clinical data, IDF is proposing to build a PPRN that would combine the eHealthRecord patient-entered data with the USIDNET patient-consented registry with the working title of the PI Patient Research Connection, or PI CONNECT. PI CONNECT will create a venue for researchers and patients to communicate about proposed research involving the network data, giving patients a voice in research, as well as giving researchers better access to the PI community.

IDF has built a strong bond with the PI community, including patients, clinicians and researchers, based on trust, reliability and understanding. Last year, nearly 13,000 patients and healthcare professionals attended more than 160 IDF educational presentations in 123 cities in 37 states. IDF answers patient inquiries and features educational materials and publications from a website that generates 33,000 visits per month. Electronic and mailed newsletters are read by tens of thousands of people. Promotion using existing IDF channels will grow participation in the PPRN while new modes of engaging the population, like the launch of a mobile application, will ensure continued value and use of the network. To expand the clinical information, the eHealthRecord will use Blue Button technology to integrate users' existing medical records into the network.

USIDNET and IDF bring strong records of success. With the development of PI CONNECT, we will be able to revolutionize acquisition of data and patient-powered research agendas. PI CONNECT will bring together the strengths of USIDNET (a robust database of longitudinal patient information and a tradition of clinical research) and the IDF patient organization (outstanding patient buy-in and a strong tradition in addressing patient concerns and the IDF ePHR). This integration will also complement each group's traditional limitations (USIDNET: recruitment skewed towards academic centers and limited patient-reported data; IDF: de-identified aggregate cross-sectional approaches), crystallizing into a productive force. By integrating efforts, PI CONNECT will enable superior outcomes research, quality of life research and identify potential markers for risk stratification. Importantly, the direct involvement of patients will focus those studies using the lens of their own experiences and unanswered questions.

Vasculitis Patient-Powered Research Network (V-PPRN)

Principal Investigator: Peter Merkel, ME, MPH

The Vasculitis Patient-Powered Research Network (V-PPRN) is the product of a more than 10-year productive collaboration among patients, patient advocacy organizations, academic clinical investigators, expert clinicians, biomedical informaticians, qualitative and quantitative methodologists, and funding organizations all dedicated to conducting high-quality clinical research in vasculitis aimed at addressing key scientific and clinical issues considered of high-priority to both patients and physicians. We propose to expand the role of patients such that they are fully involved and direct network governance, demonstrate that we will have patient-reported data collected for at least 80% of the cohort, build upon our extensive experience and expertise in incorporating data standards suitable for sharing, leverage our established infrastructure, resources, and positive and productive relationships among stakeholders, and evolve and transform the V-PPRN into a model PPRN within the overall National Patient-Centered Clinical Research Network (NCRN).

The V-PPRN is comprised of the Vasculitis Foundation (VF), the umbrella vasculitis patient advocacy group in the United States (US), the Vasculitis Clinical Research Consortium (VCRC) which includes every major center for clinical investigation in vasculitis in the US and Canada (and a significant international community of investigators), an established on-line group of patients with vasculitis dedicated to conducting meaningful research, the clinical community caring for patients with vasculitis, and experts in applying data standards in federated databases including the electronic health record (EHR), disease-specific health data, and patient-reported outcomes. These linked stakeholder groups have worked together for more than a decade with a common mission of improving the lives of those affected with vasculitis. Vasculitis is a set of rare organ and life-threatening diseases of vascular inflammation linked by similar pathophysiologies. Despite improvement in the overall prognosis of vasculitis since the introduction of regimens based on combination immunosuppressive therapy, the cumulative morbidities and mortality from both disease and treatment for most patients, the social impact, and the costs remain enormous. Given the many challenges of conducting research in rare diseases, we bring a remarkable set of skills, successful experiences, and resources to this initiative.

