



Patient-Powered Research Networks of the Autoimmune Research Collaborative: Rationale, Capacity, and Future Directions

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Abstract

Patient-Powered Research Networks (PPRNs) are US-based registry infrastructures co-created by advocacy groups, patient research partners, academic investigators, and other healthcare stakeholders. Patient-Powered Research Networks collect information directly from patients to conduct and disseminate the results of patient-centered/powered research that helps patients make more informed decisions about their healthcare. Patient-Powered Research Networks gather and utilize real-world data and patient-reported outcomes to conduct comparative effectiveness, safety, and other research, and leverage the Internet to accomplish this effectively and efficiently. Four PPRNs focused on autoimmune and immune-mediated conditions formed the Autoimmune Research Collaborative: ArthritisPower (rheumatoid arthritis, spondyloarthritis, and other rheumatic and musculoskeletal diseases), IBD Partners (inflammatory bowel disease), iConquerMS (multiple sclerosis), and the Vasculitis PPRN (vasculitis). The Autoimmune Research Collaborative aims to inform the healthcare decision making of patients, care partners, and other stakeholders, such as clinicians, regulators, and payers. Illustrated by practical applications from the Autoimmune Research Collaborative and its constituent PPRNs, this article discusses the shared capacities and challenges of the PPRN model, and the opportunities presented by collaborating across autoimmune conditions to design, conduct, and disseminate patient-centered outcomes research.

1 Introduction

People living with autoimmune conditions frequently make critical decisions about treatments involving costly and innovative medications, often with little data comparing the treatments' effectiveness or safety to guide such decisions. Furthermore, existing clinical trial research in the field has primarily utilized data from images, laboratory tests, and clinical assessments under the control of providers [1]. Such

partiality for provider-sourced data may under-appreciate or under-measure patient-reported outcomes (PROs) or other patient-generated data that patients themselves deem important [2–4]. Patient-reported outcomes constitute an assessment of symptoms or disease coming directly from the patient without interpretation by an intermediary [5]. Little longitudinal real-world evidence incorporating PROs exists to help inform patients with autoimmune diseases, and other stakeholders, about patients' experiences while receiving immunomodulating therapies, including patterns in their disease activity and symptoms. Patient-centered outcomes research is characterized by engagement of patients throughout the research process and inclusion of research questions and outcomes important to patients and care partners, such as PROs and other measures related to quality of life, disease symptoms, and safety [6, 7]. Patient-centered outcomes research can be especially important to people living with immune-mediated conditions who make choices from an array of therapy options, and want to know about the experiences of similarly situated individuals receiving such therapies [8]. In principle, patient-centered outcomes research: encourages researchers to learn how treatments affect patients' ability to manage symptoms and maintain

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Key Points for Decision Makers

Patient-Powered Research Networks conduct a range of direct-to-patient research activities comprising digital research recruitment and data collection methods, innovative informatics, including computable phenotypes, and novel methods for data linkage, and systems that promote dissemination of relevant information to patients and other healthcare stakeholders.

Four Patient-Powered Research Networks focused on autoimmune and immune-mediated conditions formed the Autoimmune Research Collaborative with individual and collective capacity to respond to research questions using existing and new data and scalable infrastructure.

their quality of life, often using information collected directly from patients; engages patients throughout the research process by weighing in on study objectives, design, conduct, implementation, and dissemination; and speeds dissemination of research findings back to patients and other stakeholders to help them to use the most up-to-date information in their healthcare decisions [6, 7, 9].

Patient-Powered Research Networks (PPRN) focusing on autoimmune conditions are well positioned for real-world patient-centered outcomes research that provides benefit to patients and other stakeholders. The PPRN model has features that confer clear advantages for patient-centered outcomes research, but are also accompanied by inherent challenges. Four US-based PPRNs formed a collaborative group for discussion, planning, action, and reflection, to build on the strength of the PPRN model and address its vulnerabilities. This article describes the shared history, characteristics, capacity, and challenges of the PPRNs comprising the Autoimmune Research Collaborative (ARC) and shares practical examples of, and opportunities for, implementing patient-centered outcomes research.

2 History and Structure: The PPRNs Comprising the ARC

Ensuring that patients, the end users of healthcare research results, are engaged in research is a foundational priority for the PPRNs that were initially established with infrastructure support from the Patient-Centered Outcomes Research Institute (PCORI) [10–12], a non-profit government-sponsored organization created by the 2010 Patient Protection and Affordable Care Act. Patient-Powered Research Networks grew out of existing patient organizations or communities in partnership with academic centers, and they use online

(Internet/Web) and/or smartphone-based portals that provide patients with the ability to propose research questions and access research opportunities directly, rather than relying on physician solicitation for participation. Each PPRN functions as a registry or secured repository of patient-generated data and observational electronic health information.

