Increasing Focus on the Patient in Patient Registries

Registry of Patient Registries (RoPR)

Draft White Papers for Fourth Edition of "AHRQ Registries for Evaluating Patient Outcomes: A User Guide"

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The Increasing Focus on the Patient in Patient Registries

Draft White Paper for Fourth Edition of "AHRQ Registries for Evaluating Patient Outcomes: A User's Guide"

Preface

This document, in the form of an e-book supplement to the third edition of "Registries for Evaluating Patient Outcomes: A User's Guide", provides an in-depth summary of the increasing focus on the patient in clinical research, as applicable to the conduct of patient registries. The User's Guide defines a patient registry as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."1 Registries may be developed to fulfill a wide variety of purposes, including describing the natural history of disease, determining the clinical and/or cost-effectiveness of health care products and services, measuring or monitoring safety and harm, and measuring quality of care. Many registries are designed to fulfill more than one purpose. The purpose of the User's Guide is to serve as a reference for establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes.

As a supplement to the third edition, this e-book expands on the existing document by exploring how patient registries may incorporate the concepts of patient-centered research. Through a review of the anticipated benefits, current challenges, best practices, and new frontiers in patient-centered research, this e-book provides assistance to researchers and stakeholders involved in the design and implementation of registries and other research. Where topics are well covered in other materials, references and/or links are provided. Case examples have been incorporated to illustrate particular points or challenges.

Introduction

The concepts of patient-centered care and patient-centered research have moved to the forefront of health care and research in recent years. Major advances in medicine have occurred over the past few decades resulting in an increasing number of diagnoses, treatments, and preventive options for patients to consider.[2] Patients are living longer with chronic conditions due to these advances, and their role in health care is shifting from that of a passive recipient of medical care to an active participant in clinical decision-making. These factors are now putting pressure on the complex, costly, and often fragmented U.S health care system to improve quality, as measured by patient experience.[3] At the same time, health care decision-makers, including patients, providers, and payers, have noted that the available evidence for health care products and services often fails to provide information that is relevant and meaningful to patients, clinicians, and other end users.[4] Consequently, stakeholders are demanding real-world evidence that meets the needs of patients and providers, so that, ultimately, patients and providers can make the most informed treatment decisions.[5]

Patient registries have been used increasingly in recent years to provide real-world evidence on the effectiveness, quality, and/or safety of healthcare products and services. The User's Guide defines a patient registry as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."[1] In comparison to other research designs, patient registries offer some unique features that may be particularly useful for patient-centered outcomes research.

The purpose of this chapter is to describe the factors driving the increasing focus on patient-centered care and patient-centered clinical research and explore the role that patient registries may play in patient-centered clinical outcomes research.

Definitions of Patient-Centered Care and Patient-Centered Clinical Research

The Institute of Medicine (IOM) defines patient-centered care as: "providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions," and included patient-centered care as one of six key aims health care systems should adopt to improve outcomes for patients.[6] The Patient-Centered Outcomes Research Institute (PCORI) defines patient-centered outcomes research (PCOR) as "research that addresses the questions and concerns most relevant to patients."[7]

The uptake of a patient-centered approach in medical care and clinical research may be facilitated by a variety of factors including targeted PCOR funding, patient-driven research design, and stakeholder-relevant dissemination strategies that intend to enhance informed clinical decision-making. Patient-centered research funds would be directed to address questions that are high priority for and relevant to patients and other key stakeholders. Patient-centered research design would take into account patient preferences and concerns early in the design phase of a new research study to align research questions with patient needs and enhance research efficiency; for example, patients may have recommendations about optimizing recruitment strategies or selecting the number or mode of administration of patient-reported outcome measures used in the study. Dissemination is also critical for increasing patient-centeredness. Dissemination of research findings to health care providers and patients should be timely and transparent, and findings should be communicated in a manner that is clear and understandable to patients. Lastly, patient-centered care relies on patients having the necessary information to make informed decisions about healthcare choices available to them, linked to health outcomes that are important to them.

Patient-centered care and patient-driven clinical research is intended to result in two primary outcomes: 1) increased satisfaction of patients and health care providers with medical care; 2) informed decision-making and uptake of research results by key stakeholders; and 2) improvement in health outcomes that are most meaningful to patients and clinicians. These concepts are summarized in Table 1.

Table 1. Goals and Benefits of Patient-Centeredness in Research and Medical Care

Theme	Goals	Desired Benefits
Funding	Research funding is directed optimally to address questions that are of high priority and relevance to patients	Improvement in health outcomes that are most meaningful to patients and clinicians Increased satisfaction of patients and health care providers with medical care
Research design	To align research questions with evidence gaps and patient needs as well as enhance research efficiency	
Availability of evidence and dissemination	Dissemination of research findings to health care providers and patients is timely and transparent, and communicated in a manner that is clear and understandable to patients	
Informed decision-making	Patients have the necessary information to make informed decisions about the health care choices available to them, linked to health outcomes that are important to them	

Though well over a decade has passed since the IOM and other stakeholders have called for increased patient-centeredness in medical care and clinical research, researchers are only beginning to quantify the extent to which the desired benefits of this shift are being achieved, and several challenges remain. In particular, challenges during the funding and design phases include the additional time and expense associated with engaging patients and other stakeholders at the beginning and throughout all phases of a research study, as well as the need for effective, documented engagement strategies. Informed decision-making by health care providers and patients is complicated by the availability and accessibility of necessary evidence, including sufficiently "personalized" evidence from population-based studies. Informed decision-making also relies on effective two-way communication between health care providers and patients about all treatment options while considering the range of outcomes that are most important to each individual patient. Fitting this type of patient-centered conversation into the constraints of typical office visit can be challenging.

The Evolving Role of Patients in Medicine, Research, and Policy

The growing demand for patient-centered research has led to several new initiatives that seek to actively engage patients. One of the most notable, in terms of its immediate impact, is the establishment of PCORI, an independent nonprofit organization. In 2010, Congress authorized the establishment and funding of PCORI; its mandate is to fund patient-centered comparative

effectiveness research that addresses critical evidence gaps in current clinical practice and that produces evidence that can be used by patients, caregivers, clinicians, and other stakeholders to support clinical and health policy decisions.

To increase the likelihood that the research it funds is patient-centered, the hallmark of PCORI's funding is a requirement for all awardees to actively engage patients and other key stakeholders in all phases of the research project.[8] To this end, PCORI has created an engagement rubric, a set of methodology standards, and a compensation framework for patients engaged in PCORI-funded studies that serve as basic guides for researchers and their collaborative partners. To reinforce the commitment to incorporating multi-stakeholder perspectives in research and to ensure proposals are responsive to stakeholders' needs, all research proposals submitted to PCORI are not only peer-reviewed for technical merit by scientific and methodological experts, but also evaluated by patients and other key stakeholders on the quality of "patient-centeredness" and "patient and stakeholder engagement." This process is critical to establishing and maintaining the credibility of patient-centered research.

In addition to the work of PCORI, a number of recent efforts are encouraging the active participation of patients, their caregivers, and patient advocates in regulatory decision-making. For instance, there has been considerable interest on the part of some regulatory agencies in adopting "adaptive approaches" for drug approval and reimbursement decisions. These approaches hinge on the early and continuous engagement of patients and other key stakeholders throughout the life-span of drug development.[9] The push for adaptive approaches has been driven in part by patient demands for early access to medications. Innovative clinical trial designs, stronger understanding of disease processes, and improved availability of monitoring tools for post-licensing surveillance using real-world data have also supported the development of adaptive approaches to drug approval and reimbursement.[9]

One example of an adaptive approach is the European Medicines Agency's (EMA) Adaptive Pathways Program, launched in December 2014 to improve the timely access of new drugs for patients.[9-11] Through this program, the EMA can provide accelerated treatment approval for specific subgroups of patients with unmet medical needs while requiring additional research to be conducted to support future expansion (or restriction if necessary) of the regulatory approval and reimbursement for that drug. Due to the uncertainty and trade-offs involved, the EMA requires that patients and other relevant stakeholders be engaged in the decision-making about the design of the research that needs to be conducted to support future decisions about expansion of the regulatory approval.[10]

The U.S. Food and Drug Administration (FDA) has taken several steps to formalize the integration of patient perspectives into the regulatory process, including establishing a Patient Engagement Advisory Committee.[12] The purpose of this committee is to provide advice to the FDA Commissioner on a variety of patient-related topics, such as the inclusion of patient preference and PRO measures in study design, benefit-risk determinations, and areas of unmet clinical need. Another effort to directly incorporate patient perspectives is the FDA's Patient-Focused Drug Development Initiative, a commitment under the Prescription Drug User Fee Act (PDUFA) to obtain patient views on specific conditions and currently available therapies to treat those conditions. Over 20 public meetings are planned to be held focusing on specific disease

areas over the five year authorization period of "PDUFA V", with the output summarized in "Voice of the Patient" reports to be made available on the FDA's website.[13]

Additionally, the FDA published guidance in 2009 on the inclusion of PRO measures as evidence for treatment benefit, demonstrating its support for the inclusion of patient-centered outcomes as endpoints in industry-sponsored clinical trials that may contribute to regulatory approval and product labeling.[14] Following the release of the initial draft guidance in 2006, the FDA approved nearly a quarter of all new molecular and biologic license applications incorporating PRO evidence, along with other evidence sources for labeling claims during the period of 2006-2010.[15] More recently, in May 2015 the FDA published draft guidance on the inclusion of patient preference information to support product labeling for diagnostics and therapeutic devices, further underscoring the agency's recognition of the importance of understanding what benefits and risks are most important from a patient's perspective.[16]

To improve the availability of valid and reliable PRO measures, the U.S. National Institutes of Health (NIH) has funded the Patient Reported Outcomes Measurement Information System (PROMIS) initiative. Initially developed in 2004 and expanded in 2010, the PROMIS initiative develops, maintains, and validates its own unique set of PRO instruments to measure physical, mental, and social health outcomes in adult and pediatric populations with chronic disease.[17] Importantly, all the instruments have been designed for self-administration by adults, children, or caregivers, reflecting the growing emphasis on PROs as important health measures.