Utilizing resources provided by a PCORI award and the NCRN, the V-PPRN is poised to increase our membership and patient representation, expand data access and availability, and address disease-specific outcomes. The V-PPRN will be a vibrant, flexible, sustainable patient community ready and committed to participate in clinical research through sharing of electronic medical records to address important issues facing patients and other stakeholders.

This application outlines the existing infrastructure of the V-PPRN, the outstanding scope of our Network from both the patient and investigator perspectives, our capabilities including capture and merger of electronic health records from patients with vasculitis with patient-provided outcomes, plans for feasible growth and change to fulfill the requirements and great potential of a PCORI PPRN, and evidence of our leadership structure in which all stakeholders have a substantive voice in decisions and prioritization of the research agenda.

The DuchenneConnect Patient-Report Registry Infrastructure Project

Principal Investigator: Holly Peay, MS

DuchenneConnect is an established patient-report registry for Duchenne and Becker muscular dystrophies, and it is a model for rare-disease registries. The registry platform and functionalities, created through collaboration between DuchenneConnect and PatientCrossroads, have been extended to support registries for more than 250 disorders. DuchenneConnect has over six years of experience and has collected a robust, longitudinal patient-report dataset that has been utilized by industry, clinicians, and academic researchers for uses that may lead to advances in Duchenne/Becker muscular dystrophy (DBMD). Parent Project Muscular Dystrophy, a parent-led foundation, founded and supports DuchenneConnect.

DuchenneConnect's years of experience have provided important lessons learned, as well as a clear understanding of registry needs. We must balance obtaining sufficient and robust information with the monitoring burden and providing participation benefits back to registrants. We must explore novel data collection approaches. This includes EHR integration to reduce registrant burden, allowing evaluation of the accuracy of specific patient-report outcomes, and improving our capacity to answer questions about natural history and care. We must improve the standardization of registry items while continuing to be responsive to data required to answer emerging research questions. We must build on our history of successful data sharing with the TREAT-NMD neuromuscular registry network and academic and industry collaborators with improvements to coding and standardized information exchange. Though the registry is currently guided by a multidisciplinary advisory committee that includes parents and individuals with DBMD, we must more systematically engage advisors, registrants, and the broader DBMD community in posing questions of interest. We must develop a multifaceted outreach approach to reach a more demographically representative and larger proportion of DBMD patients. Finally, we must continue to seek out

opportunities such as PCORI's Network to engage in innovative efforts that have the possibility to improve patient empowerment, care recommendations, and/or our understanding of DBMD natural history.

In 2011, DuchenneConnect began a successful first step toward comparative outcomes research through collaboration with the Department of Human Genetics at UCLA. This collaboration provided clinically relevant results that are of importance to the patient community. The experience invigorated DuchenneConnect to begin our next phase of growth—exploring information needs of our community, and working to address those needs through collaborative research that is efficient and cost-effective. We are extremely enthusiastic about the possibility of maturing the registry with input and support from the PCORI Network, while concurrently sharing our experiences (and ultimately data sets) with the Network partners. Many of DuchenneConnect's achievements through this program would become available to other disease registries under the PatientCrossroads model, thereby extending the reach of PCORI-led PPRN recommendations and improvements to a broader range of patient networks.

DuchenneConnect has always employed a collaborative growth model. The proposed project team brings impressive professional expertise and organizational resources that allow us to tackle challenging problems. Collaborators from PatientCrossroads and Geisinger Health System are prepared to identify and solve problems related to electronic health information integration. Geisinger will provide bioethics consultation and IRB access. UCLA collaborators will work with DuchenneConnect and PatientCrossroads to improve data standardization and export, and explore novel approaches to reach a more representative registrant population using large data sources. PatientCrossroads will implement advisor- recommended improvements to the data collection interface, as well as new capabilities for registry access and data input. DuchenneConnect welcomes the opportunity to engage with other PPRNs and CDRNs to explore the challenging and important issues that emerge from PCORI's Network goals—an effort of particular appeal to rare disease communities, where traditional research approaches may be especially difficult to implement.