In 2019, four PPRNs formed the Autoimmune Research Collaborative: ArthritisPower (rheumatoid arthritis, spondyloarthritis, osteoarthritis, and other rheumatic and musculoskeletal diseases), IBD Partners (inflammatory bowel disease), iConquerMS (multiple sclerosis), and the Vasculitis Patient-Powered Research Network (multiple forms of vasculitis). The four constituent PPRNs of the ARC have a shared history rooted in the development and launch of the National Patient-Centered Clinical Research Network (PCORnet) that began in December 2013 when PCORI's Board of Governors approved phase I, 18-month funding for an initial group of 29 partner networks. These networks included health system-based Clinical Research Networks, patient-initiated PPRNs, and a Coordinating Center to lead development of the PCORnet Common Data Model, harmonization of data and processes, and fielding of PCORnet data queries [12]. A second phase of infrastructure development involving 13 Clinical Research Networks, 20 PPRNs, two Health Plan Research Networks, and the Coordinating Center operated from the fall of 2015 through 2018. While Clinical Research Networks "... are based on electronic health record (EHR) data and other electronic sources related to large patient populations within health care systems," and Health Plan Research Networks are based on claims data from health plans, PPRNs mobilize communities of patients with a single medical condition or several related conditions who participate in research that generates new knowledge for patients similarly affected by the condition(s) [13]. Patient members of PPRNs contribute their self-reported and EHR data, and help to guide and govern the network's research activities [11]. In 2016, four PPRNs chartered the PCORnet Autoimmune and Systemic Inflammatory Syndromes Collaborative Research Group to develop new research across common areas of interest within PCORnet and to advance network sustainability.

In its current pared-down form, PCORnet includes nine Clinical Research Networks, two Health Plan Research Networks, a Coordinating Center, but no PPRNs [14]. Although funding constraints have meant that PPRNs were no longer considered part of PCORnet beyond phase II, the four PPRNs leading the Autoimmune and Systemic Inflammatory Syndromes Collaborative Research Group formed the ARC (or "the Collaborative") to build on momentum from their prior work. The ARC offers a mechanism for research collaborators to engage one or more PPRNs simultaneously for projects across autoimmune diseases. The Collaborative's

purpose is to individually and collectively cultivate innovative patient-investigator partnerships in autoimmune patient-centered outcomes research that engage and evolve our shared PPRN infrastructure.

Each PPRN member of the ARC is a partnership of patients, care partners, researchers, and non-profit advocacy organizations that engage directly with patients, typically outside of clinical settings and often digitally or online: a “direct-to-patient” approach to research. Although randomized controlled trials are the gold standard for health research, they are often restrictive because of the costs of enrolling sufficient numbers of eligible patients at traditional clinical sites [15]. Meanwhile, as large patient communities on the Internet have formed to share experiences and advice about living with specific medical conditions [16], these online communities have enabled adoption of a direct-to-patient study design. Direct-to-patient study design allows researchers to engage directly with patients through a virtual or remote connection rather than through brick and mortar clinical sites [15, 16]. Such obviation of the need for recruitment at clinical sites means researchers can access large cohorts of eligible patients previously unavailable through traditional methods owing to limitations associated with geography or a lack of awareness of research opportunities among eligible members of the patient population [17]. Further, it opens the door for all patients to access research opportunities, regardless of the settings in which they seek their medical care.

Given their close affiliation with patient advocacy, education, and/or support organizations, and ability to operate outside the confines of traditional academic or clinical settings, PPRNs are equipped to function as research and innovation networks. Patient centeredness is a defining feature of each PPRN, and participation is open to all eligible US and, in some cases, non-US patients, whether they reside in urban or rural communities, or are seen in academic or private practice settings. Studies often focus on types of data that help convey the patient experience using novel measures of quality of life (e.g., PROs) and activity (e.g., wearables, biosensors) [18–22]. As detailed in the next section, each PPRN is an enduring infrastructure with participant data that can be analyzed alone or in combination with other data, and with participants who can be contacted repeatedly (e.g., by e-mail, social media, or in-app messaging) to participate in any number of studies. Patient-Powered Research Networks thus consist of “re-usable” infrastructures to improve research efficiency, and can provide data or facilitate data linkage that may be used flexibly for clinical, regulatory, administrative, or informatics aims [18–22]. Table 1 provides an overview

of the PPRNs, including conditions of interest, common features, and opportunities for researchers and patients to propose collaboration.