Pharmaceutical companies are also beginning to actively engage patients to enhance the relevance of outcomes studied during drug development as well as the breadth of treatment options evaluated. Pharmaceutical companies are undertaking a variety of different approaches to increase patient engagement. For instance, Sanofi hired a Chief Patient Officer, whose role is to "infuse the patient perspective into all of our activities, ranging from early stage R&D [research and development] to product launches".[18] Others, like Pfizer, are reaching out to patients through online crowdsourcing platforms and still others, like Genzyme, have formed internal patient advocacy groups.[19, 20] Finally, at least one pharmaceutical company, Roche, has developed a set of good practice guidelines to inform their patient engagement efforts.[21]

Lastly, it is important to note the critical role played by patient advocacy groups. An increasing number of well-organized, vocal patient advocacy groups are actively contributing to the research landscape in a variety of ways. For instance, some patient advocacy groups are driving research agendas through funding grants and facilitating collaborations across academic sites; serving as valuable clinical trial recruitment partners, particularly for rare conditions, while leveraging innovative outreach strategies to diversify enrollment in trials; and enhancing capacity to develop biomarkers or other clinical screening and monitoring tests for therapeutic products.[22] Patient-advocacy groups also actively participate in and lead conversations on the need for legislation and continued meaningful participation of patients in all aspects of health care and policy.

In summary, patients are actively participating in and shaping the way that health care, research, and regulatory decisions are made in many ways. All of these efforts share a common goal of improving the ability of patients, their caregivers, and clinicians to make informed health care decisions.

Patient-Centeredness and Patient Registries

As a result of these initiatives and other efforts, investigators are increasingly integrating a patient-centered approach into their clinical research. Specifically, greater attention has focused on the need to conduct research that answers questions and examines outcomes that are important to patients, their caregivers, and clinicians. The overarching goal of these efforts is to increase the likelihood that the evidence produced will be used to support clinical and health policy decisions.

Registries have long offered researchers the opportunity to incorporate patient, provider and health system perspectives while collecting and analyzing health information and outcomes. The inherent features of registries that allow them to readily address research questions and concerns most relevant to patients are the focus of this section.

Patients can also provide perspectives on what's important for a registry to examine to be able to meet their needs and expectations, how investigators can best engage with patients, how to best collect the required data, and how the registry could provide additional value to patients beyond data collection. Selected results from recent research that incorporated patient focus groups on participation in registries are also described here.

Ability of Registries to Meet the Needs of Patient-Centered Research

With some specific exceptions, such as pregnancy registries, registries are usually designed to address multiple questions of interest, often over long periods of time. As such, registries are able to incorporate both questions that patients prioritize as being of central interest to the understanding of their condition and their treatment options as well as questions that may address concerns of other stakeholders. Registries are often designed to examine changing patterns of treatment and the outcomes of treatment over time, as well as other new questions that may arise over the span of the registry. Patients are also important and reliable sources of information for data known only to them, such as time and dose of medications used as needed, e.g., migraine medication, and personal habits that may affect drug effectiveness or safety.[23]

PROs are frequently incorporated into registries to capture unfiltered measures of general and health-related quality of life, clinical, and functional measures directly from patients. Indeed, a key area in which patients may provide important recommendations is in the selection of the most relevant and appropriate measures to address a specific research question. Therefore, patient input is sought prior to and/or during the development of the registry protocol.

Key Features of Registries Relevant to Patient-Centeredness

As noted above and described within the User's Guide, patient registries may be designed to fulfill many purposes, and not all registries are designed to be patient-centered. However, several features of registry design and implementation may further strengthen the extent to which the registry is patient-centered. A full review of these and other features of registry design and best practices for their implementation may be found in the Third Edition of the AHRQ Registries Guide.[1] A brief summary of these key features is presented in Table 2 below.

Table 2. Features of Registries that Enhance Patient-Centeredness

Features of Registries	Strengths in reflecting the interests of patients	Areas of concern for patients
Can address multiple research questions	Questions of high priority to patients may be readily integrated alongside questions addressing other stakeholder concerns; clinical, PRO, and other endpoints may be integrated	Data collection may become too burdensome if excessive time is required to provide required data points (e.g., too many PROs, too frequent visits or contacts)
May enroll large numbers of patients with broad inclusion criteria	Can include patients often excluded from trials, including those with comorbidities, elderly, pregnant women, minority populations	Some subgroups may be too small in number to allow for robust or statistically significant results, despite patients' interest in seeing results for patients similar to themselves
Collection of long-term follow-up data	Reflects the natural history of disease over time, temporal trends (e.g. increased life expectancy)	Patients may experience participation fatigue and some may drop-out
May use multiple modes of data collection	Direct-to-patient methods can reduce visit time in provider's office, mobile devices may increase convenience of survey response and allow collection of other types of health measures, wearable biosensors may collect continuous assessments of physical activity, sleep, vital signs and other measures with low burden to patients	Surveys must be designed for ease of administration on specific devices or may pose burdens to completion; wearing of biosensor devices may be initially novel but become inconvenient to be worn consistently over long periods of time; new technology releases and device updates may occur during study period and impact data collection

Features of Registries	Strengths in reflecting the interests of patients	Areas of concern for patients
May incorporate direct reporting of individual patient data, as well as additional community and educational "value-adds"	Longitudinal summaries of individual patient data that could include comparison to registry population aggregate measures, help patients track their own health over time; periodic reports of research results in accessible language to patients to allow them to benefit directly from participation. Patient communities are a motivating interest for many patients, as are health tracking apps and educational offerings.	Sharing patient results during registry participation might alter patient or physician behavior. Patients may prefer that their PRO data not be shared with providers. Patient communities including discussion forums and message boards may require a moderator to ensure a supportive environment is maintained.

Patient Perspectives on Registry Participation

Recently, several studies were conducted with different patient focus groups to understand their views on patient registries; the methods and results of these studies are published in more detail elsewhere.[24] The opinions of three targeted patient groups were solicited: those already enrolled in a chronic disease registry, those with chronic illnesses not enrolled in a registry, and a similar group with chronic arthritis who spoke only Spanish and had never been approached about enrolling in a registry. In total, 23 patients from the three groups described above participated in 60-minute facilitated discussion sessions. The following themes, presented in *italics*, emerged from these discussions.

Convenience: In all three focus groups, patients emphasized the need for the logistics of participation to be convenient. However, there was wide variation in what was considered convenient. Some patients preferred that study visits coincide with clinical appointments, while others preferred the opportunity to participate on a more flexible schedule with mailed surveys. Patients also expressed a range of views regarding the acceptable frequency of participation, as well as the desire to interact with research staff. Spanish-speaking patients indicated that translated research materials would facilitate their involvement, a consideration that would extend beyond Spanish-speaking patients in the US, to the overall desirability of having research materials available in the native language for any registry participants. Improving the convenience of registry participation may play an important role in patient responsiveness and retention, as well as increase the likelihood of achieving the registry objectives.

Motivation(s) to participate: Motivations such as altruism and the desire to help others through research were discussed, and have similarly been documented in other studies. [25-27]

Another motivation of focus group patients to participate in registries was in using registries as an opportunity to connect with other patients, and creating or joining a patient community. Focus group participants who were current members of a registry described specific features that the registry provided, including educational sessions and live feedback opportunities that allowed interaction with investigators and other patients and supported a sense of community. Social support may increase motivation and engagement among registry participants through sharing of lived experiences with their shared condition or treatment.

Focus group participants also wished to receive longitudinal information on their own disease/treatment activity compared with other patients in the aggregate cohort. This information could be provided by the registry directly or through a patient's health care provider. However, considerations of how to present such information – graphically or in tables – and when it should be presented – at clinical visits, registry visits, or in the mail – must be weighed carefully. Additionally, disseminating this information should be weighed against the possibility of modifying patient or physician behavior as a result of registry participation, and what type of support is appropriate in interpreting the information shared with patients.

Perceived relevance to their experience: Questionnaires that are perceived as relevant by patients may increase their interest in enrolling in and staying involved with a registry. Focus group participants suggested that patients want to communicate their "lived experience" with their condition, and that researchers should ask about the non-physical aspects of disease, such as mental and emotional health. In that context, they described the experience of answering certain types of questions as having "therapeutic" benefit. Focus group patients also indicated that questions of unclear relevance were an annoyance and might detract from their motivation to participate. Patients wished to see questions and issues of concern to them reflected in registry data collection, and indicated that in the case of poorly understood questions or assessments, linking these to the registry's objectives would be helpful. Essentially, patients wanted to know that the information they provide is useful in addressing registry objectives and is being interpreted accurately by researchers; this finding in itself was an endorsement of the need for patient engagement in registry planning, implementation, and dissemination of results.

Privacy and trust: Multiple patients shared the concern that participation in a registry could pose a risk to privacy and confidentiality of their health information. This concern has been shared by other patient groups from previous research as well.[26] Feelings of distrust were especially pronounced among the Spanish-speaking patients, who were afraid they would be treated like "guinea pigs." This was consistent with prior studies suggesting a general distrust towards research in minority populations [28-30].

Challenges in Developing and Operating Patient-Centric Registries

Developing and operating registries in a patient-centric way comes with considerable challenges. By their nature as longitudinal data collection sources, however, registries provide a clear opportunity to initiate and continually improve stakeholder engagement – activities aimed at promoting meaningful research with minimum burden and maximum benefit. Stakeholders may include diverse groups such as patients, caregivers, clinicians, researchers, and biopharmaceutical companies. We describe challenges and solutions associated with long-term engagement of stakeholders using examples from two registries, the Arthritis-Power registry and

the DuchenneConnect registry. Both are Patient-Powered Research Networks (PPRNs), which are part of PCORnet, a national, patient-centered research resource funded by PCORI.[31] Goals for the PPRNs are similar to those for many disease registries, with each network being focused on a specific condition and/or community of interest with an objective of creating a standard database that can be used to address future patient-driven research questions. A hallmark of the PPRNs is to include patients as partners in the governance structure of the network and to collect patient-reported outcomes relevant to the community they serve to support patient-prioritized PCOR questions.

Challenges to Gathering Patient Perspectives during Registry Design

Stakeholder engagement is vital when new registries are being developed or existing registries are being repurposed. Such engagement can provide a path through common challenges, described below.