NephCure Kidney Network for Patients with Nephrotic Syndrome

Principal Investigator: Bruce Robinson, MD, MS

Focal Segmental Glomerulosclerosis (FSGS), Minimal Change Disease (MCD), and Membranous Nephropathy (MN) – collectively referred to as primary Nephrotic Syndrome (NS) – are rare but serious kidney diseases that pose a substantial physical, psychological, and financial burden for those affected and often lead to kidney failure requiring dialysis or other major medical complications.¹⁻⁶ Diagnostic, prognostic, and therapeutic advances in the field have been stunted by the rarity of the condition, resulting in a patient experience marked by significant lag times to receive a proper diagnosis, limited effective treatment options, and numerous barriers to efficient coordination of care. Clinical data are frequently housed in the local institutions of care providers and are thus siloed across the United States. We propose a collaborative effort to develop the NephCure Kidney Network (NKN) as a Patient-Powered Research Network (PPRN) to serve as a resource for future comparative effectiveness research (CER) of relevance to patients with this disease. This new PPRN will allow important clinical and patient-reported data to be contributed, under patient control, to a centralized repository, facilitating rapid development and execution of research studies.

The proposing team is composed of experts from Arbor Research Collaborative for Health (Arbor Research), the NephCure Foundation (NCF), and the University of Michigan (U-M), specializing in adult and pediatric clinical nephrology, clinical research in NS, epidemiology, patient advocacy, and data management. We will build on NCF's recent development of the NKN as part of the pilot project of the National Institutes of Health (NIH) Office of Rare Diseases Research (ORDR) to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR), scheduled to launch in fall 2013. Under this award, the proposing team seeks to transform the NKN from a static repository of limited cross-sectional data to a rich clinical and patient-reported outcomes (PRO) database, with

patients as active participants to facilitate efficient and accurate CER. We propose the following aims for the 18-month award period:

- 1) Establish a network governance structure that includes substantial patient representation to ensure patient involvement in policy development and key decision-making.
- 2) Successfully recruit a minimum of 1,250 patients with distributions of demographic and clinical characteristics sufficient to support CER across a range of populations.
- 3) Establish strategies for network member engagement to maintain willingness and readiness to participate in CER.
- 4) Develop a set of standardized data elements designed for interoperability across research networks.
- 5) Develop the capacity and conduct proof of concept testing for data collection via mobile applications.
- 6) Develop the capacity and conduct proof of concept testing for electronic health record (EHR) data collection.
- 7) Assess patient willingness to contribute biosamples and develop the capacity for collecting, storing, and tracking biosamples in the future.

Interoperability with currently existing and future disease networks is one of the hallmarks of the NKN. When launched, the NKN will be implemented using the Patient Crossroads (PXR) CONNECT platform, designed specifically for use of common data elements (CDEs) and standardized terminology to facilitate mapping across all participating networks in the GRDR pilot program. Additionally, the NKN has plans to extend beyond the GRDR, with collaborative agreements in place to share data with the National Registry of Rare Kidney Diseases (RaDaR) in the United Kingdom (UK). With firm dedication to data interoperability, an open and proactive approach to sharing and collaboration, and a strong record and commitment to protection of human subjects, the NKN is a promising resource for future CER related to NS and other chronic kidney diseases (CKD).

The establishment of a research network with readily available clinical and patient-reported data, an organizational structure that includes patients in the governance process, and direct partnership with patients who are seeking opportunities to be a part of the solution to better health will facilitate much-needed advances for patients with this rare and devastating condition. Success of this network will undoubtedly have broader applications to conditions with clinical overlap (such as obesity and CKD) as well as to other rare diseases sharing similar barriers to research progress.