The ARC convenes these four PPRNs monthly to plan and conduct studies and discuss common topics of interest. For example, in March 2020, the ARC mobilized rapidly to document patients’ attitudes, behaviors, and experiences early in the coronavirus disease 2019 (COVID-19) pandemic. The ARC’s core team flagged the COVID-19 illness caused by infection with severe acute respiratory syndrome coronavirus 2 as particularly worrying to patients with autoimmune disease because of their elevated risk of serious infection compared with the general population, and compounded by their underlying immune dysfunction and reliance on immunomodulatory therapies [23–25]. To better understand how the COVID-19 pandemic affected these patients, the ARC launched a prospective longitudinal survey to harmonize and capture data across the networks, leading to a number of timely analyses of autoimmune patients’ real-world attitudes, behaviors, and experience.

The ARC was uniquely prepared to rapidly deploy COVID-19 research because of its existing infrastructure and that of its constituent PPRNs, including: (1) standing meetings with a ready-made team of researchers and patient research partners from different institutions and across conditions who convened on a regular basis, (2) past experience harmonizing survey items to collect patient data, (3) well-established data capture portals and mechanisms for custom survey administration, (4) enduring relationships with patients and patient organizations with a history of demonstrated responsiveness to patients’ concerns, (5) online patient networks for direct participant recruitment and dissemination of findings, (6) connections to health systems for relevant EHR data, (7) standing institutional review board protocols that allow for the swift assembly of a common protocol adaptive to PPRN-specific requirements, and (8) ongoing funder contacts to rapidly mobilize support for expenses. The project successfully resulted in patient-advised survey development, data collection, analysis, and dissemination within a few months. Publications resulting from this effort reported that patients with autoimmune diseases had a high level of concern about COVID-19 and frequent disruptions in office visits, routine monitoring, and disease-modifying anti-rheumatic drug use, usually without physician approval, all of which varied geographically [26–28]. As a result of these findings, efforts are now underway to optimize telehealth in rheumatology, produce patient-facing websites (e.g., eRheum.org), and to bring together a multi-stakeholder coalition to examine the optimization of vaccine confidence among patients with autoimmune disease.

Table 1 Patient-powered research Networks (PPRNs) comprising the Autoimmune Research Collaborative (ARC)

	ArthritisPower	IBD Partners	iConquerMS	Vasculitis PPRN
Primary condition(s) of interest	Rheumatoid arthritis, spondyloarthritis	Crohn's disease, ulcerative colitis	Multiple sclerosis	All forms of vasculitis
Web portal	www.ArthritisPower.org	www.ibdpartners.org	www.iConquerMS.org	www.VPPRN.org
Number of consented patient members ^a	> 29,700 (> 18,600 rheumatoid arthritis or spondyloarthritis)	> 16,100	> 6500	> 3500
Partnering organizations	Global Healthy Living Foundation; University of Alabama at Birmingham	Crohn's & Colitis Foundation; University of North Carolina at Chapel Hill	Accelerated Cure Project for MS; Center for Evolution and Medicine, Arizona State University; National MS Society; Smart Patients; RealTalkMS	Vasculitis Foundation; University of Pennsylvania
Process for researchers to propose research topics and collaboration	Contact PI to schedule discussion with ArthritisPower Patient Governor Group	Register on "For Researchers" page and schedule consultation with IBD Partners team	"For Researchers" page with "contact us" links to initiate discussions with Research Committee members	Contact PI and network manager to submit research idea and then proposal summary
Process for patients to propose research topics and collaboration	Contact PI to or ArthritisPower Patient Governor Group to schedule discussion or share feedback and research ideas with staff via ArthritisPower app	Web portal to propose research questions, vote on submitted research questions, and co-create study plans with researchers	Web portal to propose research questions, vote on submitted research questions, and co-create study plans with researchers	Web portal to propose research question
Patient governance and decision making	ArthritisPower Patient Governor Group	IBD Partners Patient Governance Committee	iConquerMS Governing Board, Research/Engagement Committees	Vasculitis PPRN Steering Committee
IRB	Advarra, Inc.	University of North Carolina at Chapel Hill	WCG IRB	University of South Florida
Data collection platform	Smartphone apps and/or web-based equivalents			
Longitudinal data available	Patient-reported outcome measures, diagnostic and medication data harmonized with the PCORnet Common Data Model			
Research dissemination outlets	Peer-reviewed publications; presentations at national/international scientific and medical meetings for rheumatology, immunology, neurology; trade press; patient-focused websites newsletters and social media (e.g., CreakyJoints.org, Acceleratedcure.org)			
Funding sources	Federal (National Institutes of Health, other), Patient-Centered Outcomes Research Institute, private foundations, biopharmaceutical industry			