1. *Maintaining a reasonable, patient-centric focus.* It is important that the registry's mission and objectives are clearly defined. This allows the registry to maintain a reasonable scope of data collection while ensuring that the data collected can answer questions of importance to stakeholders.
2. *Developing clear and ethical operating procedures and processes.* When establishing a registry (or in the early stages of launching), it is important to develop formal processes that prompt the inclusion of patient and caregiver perspectives. This systematic, integrated approach helps encourage long-term, meaningful participation by patients and caregivers and mitigate against the pitfall of "endorsement engagement" (i.e., patients invited only to validate a pre-determined concept). In addition, patients, caregivers, clinicians, and other stakeholders may have diverse priorities for how their data are used by the registry holder, preferences about types and number of research contacts they receive, and preferences about when and with whom their data is shared.
3. *Creating a positive user experience.* Data collection efforts and platforms must also be user-oriented and provide some incentive for data providers to engage and remain engaged over time. For longitudinal registries, it is especially imperative to build in education, support, and/or other community resources.

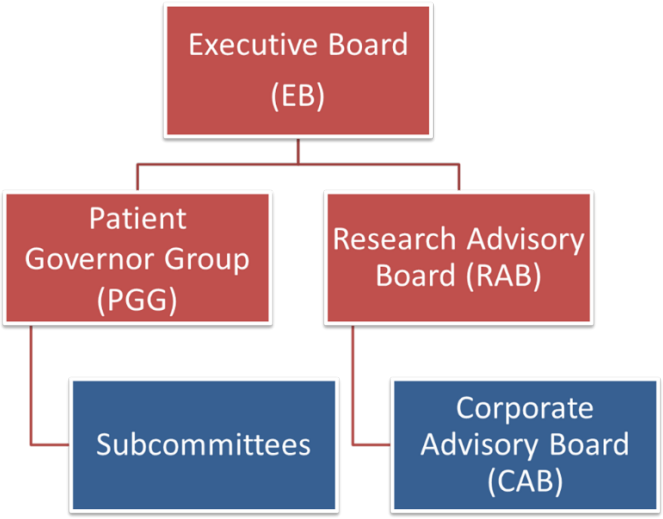
Systematically soliciting preferences in these areas comprises key initial stakeholder engagement and addresses common challenges of data collection and data access. The following overlapping strategies, presented in *italics*, may be effective ways to incorporate patient perspectives into registry formation and operations.

Establish a multi-stakeholder steering/leadership committee: Formation and maintenance of a governance body – such as a steering committee, board, or workgroup – is the most fundamental way to enable stakeholder feedback to inform the work of the registry. These committees may be composed of a mixed set of stakeholders, or of all-patients/caregivers. There are benefits and challenges to each approach.

For example, the "Arthritis Patient Partnership with Comparative Effectiveness Researchers" registry (AR-PoWER PPRN) established a governance structure that includes an Executive Board, a Patient Governor Group (PGG), a Research Advisory Board, and a Corporate Advisory

Board. The hierarchy of these governing bodies is shown below in Figure 1. The governance structure was developed in collaboration between investigators and patient community members. The PGG is the patient steering committee and is composed of 11 patients from a variety of professional, geographic, and demographic backgrounds with conditions relevant to the research mission of the registry. The PGG receives input from the wider patient community via online surveys and through a "Send Feedback" function on the registry's website and mobile app.

Figure 1. Governance Structure of the AR-PoWER PPRN



1. The Executive Board includes the Principal Investigator (PI) and one Co-PI, and the Executive Director and a Board Member of the Global Healthy Living Foundation, a non-profit disease advocacy organization for arthritis patients which is a founding partner organization in the AR-PoWER Registry.
2. The Patient Governor Group (PGG), which includes approximately 10 patients and a designated Chair, reviews & decides which topics to advance for further consideration based on priority of the evidence need.
3. The Research Advisory Board (RAB) is made of up of about 10 rheumatology researchers from UAB and also has a designated Chair, reviews topics for feasibility & funding. The RAB Chair presents recommendations to the Executive Board
4. The PGG/RAB Chairs present recommendations to Executive Board for approval of projects to be conducted in AR-PoWER.

Early in the development of the registry, six highly engaged patients (CreakyJoints advocates and/or bloggers) helped define the role of the Patient Governors (PGs). In the first year, PGs participated in an in-person kick-off "Summit" and conference calls approximately once per month for registry updates and discussions in which they were asked to provide input and make decisions about the registry including initial feedback related to software development. As part of their training during the start-up period, PGs completed the Collaborative Institutional

Training Initiative Human Subjects Protection training and the Cochrane Collaboration's Evidence-Based Healthcare modules.

Define criteria for Patient Governor Selection (AR-PoWER):

1. Experience advocating on behalf of rheumatologic conditions or for own diagnosis and/or treatment
2. Facilitative and collaborative approach to group discussion and decision making
3. Commitment to fostering representativeness across demographic factors (i.e., supportive of the need for the Patient Governor Group & the patient-centric registry to reflect gender, age, race/ethnicity, regional diversity)
4. Willingness to be a public face of rheumatology research
5. Existing relationship and involvement with the patient advocacy organization (CreakyJoints)
6. Skills necessary for patient-powered research (e.g., outreach/recruitment, public speaking, social media, IT, research design/analysis/dissemination)
7. Dependable, committed and responsive

The DuchenneConnect PPRN uses a slightly different model. The highest level of oversight comes from the advocacy organization Parent Project Muscular Dystrophy (PPMD), the owner of the DuchenneConnect registry, through the PPMD Board of Directors and leadership. Thus, DuchenneConnect's activities must be responsive to the mission and vision of PPMD. The DuchenneConnect registry was founded with direction from a large, multi-stakeholder advisory committee comprised of patients, caregivers, clinicians, translational scientists, and biopharmaceutical company scientists. This committee remains active in reviewing policies and providing scientific oversight.

Guidance in day-to-day operations comes from the smaller Leadership Committee made up of parents and individuals with Duchenne/Becker muscular dystrophy. Leadership Committee members were identified through a nominations process where individuals could self-nominate or identify a candidate. PPMD leadership and DuchenneConnect's project staff selected the committee members to represent diverse experiences and skill sets. As the registry has grown and matured, the leadership committee has taken oversight over consent, data access, research prioritization, and engagement activities They meet in person at least once a year and participate in monthly conference calls. They engage in trainings to empower their participation in the network, while also providing reciprocal training to project staff based on their lived experience. Project staff are a diverse group of researchers, health care providers, patients, relatives, and advocates who meet at least weekly to manage the Registry and conduct community engagement. Since the project staff is involved in data collection, all staff complete human subjects research protections trainings. The DuchenneConnect project staff and Leadership Committee receive regular input from the Duchenne community from surveys, social media outreach, focus groups, and PPMD's annual conference.

For both the AR-PoWER and DuchenneConnect PPRNs, leadership/advisory committee activities include a diverse set of activities such as establishment of a group charter and leadership rules, participation in research prioritization activities, data access and research collaboration guidance, selection of relevant PRO domains (i.e., symptoms such as fatigue) to be

routinely captured for all registry participants, informed consent processes, guidance on disseminating research findings back to participants, and assistance in the development of documents to facilitate queries from patient members, research partners and external collaborators.

Challenges to Incorporating Patient Perspectives over the Registry Lifecycle

Patient-centered registries require engagement that extends beyond the development phase. Common challenges across the registry lifecycle are briefly described below.

Sustainable model for engagement of many registrants: Patient/caregiver-oriented committees offer one means of gathering regular input from patient representatives. However, it is also important to hear from a wider representation of patients, caregivers, or other stakeholders both anecdotally and systematically, via in-person or through online focus groups, one-on-one interviews, surveys, webinars, social media communities, chat forums, or conferences. These approaches can also address another potential pitfall of expecting a small number of patients to speak for "all" others.

As previously noted in the section "Ability of Registries to Meet the Needs of Patient-Centered Research", patients have requested that research networks offer opportunities for patients to connect with other patients within the registry. Participants may find support and benefit in sharing their experiences with others who are experiencing similar challenges to their health and economic, social, and emotional well-being. Supporting these relationships may help build a foundation for long-term registry engagement.

Patient advocacy groups can play additional roles in providing support opportunities and building a sense of community around registry data collection and research studies. Some methods include providing a forum for engagement about research priorities; social media interactions sharing information about the study through the enrollment, implementation, and dissemination phases; in-person and virtual social support; virtual "research club" interactions to review and discuss relevant peer-reviewed publications; authoring and distributing literature on care and management and the patient experience; and regional support groups.

Patient-responsive infrastructure: A serious challenge for many registries is developing an approach that is geared towards long-term participant involvement while reducing participant burden and 'survey fatigue'. Asking patients to contribute data repeatedly over time is facilitated when registries offer something immediate and concrete to patient registrants in return. Additionally, in the longer-term, providing a report of how data were used also discourages survey fatigue. For "Arthritis-Power" (AR-PoWER PPRN), a website and mobile app were developed that provide access to education and news, as well as a longitudinal personal health tracker (of symptoms or other PRO data) to facilitate health care decision-making. New features, such as a symptom journal, were later added to the app in response to input from patients. The DuchenneConnect registry offers a comparison of each registrant to aggregated data from the registry community, modular surveys with a smart-phone friendly interface, educational content related to the topic of the surveys, access to clinical experts and those in therapeutic development, summaries of all active clinical trials in Duchenne, and lay reports of results.

Challenges Associated with Representation of Minorities among Patient Stakeholders

Minority participation is important for all registries and their associated research, because this representation touches on issues of equality and the elimination of healthcare and research disparities, which are core values for improving the healthcare of all individuals. It is critical to bear in mind historical precedents across the entire spectrum of clinical research when considering the participation of disenfranchised groups; the literature on minorities' distrust, poorer access to healthcare, and other barriers to research study participation needs to be weighed.[32] While achieving diverse representation is difficult in all registries, there are different types of challenges and approaches in rare and common disorder communities. We have found it useful to explore motivations and preferences for registry and research participation across different groups to understand how to be most inclusive. Moreover, inclusion of diverse patient groups will contribute to better understanding about treatment heterogeneity, which will benefit patients, health care providers and health systems.

Challenges in Responsiveness to Multiple Stakeholders' Needs

Most registries address the interests of multiple stakeholders, and this should be conceptualized and explored as an opportunity rather than perceived as a challenge. Though participant engagement is vital in developing meaningful and acceptable research protocols, it remains the responsibility of scientific partners (e.g., academic, government, or industry researchers) to maintain the research rigor of a patient-centric registry, since the ultimate purpose of a registry is to conduct meaningful, reliable research that meets scientific standards. If appropriate methods are not used, it threatens the integrity of the research findings, which then cannot meet the needs of the patient community. At the same time, registries should provide clinically meaningful results that are important to the lives of patients and caregivers. To empower patients and caregivers to articulate their research priorities, scientific partners should strive to activate and build the capacity of multiple stakeholders to participate in research activities as discussed, in *italics*, below.