Rare Epilepsy Network (REN)

Principal Investigator: Janice Buelow, PhD, RN

The Rare Epilepsy Network (REN) PPRN is an initiative created by and for patients with catastrophic rare epilepsies. The REN's goal for this proposal is to build a patient-centered and driven data base designed to provide the patients and their families an opportunity to participate in research that will improve lives and quality of care for people with rare epilepsies. Our PPRN is led by the Epilepsy Foundation (EF), a patient advocacy organization dedicated to the welfare of the almost 3 million people with epilepsy living in the US. EF will lead this grant through our Principal Investigator, Dr. Janice M. Buelow. Dr. Buelow is director for all programs and research at EF and interfaces with all EF affiliates in the US and with each of the patient advocacy organizations that compose the REN. Network organization: Each of 7 partnering organizations is represented by a caregiver who has a loved one with the disorder (Figure 1). They are joined by two co-investigators/epidemiologists, Drs. Hesdorffer (Columbia University) and Kroner (RTI International), and a consultant neurologist Dr. French (NYU). Columbia University will design the clinical database and manage the data and harmonization.

RTI will host the database and serve as the genetics and biospecimen repository. Dr. French, an expert on epilepsy clinical trial design and new strategies for drug approval, and director of the Epilepsy Clinical Trials Consortium, will assign epilepsy seizure type and syndrome. Governance: The key considerations for our patient network governance include policy creation, development of standards, outreach and member engagement to create a robust patient-centered research enterprise for rare epilepsies. The inclusion of the leaders of the partnering organizations as members of the SC ensures that caregivers and individual organization members are involved

directly or indirectly in all aspects of REN decision making on data elements, policy formulation, research questions, data sharing, dissemination and social participation, responsiveness of patients, safeguards of privacy, and sustainability. Clinical Database: The REN will use Consilience Software's Maven database and their extensive experience implementing health information interfaces to import clinical information into databases. A major reason that the REN selected the Maven database was Consilience's experience using HL7 to populate databases with the electronic health record (EHR).

Two integration interfaces will be used - an automated HL7 import interface and a user- initiated blue-button generated HL7 data upload. Maven will enable the automated HL7 message portion through secure FTP. Other assets of Maven include the ease of configuring the database fields, and easily created real time data checks within and between tables with queries sent to patients while they are entering data. In addition, creation of customized automated reports is straight forward for documenting our progress to PCORI and the REN patient organizations. All data will reside on secure network servers in two RTI data centers. RTI's networks are fully compliant with FISMA data security standards and are protected by industry-standard firewalls that require data to be encrypted in transit thereby protecting the submitted EHR data. Sample, Recruitment and Retention: We currently have 857 patients in the REN and expect 690 to have data entered by the end of month 6. We expect that the size of the REN will increase 75% to 1500 by month 18. Each REN organization and EF has identified specific recruitment strategies including web-based and face to face recruitment.

Data Collected: Where possible we will use NIH common data elements (CDE) for epilepsy and other data elements for caregiver-reported patient outcomes. At baseline, the epilepsy CDEs will be used for demographics, seizure type and adaptive behavior. Additionally we will collect other data such as assessment of intellectual function and comorbidities. Follow-up information will be collected every 6 months. Sustainability: We will apply for future funding through public and private sources. EF is prepared to sustain this database through their own fund-raising efforts and to make the database available to all rare epilepsy organizations in order to foster research. EF has a strong commitment to supporting the best research possible to both improve care and to promote cures of epilepsy for patients. We believe that REN data base represents a strong mechanism to support our cause.