IRB Institutional Review Board, PI principal investigator

^aNumber of consented PPRN patient members as of March 2021

3 Discussion: Common Capacity, Characteristics, and Challenges

The ARC's Autoimmune COVID-19 Project illustrates well that the Collaborative and its constituent networks share a common capacity and characteristics that enable efficient and flexible research design, rapid study implementation, and timely dissemination of research results. Patient-Powered Research Networks seek to leverage and enhance these as part of the ARC, while working together to identify and address potential challenges that accompany the PPRN model. Because PPRNs are by definition situated in, led by, or in close partnership with patient advocacy organizations, there exist opportunities for conducting research that engages with and returns value to patients over time. The research, education, and advocacy efforts of patient organizations complement one another as these organizations can identify gaps in knowledge and then take steps to address those gaps via patient-directed information campaigns and policy proposals. As patient advocacy organizations are distinct from pure research institutions, they must hire staff and put systems in place to guide the focus, sustainability, rigor, and representativeness of their human subject research to be optimally effective.

Unlike other longitudinal registries created to answer a specific set of pre-determined research questions, PPRNs were established to be responsive to the needs and interests of their stakeholders. This dynamism creates substantial flexibility for PPRNs and the ARC to be responsive to the needs of many stakeholders, notably patient partners. Moreover, as patient organizations are often in contact with an array of relevant healthcare stakeholders (i.e., patients, care partners, researchers, physicians, policy makers, biopharmaceutical or equipment manufacturers, regulators, and other patient organizations operating within a specific condition), PPRNs are able to quickly convene multiple stakeholders, an important option for patient-centered outcomes research [29]. These relationships can be instrumental in designing, funding, implementing, and disseminating studies on timely topics, as the COVID-19 project demonstrated.

Although PPRNs no longer rely on PCORnet infrastructure support from PCORI, this expectation was factored into the planning and development of the networks. In the first two phases of PCORnet infrastructure development, PCORI milestones required PPRNs to develop and submit plans to achieve sustainability by the end of the funding period, including seeking infrastructure or research support from a wide variety of other sources (e.g., National Institutes of Health, PCORI, foundations, industry). As PPRNs' research focus is not intended to be tightly controlled by a single academic unit or researcher, PPRNs' research agenda can flexibly respond to patients' concerns. However, this patient-responsive mandate is not without its challenges. Given the

high rate of autoimmune disorders among Spanish speakers in the USA [30, 31], a limitation of PPRNs is the requirement of English proficiency for participation in most studies. To address this challenge, ArthritisPower is launching a completely Spanish version of the network's smartphone application and PRO measures in 2021. Nevertheless, recoding a legacy infrastructure in multiple languages is difficult and time consuming, something that future researchers should heed when building new systems. Patient-friendly research topics may also present hurdles. Whereas patients often prioritize issues such as nutrition or remedies they perceive as being in their immediate control (e.g., changes in diet, or use of marijuana to cope with pain), such topics are often accompanied by logistical or financial barriers that make them difficult to study. The many impediments to conducting trials regarding nutrition [32, 33] or cannabis [34–36] are well documented. For example, although many patients with inflammatory bowel disease have reported the dietary changes that work well for them personally, engaging an adequate sample of patients with different phenotypes to reach strong conclusions from these patient reports is challenging [37]. Therefore, PPRNs depend upon their governance structures, including the prominent role of patient governance, to compare and rank various project proposals and shape a research agenda over time with an eye to returning value (e.g., information, guidance in treatment decision making, new therapies) to patient stakeholders of the PPRN.

Patient leadership in governance [38], along with clearly communicated input from other stakeholders, helps establish common ground within the PPRNs in the ARC to shape and advance projects that align with patient interests. Patient governance and patient organizations' coordination and leadership represent strengths of the PPRN model. But as with any individual, research team, or organization, conflicts of interest must be made transparent. When there is an opportunity to conduct a project with financial or staff support from an industry partner, these external entities are invited to present to the patient governance body, which has the opportunity to pose questions and make decisions about study direction and design. A related imperative for patient organizations leading PPRNs is to hire staff with research expertise. Without a firm commitment from organizational leadership to recruit experienced staff and implement required systems, the staff members engaged in research activities may lack adequate support and understanding regarding the time and logistical or ethical processes required to design and conduct human subject research.