Activating a registry: Patients can play a fundamental role in research engagement and advocacy. Patients should be empowered and encouraged to identify their unmet needs, the health care decisions they make, and the information that is (or is not) available for them to make these decisions. Patients do not have to be able to articulate their needs and experiences as research questions, since the research team can assist in the translation. The research questions derived from such discussions can be prioritized by stakeholders and then voiced to decision makers.

Building capacity: The training and development of patient stakeholders to be full participants in research is critical. Different stakeholders have different needs, interests, and capabilities. Whereas many patient and caregiver partners have little or no familiarity with research, most providers have at least some experience conducting health research. Patient partners may need education about the scientific method, research design, and unfamiliar language or acronyms. Other stakeholders, such as providers or regulatory bodies, may also need training in how best to work in partnership with patient groups or representatives. Patient advocacy groups may be a valuable resource to assist providers with this training and to increase understanding of the common goals shared by all stakeholders. Within the registry community, all patients and

caregivers benefit from higher-level education to understand general research principles, approaches, common benefits and risks of research participation, and questions to consider.

Challenges in Disseminating Registry Findings to Patients in a Useful Manner

Transparency about data use and research findings combats the perception of "helicopter research," where participants perceive that researchers obtain data and then are never heard from again. Patient-centered registries have the opportunity to engage in a different approach where both registrants and their data are valued and respected. For example, the DuchenneConnect registry provides registrants with a report of when their data is used, and by whom and for what general purpose.

Once research is complete it is important to compose a research summary document that is easily accessible and understandable to the general public to prepare for dissemination of findings. The summary document may include an overview of key findings and a fact sheet in non-scientific terms. This summary document can be sent to all research participants along with a letter thanking them for their participation. Once finalized, findings can be further disseminated through at least two broad channels:

1. Patient organizations provide many opportunities for dissemination of results to the patient communities. Dissemination activities may include presenting study results to patients at face-to-face and online patient education events and webinars, organization newsletter articles, blogs, press releases, and social media posts and/or conversations on Facebook, Instagram, Snapchat, Periscope, Twitter and YouTube. These traditional and social media streams permit results to be disseminated repeatedly in a way that can enhance penetration into the patient community. Findings can also be shared via legislative advocacy and patient/provider mobilization activities.

2. Scientific meetings and conferences provide opportunities to present results via project-related issue briefs, slide presentation sets, and printed materials.

Data holders should prioritize dissemination in their data use agreements. DuchenneConnect, for example, requires in their data use agreements a lay report of findings, requests that a high-level summary be released prior to publication, provides a webinar forum for results to be provided to the lay community, and is able to publish findings independently if researchers do not publish in a reasonable timeframe.

Ethical Challenges in Patient-Centered Registries

Though registry data collection is typically considered to be moderate or low risk, there are important ethical considerations. First, valid informed consent is essential. In an attempt to make participation in a research registry attractive to patient participants, the registry may be touted as a "health tracker app" or other tool. It is important to remind participants that their participation constitutes research and to give patients ways of opting out of participation to ensure that participation remains voluntary. Participants must understand why the data are being collected and the ways the data may be used. Transparency regarding access to the data, including whether patient reported data will be shared with their health care provider or health care insurer or if there is a mechanism for sharing of data with external researchers who apply for access should

be provided. Also, part of registry planning should include consideration of what will happen to the data and any ongoing research when the registry ends, due to loss of funding or at a pre-planned time point. These policies should be clearly stated in the informed consent.

It is vital to engage patients, caregivers, and other stakeholders in developing a consent process that is robust and meaningful, yet flexible enough for participants so that they may participate to a large degree but opt out of some response options or data linkage or data sharing options that may otherwise discourage participation.

Finally, to support a culture change where patient and caregiver engagement becomes the norm, it is vital to engage patients and caregivers in developing systematic evaluation approaches to quantify and qualify outcomes of engagement. As in the development of any other research question, stakeholders should help identify meaningful outcomes associated with engagement activities and work with research teams to determine approaches to measurement. The results of the research should be disseminated through both lay and peer-reviewed venues.

Resources for Building Patient-Centric Registries

Summarized below are references that provide extensive detail in different areas of observational research methods, registry methods and considerations, as well as a comprehensive inventory of research networks and registries.

PCORI Methodology Report and Related Guidelines

As mentioned in the section "Definitions of Patient-Centered Care and Patient-Centered Clinical Research", PCORI led the development of a set of minimum standards for PCOR, summarized in the PCORI Methodology Report, which includes 47 standards that PCORI-funded research must adhere to, and also serves more broadly as guidance to other researchers.[33] Standards cover areas including formulating research questions, patient-centeredness and engagement, data integrity, statistical methods, and the design of registries and data networks. Specifically, for the design and features of registries, the PCORI Methodology Report provides standards for the following: the type, extent, and length of patient follow-up; transparency of data use agreements, informed consent agreements, and data security documentation for institutional review boards; data quality assurance via structured training of data abstractors, use of data quality checks, and procedures for data review and verification; documentation and explanation of any protocol modifications; consistent data collection with clear, operational definitions of data elements; systematic, unbiased patient enrollment; monitored and minimized loss to follow-up; and collection of data to address confounding.[33]

AHRQ Registry Users' Guide Handbook

The *"Registry User's Guide"*, developed under a contract with the Agency for Healthcare Research and Quality (AHRQ) in collaboration with the Centers for Medicare & Medicaid Services (CMS) through the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network of AHRQ's Effective Health Care (EHC) Program, was first published in 2007 as a reference for "establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes." Since then, the User's Guide has been subsequently updated with additional information and new chapters on emerging and expanding

areas of science impacting registries. Ongoing updates ensure a comprehensive reference source for researchers and other stakeholders involved in registry planning, design and implementation. As noted earlier, this document is an e-book supplement to the 3rd edition of the *Registry User's Guide*.[1]

Inventory of Registry Networks and the Registry of Patient Registries (RoPR)

PCORI maintains a comprehensive inventory of research networks, including the PPRNs and Clinical Data Research Networks (CDRNs), which are part of PCORnet, and registries.[34] The report summarizes key findings about patient engagement for each type of network, creates a taxonomy for the three types of collaborative networks, and an inventory of all identified networks and registries.

The RoPR was designed and funded by AHRQ for the purpose of providing a searchable, central listing of registries, linked to ClinicalTrials.gov. Information including the purpose, design, disease area, outcomes is available for each participating registry on a voluntary basis, and the RoPR is intended to be of use to researchers seeking to develop a registry in a specific area, as well as to patients and other stakeholders seeking this information.

Patient-Advocate Organizations or Voluntary Health Agencies and Non-Profits

While there is not a single comprehensive source listing all active patient-advocate organizations in specific disease areas, the National Health Council does maintain a list of numerous patient-advocate organizations or "Voluntary Health Agencies" across a range of diseases and conditions.[35] Professional organizations and foundations dedicated to research and support of patients with specific conditions are additional sources of links to active patient advocacy groups.

The White Dress Project is an example of a non-profit patient advocacy organization dedicated to raising the awareness of uterine fibroids and raising funds to support research on this condition. Its members, women living with uterine fibroids, find support and benefit in sharing their experiences with symptomatic uterine fibroids and the impacts fibroids have on their economic, social, and emotional well-being. These impacts include the financial burden of treatment, the daily emotional toll of symptoms, and frustration from lack of access to care, lack of broader education about the condition, lack of definitive research regarding comparative effectiveness of treatment options, and dissatisfaction with the available treatment options. The White Dress Project advocates to address the previously described challenges of "helicopter research", as it is felt that very little research on fibroids is disseminated effectively and clearly to patients. Members of The White Dress Project attend conferences, join forums and make efforts to directly connect with researchers, scientists and physicians to serve as a vehicle for sharing the latest information on the condition and treatment options with the patient community. Additionally, the White Dress Project has advocated for legislation in multiple states, to declare July as Fibroids Awareness Month and works to communicate the importance of continued education and awareness to legislators through legislative study committees and forums.[36]

Conclusion

The growing focus on patient-centeredness in clinical research, medical care, and regulatory science has great potential to increase the availability and dissemination of evidence that can be used to inform health care decision-making. With the expansion of patient-centered research programs, the evaluation of stakeholder-driven research questions and relevant health outcomes will address critical evidence gaps where decisional dilemmas remain.

Patient registries may play an important role in the development of patient-centered research. Results from patient focus groups regarding patient perspectives around participation in registries and other research show that patients are concerned with the level of convenience and accessibility of participation, translation of materials for non-English-speaking patients, risks to privacy, directionality of data sharing from patients, and whether data collection tools focused on areas relevant to their experience, including mental and emotional health. Patients also want timely communications of the results of the research they participate in, a concept that is being built into the PPRN programs and others.

This chapter provides a broad introduction to the subsequent chapters that take a deeper look at the following topics relating to patient-centeredness in registries: engaging patients as stakeholders throughout the registry lifecycle; the use of digital health technologies in registries; direct-to-patient registries and other patient-centric designs, and patient-generated registries.

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Engaging Patients as Partners Throughout the Registry Lifecycle: White Paper +

Draft White Paper for Fourth Edition of "AHRQ Registries for Evaluating Patient Outcomes: A User's Guide"

Introduction

Given the intent of patient registries is to understand patient experiences and outcomes, the process of designing, operating, and evaluating evidence from registries can often benefit from patients' perspectives. Engaging patients, caregivers or organizations ("patient partners") that represent the perspectives of the population of interest as partners throughout the registry lifecycle can help to: (1) ensure that the registry effectively collects and measures outcomes that are relevant to patients; (2) ensure that the registry design effectively recruits and better retains patients; (3) increase transparency of study objectives, processes and policies (e.g., measures to safeguard data privacy) that, in turn, enhance the credibility of the registry; and, (4) ensure that the research, reports, and other registry outputs address patient priorities to the extent possible and ultimately are used to inform healthcare decision-making.