The Community-Engaged Network for All (CENA)

Principal Investigator: Sharon Terry, MA

The Community-Engaged Network for All (CENA), led by Genetic Alliance, is comprised of 10 disease networks. Genetic Alliance (GA) is an established umbrella organization supporting a network of 1000+ disease advocacy organizations (DAOs), including the 10 DAOs in CENA. Each DAO has a preexisting participant-powered network. Through CENA, online registries for each condition will be launched and/or upgraded, and additional participants will be invited and engaged in participant-centric research. The DAO networks will benefit from an award-winning registries platform and technical assistance for engaging communities to safely share their information online, as well as community building and collaboration between condition communities. CENA will use and improve participant-led governance models that GA has pioneered for more than a decade, bringing leaders and affected individuals from each condition community together to oversee CENA. CENA also includes two leading academic institutions, the Universities of California San Francisco (UCSF) and Davis (UCD). These partners will test the ability to recruit patients from academic medical centers into participant-led models. Through a partnership with another PPRN applicant (Health eHeart) at UCSF we will also assess the utility of CENA for recruiting for a comorbidity (cardiovascular disease). In addition, CENA will pilot new methods of facilitating collaboration between researchers and participants by supporting a broadly accessible online environment where communities and researchers have equal voice in the development of research hypotheses.

The ten DAOs participating in CENA are Alström Syndrome International, Dyskeratosis Congenita Outreach, Inflammatory Breast Cancer Research Foundation, Hepatitis Foundation International, Joubert Syndrome Foundation, KS&A, MLD Foundation, National Gaucher Foundation, National Psoriasis Foundation, and PXE International. The conditions range from rare to common and cover a broad spectrum of demographics. The DAOs were selected based on their readiness to participate in the PCORI PPRN vision. Four were selected as the

strongest networks in the existing Genetic Alliance biobank network, and the additional six were selected through a competition among DAOs facilitated by GA in August 2013 in preparation for this proposal. More than a hundred DAOs applied, and the top six were selected based on network readiness, existing resources brought to the table, and engagement with the PPRN vision.

The DAO-led communities will be supported and grown through inter-community collaboration, sharing best practices, and an award-winning platform. The Platform for Engaging Everyone Responsibly (PEER) will allow for extremely cost-effective data capture from participants in a manner that ensures granular privacy permissions management. PEER employs an interface that is gamified to maximize retention and flexible to allow for continual fine-tuning or addition of questions, including changes based on input from DAOs and academic research partners. PEER's potential to radically accelerate participant engagement and the collection of participant-reported outcomes has been recognized with wins in the Sanofi Collaborate | Activate and Ashoka Changemaker Challenges, as well as with a Forbes "Best Business Model" award. CENA proposes to fully leverage PEER through engagement with the 10 diverse communities. In addition to increasing recruitment, retention, and data collection, CENA communities will expand their recruitment through cross-condition activity, their ability to identify potential participants through common data sets (from the Universities, the Oracle Health Sciences Network, and Inspire community), and coordination in identifying underserved communities.

UCSF and UCD will invite researchers and their patients into a participant-driven network. We believe that shifting research culture from one where academic researchers reach out to participants, to one where participants lead, requires a common environment that supports dynamic and meaningful communication between DAOs' and researchers' communities. We will test whether patients at academic medical centers can be engaged through the participant-centric vision, and how best to do so. Especially for rare diseases, academic medical centers serve as specialized centers and focused points of engagement for recruitment into participant-led networks. We will ask how we might serve the research mission by providing an alternate route to recruitment for already successful studies at UCSF and UCD, such as Health eHeart, which primarily focuses on cardiovascular disease. We will assess the effectiveness and utility of drawing on participants' interest in engaging on a comorbidity even if their participation in CENA comes from initial interest in a specific (non-cardiovascular) condition. Finally, using a novel approach and tool developed at UCSF called Open Proposals, we will engage the 10 DAOs' members in a conversation with UCSF and UCD researchers interested in those conditions. As the DAOs prepared this proposal, great benefit accrued from planning to build a research network in a multi-condition forum. We believe significant benefits will continue to result from refining research hypotheses related to individual conditions in an open, transparent manner between researchers and participants, and between condition communities. CENA is offered by a collaborative (hereafter called the Team) composed of Genetic Alliance, UCSF, UCD, and Private Access; and 10 disease advocacy organizations chosen for this specific project (collectively referred to as the Steering Committee), governed by a patient Governance Board.