Given the commitment to responding to questions that arise from the evolving concerns of patients and other stakeholders, the PPRN infrastructure and data were designed to be flexible and durable enough to be used repeatedly for various and unanticipated research questions. Perhaps the most striking feature of ARC and its constituent PPRNs

is its ability to address a wide range of potential research questions owing to their adaptability regarding conducting research, using existing data and scalable infrastructure, or efficiently obtaining new data as needed for a specific project. This capacity can be grouped into four categories based on the extent to which new data, infrastructure, and external collaboration are needed (Table 2). The increase in time and effort required to conduct research that accompanies each category, and the variability both across and within the categories, is based primarily on the extent to which: (1) information is readily available for analysis and (2) existing staff and patient stakeholders or participants can be mobilized to complete research tasks, notably for data collection. Although most ARC PPRN projects completed to date are clustered in categories I and III, Table 2 shows the flexible capacity and potential opportunities to work with an individual PPRN, or to engage two or more PPRNs simultaneously through the ARC infrastructure.

3.1 Category I

Category I comprises the use of existing data from one or multiple PPRNs within the ARC. By leveraging existing data assets, these studies are highly efficient. For example, ArthritisPower used existing longitudinal data from patients with arthritis to evaluate whether instruments from the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS)

[e.g., physical function] could substitute for a commonly used Multi-Dimensional Health Assessment Questionnaire. Results showed a high degree of cross-measure score prediction [21]. Similarly, IBD Partners performed cross-sectional and longitudinal analyses to evaluate associations between PROMIS measures and validated disease activity indices [39], and iConquerMS explored the relationships between a standard assessment of physical function and PROs for lower extremity and upper extremity function (Neuro-QoL Adult Short Form lower-extremity and upper-extremity domains), revealing limitations of the standard assessment (R; H; S; L, 2020). The Vasculitis PPRN used its comprehensive patient-reported data to demonstrate the utility of patient self-reported diagnoses of vasculitis [40]. In a longitudinal study, ArthritisPower observed which PRO measures patients with arthritis considered most important to track [41]. Findings from these studies provide guidance for future projects to minimize participant burden, optimize the meaningfulness of measures to patients, and streamline research using decentralized (virtual) trials.

Existing data have also been used to examine medication safety and effectiveness. IBD Partners evaluated the real-world effectiveness of vedolizumab, focusing on patient-reported disease activity, use of glucocorticoids, and PROMIS measures [20]. Working collectively across the Collaborative, autoimmune PPRNs (ArthritisPower, IBD Partners, and the Vasculitis PPRN) used existing clinical data and health-related quality-of-life assessments collected

Table 2 Capacity of PPRNs to conduct patient-centered research individually or collectively within the Autoimmune Research Collaborative

PPRN(s) data and infrastructures		In collaboration with external partners ^a data and/or infrastructures	
Existing data and infrastructures	I.	II.	
	Secondary use of existing PPRN data	Linkage to external data sources for additional secondary use of existing PPRN data	
	Direct-to-patient recruitment for external studies	Linkage with external health plans or health systems to conduct PPRN-led direct-to-patient recruitment to studies	
New data and/or infrastructures	III.	IV.	
	Prospective survey data collection	Collaboration with external partner(s) for prospective survey data collection, patient participants for qualitative studies, or direct-to-patient translational studies, and precision medicine	
	Patient participants for qualitative studies		
	Direct-to-patient pragmatic trials, translational studies, and precision medicine		

PPRN Patient-Powered Research Network

^aExternal partners include, but are not limited to, PCORnet Health Plan Research Networks and Clinical Research Networks

longitudinally to compare how well patients respond to immunomodulating treatment and how often patients receiving these treatments experience serious adverse events [42]. Results from such real-world studies are important topics for broad dissemination to guide autoimmune patients and their doctors as they select from an expanding assortment of disease-modifying antirheumatic drugs.

Patient-Powered Research Networks maintain a roster of thousands of “research-ready” participants who have agreed to be contacted for future research opportunities. Thus, PPRNs can rapidly screen individuals based on demographic or clinical characteristics for preparatory to research efforts, and selectively provide referrals for external studies for which they may qualify. Such direct-to-patient recruitment can bypass the need to work through and contract with study centers, enabling efficient start-up. Several studies have demonstrated the quick and flexible nature of research recruitment via PPRNs. IBD Partners identified pregnant patients treated with certain medications and referred them to the Mother to Baby Registry [43]. ArthritisPower targeted patient recruitment based on condition, geography, and other eligibility criteria to assist with National Institutes of Health clinical trials studying a new vaccine among older patients with inflammatory arthritis [44], and the impact of tumor necrosis factor inhibitors on the risk of cardiovascular disease [45].