The 3rd edition of *Registries for Evaluating Patient Outcomes: A User's Guide* ("the User's Guide") acknowledges the value of involving patients in this process, but does not provide advice on how to involve patients and caregivers as registry partners. In fact, little guidance currently exists in this area and effective approaches to involving patients and caregivers as research partners more generally is a rapidly evolving field. A recent systematic review suggests that while there is a broad spectrum of engagement mentioned in the literature, much evidence is still needed to identify the best methods and to ensure that engagement is not tokenistic.[1]

This chapter will address the specific opportunities, practical strategies, and challenges of including patients, caregivers, and/or patient advocates as active partners in registry planning, operations, study design, and dissemination efforts. Table 1 provides key definitions that are used throughout the chapter.[2]

Table 1. Key Definitions Related to Patient Engagement*

Key Definitions
"Patient partners" includes patients (those with "lived experience"), family members, caregivers, and organizations that are representative of the population of interest in a particular study. Patient partners are members of the research team and involved in the planning, conduct, and dissemination of the research.
"Patient participants" or **"patient subjects"** are individuals enrolled into the study as participants.
"Stakeholder partners" may include members of constituencies based on professional, rather than personal, experience. For example, these constituencies may include clinicians, purchasers, payers, industry, hospitals and health systems, policy makers, and training institutions. Some individuals may fit into several categories.

*Adapted from PCORI Patient Engagement Rubric [2]

Rationale for Engaging Patients as Partners

"People will forget what you said, people will forget what you did, but people will never forget how you made them feel." – Maya Angelou

Participants in research studies articulate four core needs that exist across all age ranges and socioeconomic levels: (1) they want to feel they are taking control of their medical condition and well-being; (2) they want to be personally connected to the study staff; (3) they want to be treated by researchers as human beings; and (4) they want to know that their participation will make a difference.[3] Beyond meeting these core needs, involving patients directly as partners can help ensure success of research studies by enhancing study recruitment, retention, as well as the production of meaningful, comprehensible study reports.[1,4] A review of publications reporting stakeholder engagement in research revealed that stakeholder engagement, including patients as research partners, improves the relevance of research, research adoption, and stakeholder and patient community trust in research and researchers. Additional benefits of this type of engagement include better transparency of research and increased patient understanding of the research process and study findings.[5] Further, by including patient partners as active members of the study team, patient participants hopefully will be more invested in the research (as they see their own viewpoints more represented) and feel more positive about their experiences.

Registries require careful consideration from inception in formulating and prioritizing the research question(s), designing the studies, determining how to best measure exposures and outcomes (e.g., development of patient-tailored survey tools), selecting the target patient population(s), and determining the sample size and duration of follow-up. Following the design phase, considerations include operationalizing the registry, efficiently enrolling and retaining patients, and disseminating the results. Patients and caregivers have traditionally not played an active role in many, if any, critical decisions regarding clinical research studies and registries. As a consequence, research at times has not reflected patient priorities. For example, in one review of 194 published clinical studies in the dialysis literature, only 20 percent addressed at least one of ten dialysis research areas identified as priorities through surveys of patients and patient stakeholders. In the same study, four of those top ten priorities received virtually no attention across any of the 194 studies, highlighting a disconnect between traditional research teams and patient perspectives and priorities.[6] It is important that patient-centered outcomes research help patients and other stakeholders make decisions and the outcomes needed to make those decisions should be included in the research. In addition, the research design should address issues related to measurement, sample size, length of follow-up, and other considerations inherent in good research design. Engaging patients from the beginning of the planning process should increase the likelihood that the research will help healthcare decision-makers and patients make better decisions.

Registries planned without the input of patient partners risk lacking relevance, or being perceived as too burdensome for patient participants, resulting in recruitment and retention difficulties or problems with missing patient-reported outcome data. Given these risks and the substantial costs expended in setting up and running a registry, study sponsor(s) should want to ensure that the registries reflect patients' perspectives from design through implementation to assure the registry provides more satisfied patient participants and more meaningful research results. The goal of obtaining input from patients, caregivers, and/or patient organizations on registries should be to

understand the perspective of the patient regarding all aspects of the study. Early and regular patient input is critical to reach the right balance on many issues, including how patients are enrolled and communicated with throughout the study, frequency of study assessments or contacts, and patient-reported outcomes (PROs) and other clinical outcome assessments (COAs) relevant to the patient population.

Opportunities for Engaging Patient Partners Throughout the Registry Process

Patient input has been shown to benefit all stages of clinical research, from research agenda definition through implementation, and can positively impact the research participants, the researchers, and the broader community.[4,7] Several researchers have reported that involving patients, caregivers, and/or patient advocacy groups from the start of the research project has helped to expand and clarify their research questions so that they are more relevant to the patient population.[8,9,10,11,12] The opportunities to integrate and engage patient partners across the lifecycle of the registry are myriad.

Including patient partners in the research design at the outset can help researchers better understand the burden of disease and help to identify issues outside of the medical environment that could impact the research operations. For example, there may be disruptions of daily life resulting from registry participation beyond those imposed by a complex disease and patient partners may be able to suggest mitigation strategies to the research team.

More generally, including patients as full members of the registry research team can also help provide greater transparency and build trust, particularly if participants do not feel that the researchers are studying aspects of their disease that are important to the patient community. Establishing trust takes time and requires intentional and ongoing communication both during and beyond the completion of a study and can easily be lost if a participant feels misled about the nature of the research.[13] This may be especially important for conditions that disparately affect minority communities, in which there is a complicated history of unethical research practices[14] or perceptions of uncompensated exploitation[15] that may disincentivize research participation. Having patients who are representative of the target patient community as partners in the research can increase the credibility of the registry project.[16]

Patient partners can also help researchers in very targeted aspects of the research process, such as in developing and facilitating the recruitment and retention strategy. They are better positioned to understand potential barriers from the patient perspective and, as trusted members of their respective communities, they can ensure that the recruitment procedures are sensitive to the needs of the patients. These partners can be “champions” for the registry and serve as a liaison between researchers and patients, helping to identify and recruit patients and explaining the study to potential participants in lay terms. Their efforts can also include preparing and/or reviewing patient outreach materials, identifying more effective methods to increase awareness of the study in the community of patients, and developing new methods to recruit difficult-to-reach patients.[10,17,18,19,20] For example, the iConquerMS™ Multiple Sclerosis (MS) Patient-Powered Research Network (PPRN) recruitment strategy initially relied on the "trusted voice" of leading MS patient bloggers to help promote enrollment in the network.[21] Further, patient stakeholders involved in a study of intravenous drug-use dramatically reduced the time required to define the

target population and to access and recruit participants through their identification of a need for outreach services to the community and by acting as peer interviewers.[22]

Including patient partners in the discussion on data content and collection approach, including exposures, outcomes, and comparator groups, can improve these design elements. For example, McCormick et al.[23] reported adding environmental exposures for a study of breast cancer risks based on patient input. An additional consideration in the data collection approach is integrating patient input to better understand how to frame disease symptoms and for linguistic and cognitive testing of the questions and instructions.[24] This input extends to other types of written materials about their disease, including patient brochures, promotional materials, and surveys.[20,25,26] Such input can help determine the appropriate number of outcome measures, frequency and best timing to complete measures, and the length of questionnaires to help decrease patient burden. In addition, patients and caregivers can assist the researchers by providing information on the most appropriate data collection modes—paper, electronic (e.g., web-based, tablet, or smart phone), or telephone capture of patient-reported outcomes—and the frequency. Patients and caregivers may also serve as links to other data that can be used in a study or can help to assure that more complete data are collected for a registry. Many registries and PPRNs (such as Health eHeart) have enabled the collection of data from patient mobile health trackers and other web-based platforms where patients collect and store personal health information.[27]

Finally, patient partners can assist in interpreting the registry findings, describing results in a way that is meaningful to patients, suggesting additional analytic questions, and communicating results in patient-friendly language.[28,29] Patient partners can assist researchers in understanding the impact of findings, making the findings more accessible to both the patient and clinical community, making messages more powerful,[7] and enhancing dissemination of research information and findings on patient forums, blogs, Twitter, Facebook, and other social media.

Examples Demonstrating the Need for Patient Partner Engagement

There are many facets of the research process that are ripe for improved patient partner engagement. Chief amongst these areas is in recruitment and retention, often considered the "Achilles' heel" of clinical research.[30] In cases where a patient registry is required by a regulatory agency to evaluate the safety and effectiveness of a pharmaceutical product (drug, vaccine, device, biologic), registry sponsors have often had to request extensions and/or increase the number of countries or clinical sites to meet recruitment goals. In addition, many registries are designed to follow patients over many years in order to provide information on natural history and/or long-term outcomes. Keeping patients engaged in the registry over the duration of the study period can be challenging. There may be many reasons why recruitment and retention fail for a given registry. Evidence to support patient involvement is often based on successes in meeting recruitment or retention goals, rather than a post-hoc review of reasons why a registry has failed to meet its goals. While it is difficult to know if patient input at the design phase of the study would have helped, Chapter 3 of the User's Guide (Registry Design) provides an example where a difficult-to-recruit registry utilized a patient advocate with success. The chapter notes, "Employing direct-to-patient recruitment can be an effective way of reaching a patient population that otherwise would not be enrolled in the registry, and can yield surprising and

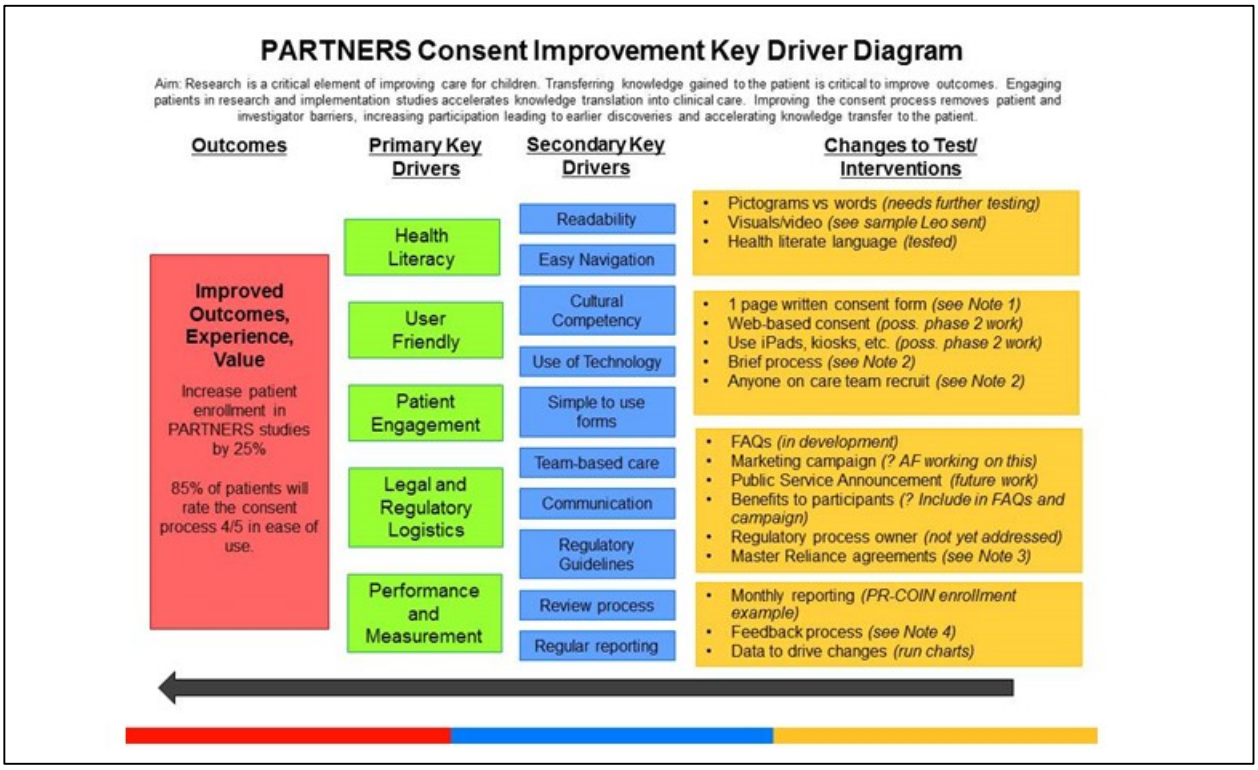
important insights into patient experience… A patient advocate was invited to consult in the registry's development and provides ongoing advice from a patient perspective".[31]

There are examples where failing to consider the patient perspective in designing a clinical trial or in developing a product has caused delays, failed products, or studies to be discontinued. The Research on Electronic Monitoring of Overactive Bladder Treatment (OAB) Experience (REMOTE) is a virtual trial where patient input may have been helpful in determining the study design, recruitment strategy, and data collection processes. OAB impacts primarily older women who are often not as technologically savvy as a younger population. The study was discontinued after failing to adequately recruit participants using virtual tools such as smartphones and the Internet. The sponsor learned that for certain diseases and severity levels, offline conventional channels work better than online channels; the virtual study design may have been better suited to a different patient population. Involving patients with OAB up front may have identified this issue and saved time and money.[32]

Another example where patient input could have increased the likelihood of success is for an inhaled insulin device known as Exubera™. When initially approved for marketing, annual sales were anticipated to reach approximately $2 billion. However, the product was not accepted by patients for several reasons, including an unusually large and unwieldy delivery system, challenges in loading the drug blister packs, dosages measured in milligrams rather than insulin units, and bioavailability of insulin that depended on user technique. Sales reached only $12 million in the first 9 months of marketing and, as a consequence, the sponsor voluntarily withdrew Exubera. Involving patients early on could have helped the sponsor identify these issues and determine whether to modify the delivery device or abandon development prior to outlay of significant resources.[33]

While these examples come out of clinical trial development programs and not registries specifically, each illustrates the pitfalls of having inadequate patient input in scenarios that are germane to registry research. One example of patient input in registries is the PARTNERs PPRN[34], which is evaluating the impact of patient involvement on the study consent process. PARTNERs is a consortium of patients, families, advocacy organizations, researchers, and healthcare providers that advance research in juvenile idiopathic arthritis, juvenile dermatomyositis and childhood onset systemic lupus erythematosus. These stakeholders are engaged in all aspects of the network operations from topic generation to dissemination of results. PARTNERs has developed a key driver diagram (Figure 1) to assess the impact of a number of patient-centered interventions for their consent process. The network leadership has identified a number of interventions with primary and secondary drivers to reduce barriers associated with the consent process for patients and healthcare providers alike. In order to assess the effectiveness of these interventions, they have identified outcomes for increased enrollment into network studies and favorable ratings of the consent process for ease of use.

Figure 1. PARTNERs Consent Improvement Key Driver Diagram



*PARTNERS PPRN Patient Engagement Workgroup.[35] Aim: Research is a critical element of improving care for children. Transferring knowledge gained to the patient is critical to improve outcomes. Engaging patients in research and implementation studies accelerates knowledge translation into clinical care. Improving the consent process removes patient and investigator barriers, increasing participation leading to earlier discoveries and accelerating knowledge transfer to the patient.

Engaging Patient Partners in Planning a Registry

As described in Chapter 2 of the User's Guide (Planning a Registry), it is important to identify registry partners and build a registry team or committee during the planning phase. Early engagement of stakeholders has been noted as an important factor contributing to successful engagement.[36] The registry team should reflect different types of knowledge, expertise, and skills to adequately plan and implement a registry. Patients, caregivers, and patient advocates are considered important partners, and as described above can add significant value to the registry team from the preliminary planning to final dissemination of results.

Considerations for Early Engagement of Patient Partners

Below are suggestions and considerations for planning when and how patients, caregivers, and/or patient organizations can be involved in the registry process.

- **Describe when in the registry planning patient partners will be involved.** As noted above, earlier is better, but it is never too late to involve patients in the planning or operational process to improve an existing registry, since registries often continue and can change over time as new measures, endpoints, biomarkers, research questions, etc. are added. For example, PCORI is funding a project that aims to inform researchers on how surveys, focus groups, and online methods compare for involving patients 65 years and older in research prioritization activities in an existing registry of adults who are 65 and older with back pain.[37]

- **Plan a thorough patient engagement strategy to ensure patient input and a patient-centered registry plan.** In developing a plan to engage patient partners, many registry and research teams develop charters or memorandums of understanding (MOUs) in a collaborative manner to help communicate clear roles and responsibilities to assure there is a clear understanding of how all parties will be involved in the registry lifecycle. Expectations regarding time commitment and types of activities should be clearly communicated to patient partners prior to engagement.[36] Table 2 considers multiple options for involving patient partners throughout the registry process – in both planning the registry infrastructure and in the registry conduct.

Table 2. Opportunities for Patient Partner Roles in Registry Planning and Conduct

Opportunities for Patient Partner Roles in Registry Planning and Conduct
Overall Registry Process
Member of governance or advisory committees
Patient/caregiver co-investigator
Patient/caregiver members of research team
Registry Planning
Develop registry collaborations and other partnerships
Conduct patient and community outreach

Opportunities for Patient Partner Roles in Registry Planning and Conduct
Develop training for patient and research community
Advise on registry participant recruitment and retention strategies
Plan for longitudinal data collection frequency and instruments
Advise on research topics and prioritization unless they are primary funding source, in which case they may lead these activities
Advise on study design and protocol development
Develop study collection methods
Determine patient-centered data elements, PROs, and clinical outcome assessments
Develop communication plans to keep the community abreast of study progress
Registry Conduct
Develop and participate in study recruitment and retention activities
Provide context on risk and benefit as a member of data and analytic review committees, or Data Safety and Monitoring Board (DSMB)
Develop and participate in ongoing communication with patient participants
Develop dissemination and implementation plans including input on how best to interpret and communicate the meaning of the study findings to patients

Assess whether training is needed. Determine if training is needed for the registry team to enhance collaboration and communication and put professional-researchers and patient-researchers on a more common footing. To engage patients in the team in a meaningful way, make sure that they are well prepared to fully contribute to the team's discussions and decisions. Also, it is important to make sure professional-researchers understand how to best communicate about the research in language understood by patients.

Determine which aspects of the registry will most need patient input. Table 3 describes several ways in which patient partners can contribute to the registry. Once these areas are identified, they should be included in a patient engagement registry plan.

Table 3. Patient Partner Contributions to Registry Lifecycle

Patient Partner Contributions to Registry Lifecycle
Identify and define unmet medical needs Formulate, advise, and/or refine research question(s)
Identify and select COAs, including PRO measures (number of instruments, length of questionnaires, invasive measures or collection of more personal information, and frequency of administration)
User-testing of forms, procedures, and PRO tools
Review and revise study documents including informed consent
Relay what patients and/or caregivers need to know about the disease or treatments to ensure this data is collected in the registry
Advise on recruitment and retention strategies
Act as patient ambassadors to help identify, enroll, and retain other patients
Help identify and include relevant patient subgroups (diversity of disease and patient demographics)
Provide an understanding of important non-medical factors that might negatively impact recruitment and retention and how best to mitigate
Identify barriers to participation – chart "day in the life of a patient"
Co-design strategy on how to best communicate with patients during study (written materials, text messaging, website, phone calls)
Participate as patient interviewers
I
Provide feedback on how the registry is progressing
Help interpret the study results and identify new analyses
Assist with the communication and dissemination of study results in patient friendly language to the right patient audience via the right medium

The importance of patient engagement in developing PRO measures and other COAs has been well established in clinical trial research and guidelines have been written to provide direction on how best to do this.[24,38] The U.S. Food and Drug Administration (FDA) Guidance on Patient Reported Outcomes[24] requires that PROs demonstrate relevance to patients based on data collected from patients establishing content validity. In addition, evidence for COAs must include data to demonstrate that the clinical outcome is linked to survival or how patients feel or function in daily life.[39] While these guidelines are not directly applicable to registry research, both patient-reported and clinical outcome measures used in registries should likewise show evidence of importance to the patient population through patient review and testing of the measure for relevance of content and cognitive and linguistic understanding.

Methods of Engaging Patient Stakeholders

Methods of engagement may vary based on the stakeholder, the type of information needed from the patients and the role that the patient partner will play in the registry. Also, dimensions of engagement can vary – from broad efforts, such as public comment on registry informed consent and input on research topics, to more focused efforts including individual patient or caregiver interviews, questionnaires, surveys, focus groups, workshops, working groups, crowd sourcing, and market-research. More intensive methods include participation in advisory panels, steering committees, or as members of the registry and/or research team; these may be most suitable for keeping patient partners engaged in decision-making throughout the registry lifecycle.