Because PPRN participants are often recruited via digital or social marketing using an “opt in” direct-to-patient approach, the resulting group of patients may constitute convenience samples of patients living with these conditions rather than truly representative samples of a broader, more generalizable group of patients. Patients seeking health information or research participation online may be more engaged than many patients recruited from clinical settings, and PPRN participant groups also tend to skew more female, white, middle-aged, and college educated [46, 47]. To some degree, this may diminish the generalizability of study findings to a more general population of affected patients. However, for most studies, including prospective studies that evaluate the effect of an exposure (medication, diet, health behavior) on an outcome (PRO, disease-specific measure), the convenience sampling does not pose a substantial threat to internal validity. Recruitment in most types of medical research involves studying not fully representative populations, especially including randomized clinical trials based at major urban medical centers with strict eligibility criteria. Each research system offers advantages and limitations, but by broadening the overall population of patients under study and facilitating rapid large-scale participation, studies through ARC bring a new dimension to medical research.

Patient-Powered Research Networks have explored potential selection bias, sometimes referred to as the “volunteer effect” [48], in their respective datasets by comparing the

demographic characteristics of their direct-to-patient membership with that of clinical PCORnet data overall. For example, based on a 2016 PCORnet query yielding demographic data on ~88,000 people with MS across PCORnet Clinical Research Networks, iConquerMS found that their network participants had roughly the same sex distribution, though age distribution in their PPRN member group skewed slightly older, and racial/ethnic subpopulations were underrepresented, compared with the multiple sclerosis population within PCORnet Clinical Research Networks. Overall, potential selection bias in PPRN samples can be mitigated by weighting opt-in responses during the analysis to create synthetic samples representative of the population being studied [49] or by linking or partnering with other datasets or organizations for targeted outreach to groups that are not well represented in the network (see Category II).

To examine the strengths and limitations of direct-to-patient trial recruitment by PPRNs, the Vasculitis PPRN compared trial recruitment of patients with a rare disease (granulomatosis with polyangiitis) using a direct-to-patient, web-based recruitment approach of social marketing strategies with a standard multi-site Center of Excellence recruitment approach. The direct-to-patient approach included a website with an interactive informed consent form to enroll in the study; the standard approach meant participants were recruited by investigators at clinical sites who administered the consent process. The study found that although the web-based method was less successful than the standard approach, it was good at confirming eligibility and was as acceptable to providers and as understandable to patients as the standard approach [15].

Patient participants are also available to be engaged as advisors on topics of interest. iConquerMS accessed its network participants to create a Patient-Focused Drug Development Council that provided continuing input on clinical trial design, outcome measures, including PROs, proposed label statements, and trial participant training materials prior to launch of phase III clinical trials for evobrutinib [19]. Patient-Powered Research Networks offer a curated approach to contacting or convening patient representatives by matching suitable patients to the needs of a particular research development project, advisory panel, or other group where patient stakeholder input is needed.

Understanding methods of patient engagement, for everything from study recruitment, to measuring what matters to patients, to patient research leadership and governance, is a growing area of interest among academic medical centers, industry, and other research entities [50, 51]. The PPRNs in ARC, individually and together, have dynamic living laboratories of patient populations through which different engagement strategies can be assessed to determine their relative effectiveness. The variability within and across patient populations under study in the ARC offers

opportunities to study multiple potential engagement strategies, allowing refinement of approaches and/or use of different approaches for different types of research. Cultivating deep patient engagement with PPRN members is both an imperative and a persistent challenge for our networks, thus a potential vulnerability of the direct-to-patient approach to research. Because PPRN participants elect to participate primarily virtually, as opposed to attending scheduled in-person physician visits at regular intervals where clinical assessments and data collection can be done, PPRNs must maintain patients' interest over time to motivate members to check their e-mail, log in to web portals or apps, and provide information about themselves. Opt-in samples from e-mail surveys also create a reporting challenge for documentation of participant response. In short, use of a traditional "response rate" should be avoided when reporting response metrics for the web-based or online surveys often used by PPRNs. It is more appropriate to instead calculate metrics such as the view rate (e.g., how many people opened an e-mail invitation and saw the survey), participation rate, and completion rate, as these use numerators and denominators that are more accurate and insightful for reporting the participation of eligible individuals [52].