One could consider a mixture of methods to engage patient partners based on the population and the input needed. Engagement through avenues such as the Internet, social media, and smartphones may work for a younger patient population, but may not work for older patients or patients without access to these devices. As with the registry design itself, the engagement strategy needs the right fit to the patient population in order to engage patients and maintain engagement. The Engagement Rubric, developed by the Patient-Centered Outcomes Research Institute (PCORI), is a useful framework for helping all stakeholders recognize opportunities for patient and caregiver engagement from the planning of a study through the conduct and dissemination. The rubric also provides examples of how research teams can demonstrate patient-centered outcomes research (PCOR) principles while working together.[2]

PCORnet is the National Patient-Centered Clinical Research Network that integrates health data for studies and catalyzes research partnerships among two types of networks: (1) Clinical Data Research Networks (CDRNs), which are mainly based in healthcare systems such as hospitals and health centers, and (2) PPRNs, which are run by groups of patients and their partners who are focused on one or more specific conditions or communities, and who are interested in sharing health information and participating in research.[39] The PCORnet networks have developed multi-dimensional methods and approaches for engaging patients to provide input into their networks and studies. For example, networks have a variety of structures for engaging patients, caregivers, and patient advocates in the governance of their networks to help make critical decisions with respect to planning and operationalizing the network and their respective research priorities. Several networks have developed electronic platforms to facilitate broader participation from patients and caregivers to provide input on a variety of aspects. Some examples include generating and prioritizing the network research agenda, shaping network consent, and crowdsourcing research proposals.

There are a number of challenges and pitfalls to be aware of in planning and conducting a registry with patient engagement and input[4] and there is currently no agreed upon best practice for engaging patients. However, this is an area of active research within several groups, including PCORI and the National Institute for Health Research, and there are proven tips that can be used to enhance patient engagement and input (Table 4).[36,40]

Table 4. Tips for Enhancing Patient Partner Engagement and Input

Tips for Enhancing Patient Partner Engagement and Input
Roles and Responsibilities
Before engagement, clearly detail expectations (e.g., anticipated commitment of time and types of activities)
Be clear about the partner roles – do not expect community members to do academic duties
Be sensitive to the time constraints of all stakeholders
Include patients in design, topics, and content for any research materials, website, etc.
Consider research events that patients can lead to increase engagement
Trust and Transparency
Engage patient partners early in the process
Create a true patient-researcher partnership community by bringing the registry team, patients, caregivers, patient advocates, and other stakeholders together for discussions
Acknowledge patient and/or caregiver contributions frequently
Maintain ongoing relationships to build trust and credibility
Conduct frequent reviews of how well patient engagement is working and if changes need to be made to improve patient input and involvement
No stakeholder's comment is considered superior or inferior to another perspective; acknowledge all contributors
Presentation of ongoing and end of study results are important to stakeholders and participants
Training and Education
Present to researchers and patients on the importance of patient-centered research to help increase awareness
Educate researchers on how to be more effective listeners so that they hear and act on recommendations from patient partners
Educate patients in how to be more effective communicators and bring their voice to the table (e.g., European Patients Academy on Therapeutic Innovation (EUPATI) and PCORI)
Be sensitive to technology limitations and how to best mitigate
Recognize that patients and clinicians often speak two different languages (e.g. medical/research versus lay language) and may need facilitators who speak both languages to make sure that patient input is considered
Preparing For and Conducting Team Meetings
Provide opportunities for people to ask questions before meetings (particularly for consumers or others who are unfamiliar with research)
Pre-meeting information materials promote comfort with the topic and enable informed discussion

Tips for Enhancing Patient Partner Engagement and Input
Team building exercises such as pre-meeting "icebreakers" are useful, especially when engaging stakeholders with differing experiences/perspectives
Make sure patients feel comfortable speaking up at registry team meetings
In registry meetings be sure to use layman's terms or provide training in medical terminology
Having someone with similar training as the stakeholder can be helpful – particularly thought to be important for clinicians
Facilitators can be useful for stakeholder engagement: - Facilitator can encourage participation and focus discussion at in-person meetings - Facilitator should be knowledgeable of various stakeholder environments (cultural understanding) - Skilled facilitator ensures all stakeholders are heard and manages dominance issues

Barriers to Patient Partner Participation

Engagement in research design, implementation and/or dissemination of results requires significant time and energy on the part of patients and/or caregivers.[41] While they may have an interest in the study, there may be other medical and non-medical factors that limit their ability to participate fully.[42] Having multiple patient partners participating throughout multiple research opportunity(s) may mitigate loss of a patient partner from the registry team due to changes in disease status or other factors. Fortunately, increasing availability of technology platforms for engagement can help facilitate these opportunities. In addition, to promote maximal patient input in the registry, consideration should be given to a number of engagement issues, including the setting or circumstances of meetings (location, ratio of patients to experts); preparing and empowering patients prior to the meeting; preparing the experts to avoid negative behaviors and medical jargon that might be unfamiliar to the patients; promoting strong facilitation of the discussion to actively manage any potential power differentials between researchers and patients to ensure equal input from all stakeholders; and understanding that this may be an ongoing process where multiple meetings may be required to develop the right level of trust and full participation of patients.[41,43,44,45] Teleconferences and videoconferences should be considered to decrease the burden of travel and increase patient participation in meetings.

In conjunction with the significant commitment of patients and/or caregivers in the registry, funding should be considered. Funding for patient engagement may be an issue, particularly in the grant-writing phase before a registry or study is funded through a grant or other mechanism. Funding for patients, caregivers, and patient advocates to provide significant time and resources may be particularly important where participation is highly dependent on financial incentives due to limited organizational capacity or other employment or family commitments. It is important to be transparent and manage patient expectations related to funding. PCORI's Compensation Framework provides guidance suggesting that the compensation for patient partners should be commensurate with their input such that if patients are full research partners, funds should be appropriated to recognize that contribution.[46] In addition, the cost of convening patient stakeholders needs to be considered – from travel and venue fees to providing food and beverages. There may be a need to educate institutional administrators on providing funds for patients and focus groups beyond the usual research reimbursement provided to patients for

transportation and parking. A United Kingdom study designed to evaluate a pre-funding bursary scheme found that a relatively modest financial outlay resulted in appropriate involvement of patients and caregivers early in the planning phase of research.[47]

Patient Partner and Community Engagement During Registry Operations

Implementation

Once the registry opens for enrollment, the focus of engagement broadens to include the patient community to ensure that enrollment and retention goals can be achieved. If patient partners were involved from the outset of the planning phase, they may have informed some of the strategies for enrollment and retention to ensure multiple patient groups were considered. They may also be actively involved in outreach to the patient community. It should be recognized that patient partners can be particularly helpful in addressing unexpected issues that might arise in the conduct of the registry, such as lower than expected recruitment, higher than expected loss to follow-up, or missing PRO data. In each case, partners may be able to determine the root causes for the issues and help find solutions. Many registries have ongoing advisory and governance roles for patients, caregivers, and advocacy group members to ensure that the patient perspective is considered as issues are triaged for troubleshooting.

Patient partners can also assist in the development of materials that are more appropriate for patients and specifically address questions of interest to patients. Patient can help evaluate whether any materials communicated to patients are written in language that patients and/or caregivers will find useful. Materials can also be cognitively tested with patients prior to finalizing to assure understanding. If the registry is conducted in multiple countries and languages, it will be important to include patients as reviewers for each language. This is important to make sure there is linguistic validation (the concepts have been correctly translated) and cognitive understanding (materials are written in language that effectively communicates information to the patients).

Ongoing Engagement

As part of the ongoing registry, it is important to maintain regular contact with the patients who are engaged at all levels, from research partners to registry participants. Engagement during the operational phase may help maintain enthusiasm and presents unique opportunities for co-learning for the registry partners and participants. The type of engagement will depend on the respective roles of the patients and other stakeholders in the registry, and issues, problems, or opportunities that may present throughout the course of the project. In registries where patients are co-investigators or members of the registry research team or governance board, engagement can be accomplished through regular teleconferences to discuss the registry conduct, regular meetings of the registry team, patient panels, or committee meetings of all identified registry stakeholders. Establishing charters and MOUs at the outset of the project will help the team determine the type and frequency of engagement the registry needs throughout from planning to operations to evaluating evidence.

Some patient participants may be unaware that they are participating in a registry, many may not be aware of the purpose of the registry, and many more are likely not to use the evidence from the research in their medical consultations.[48] Sharing information with patient participants as

data becomes available may also help keep them engaged in the research, as they understand the importance of their participation and how it can improve their health or the health of others. This sharing of data can be accomplished through multiple communication modalities and channels, including newsletters (mailed or internet) and/or webinars, blogs, conferences, and other types of presentations to important patient and stakeholder groups. Careful consideration should be given to the type of data shared with patients so as not to bias any future PRO measures, e.g., baseline characteristics, number enrolled, percentage of PROs completed, etc.

It may also be useful to include patient partners and participants in evaluations of the registry conduct. These may occur on an ongoing basis to help make improvements during and at the end of the study to learn from the successes and failures experienced. Patients may proactively identify issues that are not yet recognized based on their experiences as a participant in the registry. Where input from patient participants is needed, other approaches may be appropriate such as ongoing focus groups or surveys and offering different modalities for input to keep patients more engaged. It is important to consider that mixed methods of continuing engagement based on the patient population and their preferences may provide the most robust, actionable information.

Dissemination of Data

Dissemination and communication planning for registry results should be considered early in the research planning process. Patient partners can be helpful as the registry data becomes available in reviewing and interpreting study data and in determining best ways to communicate and disseminate the study results to reach the patient community. In reviewing the data, the patient perspective might be particularly useful in identifying additional research questions based on the registry findings and their understanding of the patient population needs. Further, patient partners may be able to identify dissemination channels that are likely to reach the broader patient population outside of the registry participants, particularly patient subgroups, and important groups of clinical stakeholders. As with methods to keep patients engaged during the registry conduct, the communication of results may best be achieved through utilizing a number of different modalities deemed most appropriate to the relevant patient populations. These may include newsletters (mailed or internet), webinars, workshops, community and scientific meetings, publications, blogs, and presentations. Including patients in the dissemination plans for study results can also help gain greater credibility from other patient and/or caregiver participants.