Considering as the denominator the entire population of e-mails sent out to potential participants in a PPRN community artificially deflates the response rate. A more appropriate denominator would be the open rate (number of participants who opened the e-mail) as an indicator of the population of individuals who were aware of the study and therefore able to make a decision about their participation. The ARC recently defined shared metrics for tracking engagement over time beyond simple numbers of consented participant membership. By developing standard definitions for PPRN member activity, such as providing longitudinal data within certain time periods, and participant contributions or interactions beyond data sharing, will help advance common ARC approaches to engaging participants and returning value to patients for PPRN participation.

3.2 Category II

Because of their reliance on a direct-to-patient structure that favors patient-reported data, PPRNs must collect or be able to readily obtain clinical data such as physician-reported assessments or specific diagnostic tests. This often means collaborating and linking data with health systems and other clinical registries outside of PPRNs' usual partnerships, requiring that each PPRN have an informed consent form in place that specifies such permissions. As the ARC and its PPRNs have put in place such consent permissions, and maintain the capacity to link to clinical or administrative records maintained by Clinical Research Networks, Health Plan Research Networks, or other non-PCORnet entities,

they are able to expand their existing data and research infrastructure for secondary data analysis or other observational and interventional studies by working with external partners such as clinical registries, health systems, or health plans (claims/administrative). These collaborations enable rich linked datasets that can enhance a study's capacity, even making patient-reported data available at the clinical point of care. Patient-Powered Research Networks can also serve as a venue for efficient, long-term, direct-to-patient follow-up for observational studies that may be ending [53, 54].

Beyond the informed consent process, other fundamental steps needed for PPRNs to perform data expansion include privacy preserving linkages to connect patient data from two or more entities, and computable phenotypes to identify patients with conditions of interest based solely on EHR or claims data. A computable phenotype refers to an algorithm that can be shared and reproduced that defines a condition, disease, clinical event, or other complex patient characteristic as precisely as possible using only information processed digitally (i.e., EHR data) [55]. To date, projects in Category II have mainly focused on the development and validation of computable phenotypes in large administrative databases and the examination of viable methods for data linkage in a manner that preserves patient privacy. For example, ArthritisPower, iConquerMS, and the Vasculitis PPRN collaborated with the HealthCore Health Plan Research Network to test computable phenotypes and engagement strategies linking PPRN data with 14 health plans [53], facilitating access to EHR data (physician encounter, laboratory results, disease activity). The Vasculitis PPRN developed and validated computable phenotypes for several types of vasculitis in three large administrative databases [56]. IBD Partners collaborated with an industry partner on developing and testing methods for the recruitment and linkage of participants from existing cohort studies to the PPRN [57]. ArthritisPower has additionally linked patient-reported data to Medicare claims data [42], and to an EHR vendor system for community medical practices to enable real-time studies linking to PRO data, bringing patient data to the point of care. These efforts underscore PPRNs' innovative methods and flexible infrastructure to facilitate access to, and augment patient-generated data.

3.3 Category III

Existing research infrastructure (regulatory, informatics) allows for efficient start-up, recruitment, and prospective data collection. As the Autoimmune COVID-19 Project demonstrates, PPRNs can reach large numbers of patients quickly to collect new data and data types, for cross-sectional or longitudinal studies. Patient-Powered Research Network patient members can be screened with existing data to select for certain characteristics (age, disease type, clinical

characteristics) and new survey information can be combined with existing registry data for more efficient studies. There are many examples of such work among the individual PPRNs in the ARC. The Vasculitis PPRN rapidly conducted surveys using new data forms to study work disability [58], patients' pathways to arriving at a diagnosis [59], and patient preferences for glucocorticoids and health-related quality of life among patients with vasculitis. IBD Partners implemented a new survey module to evaluate patient activation and learned that patients with higher levels of patient activation are more likely to be in remission [60], and iConquerMS has implemented targeted surveys for evaluation of: patient access to insurance; effectiveness of adult day care facilities; and attitudes to disease-modifying therapies and willingness to pay for them [18, 61, 62]. Each of these studies shows that new data elements can be added within the PPRN infrastructure at any time, and that prospective studies can be initiated quickly to address any number of research questions about autoimmune patient attitudes, behaviors, experiences, and preferences.

Patient participants are also available to be recruited directly by PPRNs or ARC for qualitative studies. For example, IBD Partners conducted a qualitative study to evaluate patient perceptions of biobanking and situations in which patients would be willing to donate samples. A series of one-on-one interviews informed the development of a full survey that was successfully distributed to the larger PPRN population [63].

Direct-to-patient pragmatic trials can also be embedded in one or more of the PPRN platforms. If study focus and eligibility criteria are broad and clinician involvement minimal or not required, this can be an effective method to complete a trial, often without the need for clinical site visits. IBD Partners, for example, conducted a randomized controlled trial comparing two diets in patients with Crohn's disease in remission, finding that the amount of red and processed meat consumed was not associated with flares or relapses [64]. Patient-Powered Research Networks can further add a new infrastructure, building on their existing patient engagement platforms to conduct studies. ArthritisPower built a custom mobile app workflow for prospective PRO data collection among patients with rheumatoid arthritis to characterize the extent to which activity measures collected from a smartwatch agree with PRO measures [22]. This means that customized protocols or workflows to guide participants through study tasks, including use of novel digital health technologies such as wearables, can be created or incorporated by PPRNs for the collection of new data types.

3.4 Category IV

The ARC or its constituent PPRNs can also collaborate with external partners to collect prospective survey data, recruit

patients for qualitative studies, or gather new clinical or translational data. For example, biosamples (salivary DNA collection, stool collection for microbiome analysis) may be collected to facilitate translational or precision medicine studies and there are a number of possible options for doing so: (1) collection by diagnostic laboratory services company through which participants are shipped a blood collection and pre-paid shipping kit with masked, de-identified, and bar-code-labeled tubes to bring to a participating laboratory for blood draw and processing; (2) collection by a health-care provider that is either participant or (3) provider driven where a healthcare provider's office performs the blood draw and processing using a kit brought in by the participant (option 2) or available to the provider (option 3); (4) specimen collection by a home health nurse; or (5) collection via a home saliva kit, a DNA-only option, where participants receive a pre-paid shipping kit, spit into a tube, and mail it back. IBD Partners conducted a pilot study to compare the feasibility of various biospecimen collection procedures and found that home saliva kits yielded the highest return rate [65]. In an ongoing follow-up study, IBD Partners identified patients with selected rare phenotypes to contribute saliva for DNA extraction and a genome-wide association scan. iConquerMS has also piloted saliva collection from a small subset of its membership with IRB approval, kits, and consents. These category IV pilots demonstrate the open and flexible nature of PPRNs to expand their available data and to engage with patients in new ways for future studies. As the study examples presented here demonstrate, the substantial flexibility of the PPRNs, individually or together, support a range of direct-to-patient research activities from a quick and efficient secondary analysis of single network data to more sophisticated collaborative efforts with external partners where new data must be gathered or combined.

4 Conclusions

Patient-Powered Research Networks have the capacity to conduct a range of real-world, direct-to-patient research and engagement activities comprising virtual study recruitment and data collection methods, innovative informatics such as novel methods for data linkage, and systems that promote dissemination of relevant information to healthcare stakeholders via digital health. While the role of patient-generated data to provide data for real-world evidence is still evolving, relevant direct-to-patient innovation and patient-centered outcomes research is already underway within the ARC and its four constituent PPRNs for arthritis, inflammatory bowel disease, multiple sclerosis, and vasculitis.

Research conducted by, or in collaboration with, patient organizations can return value to patients in a variety of ways for participation in the PPRN or in specific studies. Ideally,

when PPRNs are aligned with principles of patient-centered outcomes research, they engage with patients repeatedly over time to identify patient concerns and turn them into patient-centric research questions and study designs, recruit patients to participate in studies, enlist patients in registry governance and in the analysis and interpretation of findings, provide educational content to patient communities using the most up-to-date evidence, and advocate for health policy to patients' benefit. From its origins in PCORnet, the challenges confronting PPRNs were spelled out in the expectations of such a shared infrastructure:

"... collecting relevant clinical data, including information from patient self-reports and from their network's EHRs; harmonizing data so that they can be useful to ... [other partners]; increasing the numbers of patients with a single condition who are registered and willing to share data, participate in research (including interventional studies), prioritize research questions, and disseminate results; establishing patients' trust with respect to the privacy and security of their personal information; streamlining the consent and IRB processes while protecting patients' rights; and meaningfully engaging patients in the networks' governance" [12].

The four PPRNs that make up the ARC have met these expectations and continue to grow and improve their infrastructure together.

The ARC provides a single point of entry for research into multiple autoimmune diseases that share important similarities, along with a wide net of collaborators and experts, including physician researchers and patients, to draw from. The focus of collaboration is to share resources and work, and to learn from each other to constantly improve individual PPRNs. The COVID-19 project and shared metrics for tracking engagement over time represent recent examples of working together in the ARC to develop shared definitions and solutions that will improve such an infrastructure. As COVID-19 vaccination is rolled out, the ARC is initiating projects to better understand the reactions of patients with autoimmune diseases to the vaccine and to combat misinformation while increasing vaccine confidence and trust in our patient communities.

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All statements in this article, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or Methodology Committee.

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Declarations

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