Challenges, Opportunities, and Need for Further Research

Throughout the chapter, we have identified a number of opportunities and challenges in engaging patients as part of the registry research team that have been documented in the literature.[4,7] This section discusses some of the most significant challenges and opportunities for improvement in engaging patients in registries.

Challenges to Patient Partner Engagement in Registries

Researcher/Patient Partnerships

An acknowledged issue has been in convincing some researchers of the benefit of involving patients and/or caregivers in the research process. As one researcher described, 'I have a negative view because…people did bring their own agendas…and I really think that's a bad thing in research, to bring your agenda to the research strategy and proposal'.[49] Evaluation of patient-expert partnerships in research has demonstrated that there needs to be sufficient pre-planning to enhance the ability of patients to have a strong voice in meetings. This issue should be discussed early during planning to make sure that all members of the research team understand the importance of patient and/or caregiver involvement and the expectation that the research will benefit. It may be helpful to highlight results from other studies where patients have positively impacted research.[49] In reality, many researchers have limited experience in working with patients as partners and there is notable room in the research community to build capacity and expand their teams to include patients and other stakeholders. Some research teams have retained consultants with expertise in organizational development to help address any potential differences in research experience and ensure productive group dynamics. PCORI's pilot projects identified training as one of the most commonly reported challenges to engagement; 30 percent of respondents identified lack of stakeholder training/background, and 24 percent of respondents identified lack of research team training/background.[50]

While the expertise that patients and caregivers bring offer the perspective of their "lived experience", it is important they consider what aspects of that experience are generalizable to the broader patient community and relevant to any research initiative. Furthermore, while patients do not need to have comparable expertise as a researcher on the science and methodology, they need enough information to successfully contribute to the tasks assigned to them and understand the implications of their contributions to the research lifecycle. This can vary greatly depending on the type of research project. Some patients have become research advocates and have gone through substantial training on research methods, translational science, and the operations of the medical research enterprise. The EUPATI, funded by the Innovative Medicines Initiative, was established to provide scientifically reliable, objective, comprehensive information to patients on research and development of new medicines. The goal is to increase the capacities and capabilities of well-informed patients and patient organizations to be effective advocates and advisors in medicines research.[51] While the training is for medicines research, many of these trained patients can serve as effective patient partners for registry research. However, what is not known is how much training and what type of training is required to make patients effective research partners. Ongoing research in this area will evaluate approaches to training patients for this expanded research role.

Of note is PCORnet's goal is to transform clinical research by engaging patients, care providers, and health systems in collaborative partnerships that leverage health data to advance medical knowledge and improve health care. PCORnet brings together health research and healthcare delivery, which have been largely separate endeavors. By doing so, PCORnet explores questions about conditions, care, and outcomes that matter most to patients and their families. Integral to PCORI and PCORnet is to evaluate patient and caregiver contributions to the research process. The 2015 PCORI Annual Meeting acknowledged a number of challenges; for example, it was recognized that patients and healthcare provider experts involved in research speak different languages and that training of both and/or the use of a facilitator who speaks both languages can improve patients' contributions to research.[52] It is expected that the research being conducted under PCORI and PCORnet will significantly add to the understanding of how best to include patients as research partners and to demonstrate the value of patients' involvement as patient-researchers. The value demonstration should be helpful in convincing skeptical expert researchers. Both patients' input and experts' ability to listen will improve with practice and mentorship.

Identifying Appropriate Patient Partners

Another challenge may be in identifying the most appropriate patient partners to participate as part of the registry team or in the various roles that may benefit from patient input. While lived experience is a critical perspective that patients and caregivers bring to research, many patients have negative experiences with research and/or the healthcare system in general. Those experiences can be difficult to overcome to make meaningful contributions to the research team. In particular, personal beliefs about health experiences that may not necessarily be science-based can be an issue and highlight the need for researchers and others skilled in patient engagement—such as medical anthropologists and professional facilitators—to identify important research questions and outcomes that are often woven into patient stories. Patient advocacy groups may participate in research and/or provide useful leads to patients who have leadership experience or other skills that may make them effective partners for research teams.

In addition, there may be challenges related to utilizing patient advocacy organizations as sources for patient stakeholders, including:

> Existence of multiple organizations that may have some level of competition for funds, attention, and/or preferences for different approaches to treatment, etc.;
>
> Potential conflicts of interest that may affect decision-making or policy positions.[53] Although much of the focus on conflict of interest with patient advocacy groups has focused on financial ties with industry,[54] there are other potential sources of conflict. For example, cancer patient organizations frequently emphasize the benefits of screening based on the experience of being a cancer patient[55], when the harms (such as false positives or over-diagnosis/over-treatment) are of greater concern to "average" patients.

Patient Partner Roles in Registries Utilizing Existing Secondary Databases

Another potential challenge is determining patient partner roles in registries that rely solely or in part on claims, electronic health records, or existing health register and biobank data (e.g.,

Nordic countries). Since these registries are based on data collected as part of medical practice or as part of a healthcare system, the opportunities for contributions across the registry lifecycle (e.g., research recruitment and related issues) may be more limited. However, patients could help develop research questions using the existing data based on what is of interest to the patient population and guide researchers in the best ways of communicating results to patients. In addition, patients may recognize gaps in the existing data and how to best collect that information to provide a fuller picture of the disease from the patients' perspective (e.g., surveys, PROs, or other COAs). There are several opportunities for these types of registries to expand their data collection to conduct potentially more meaningful patient-centered research.

Increasingly, some registries are starting to see the value in partnering with patient groups in efforts to have more complete data encompassing clinical features, such as severity and symptoms, biological labs and clinical tests, and social and behavioral characteristics. PCORnet is a great example of several networks that have expanded or combined their original data to include patient contributed data. For example, PI-Connect is a PPRN focused on primary immunodeficiency that joins data collected through the Immune Deficiency Foundation's (IDF) electronic personal health record (ePHR) and their existing registry of physician-generated data known as the United States Immunodeficiency Network (USIDNET). USIDNET is a patient-consented registry funded by the National Institutes of Health (NIH) and managed by IDF, containing validated clinical, molecular, and laboratory data from patients with primary immunodeficiency in the United States and Canada. Through PI-Connect, IDF is merging these two data sources to facilitate a more robust registry characterized by patient and EHR data. Patients can play a critical role in partnering with various healthcare stakeholders to promote and facilitate data sharing for improved and clinically meaningful research.[56]

Areas for Future Research in Patient Engagement

Concannon et al.[5] suggests three areas for future research related to stakeholder engagement: 1) descriptive research on stakeholder engagement in research; 2) evaluative research on the impact of stakeholder engagement on the relevance, transparency and adoption of research; and 3) development and validation of tools that can be used to support stakeholder engagement in future work. There is currently no agreed upon method to gather data on engaging patients throughout the research process as either patient-partners or patient-participants. PCORI is exploring multiple methods of engagement and assessing these methods, which is guided by a conceptual model of conducting patient-centered outcomes research (PCOR) that provides a structure for understanding engagement in research. This conceptual model is intended to identify required elements for PCOR grant proposals, provide a way to describe patient-centeredness in research, and provide a basis for evaluating the quality of engagement in patient-centered research. While growing interest in research engagement has led to engagement-specific frameworks and definitions, no single conceptual model has yet connected enabling elements to specific research related actions and to intended research outcomes.[50]

PCORI also funds quantitative and qualitative data analysis on the impact of engagement on research, including the value of patient-recommended outcomes for advancing knowledge of research topics, the speed of dissemination of research results, and the speed and comprehensiveness of uptake of relevant research findings into clinical practice. One awardee group is examining whether Community Review Boards (CRBs) represent an effective method

of obtaining patient stakeholder input and whether CRB input results in research that is more patient-centered. Another project is assessing the impact of patient and stakeholder engagement on the development of patient decision aids.[50]

The additional cost of including patients as partners may also be an issue, as patient engagement may have a negative impact on the study budget, timelines, and efficiency. Return on investment expectations need to take a long-term perspective as research teams learn to improve how patients are engaged and the benefit that will result. The measurement of benefit of patient engagement raises a future research area that aims to develop valid qualitative and quantitative metrics to measure success or value of patient engagement in registry research. There may be indirect quantitative measures related to recruitment or retention in the study, or more qualitative assessments such as satisfaction with the study and attitudes about study process (e.g., ease of understanding informed consent, convenience of study visits and procedures).[3] However, these types of indirect measures, such as retention in the study, may be evaluating more than just the patient-centeredness of the research (e.g., patients may drop out of study due to lack of efficacy of the drug tested or for safety reasons). As patient assessments are gathered, another challenge is to consider will be how the registry organization will act on the patient feedback. If patients are taking the time to offer feedback, they will expect a response or some action to their input. Will the organization be able or willing to adapt their research process to what patients want?

Conclusions

"[Patients] are why research is done, and we all want meaningful research done that actually furthers the conversation and improves health outcomes. What I see as a benefit [of patient engagement in research] is that we start having more transparent research, that we have higher quality research. And not only that, research results actually have the impact that they're meant to have." – Patient Advocate[57]

Patient partner engagement in research, including registries, is a relatively new and rapidly evolving and promising practice. Planning a registry to include patient input requires several key steps to be successful. Early consideration for including patients and caregivers as partners is critical in the planning phase and throughout the lifecycle of the registry to ensure a registry answers relevant research questions, provides transparency and credibility, and ultimately generates data that reflects outcomes important to patients and that improves patient outcomes through informing healthcare decision-making. In addition, patient input should help provide more efficient registries that meet recruitment and retention goals with less missing data by focusing on data that are relevant and important to patients and not too burdensome to collect. As more research is conducted and evidence accumulates on how to best engage patient partners and the value of patient input into registries, an increase in patient engagement can be expected across registry research. In fact, in many ways, it is already becoming part of best practice. At a minimum, the inclusion of patient and/or caregiver stakeholders will make registry research more relevant to the group that has the most to gain – patients.

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Digital Health and Patient Registries: Today, Tomorrow and the Future: White Paper +

Draft White Paper for Fourth Edition of
"AHRQ Registries for Evaluating Patient Outcomes: A User's Guide"

Abstract

As use of new technology increases in medical practice and clinical research, registries are uniquely positioned to leverage these innovations to support real-world data collection. In particular, digital health is emerging as an important trend. Digital health is not limited to the use of mobile devices, but rather includes patients, care-takers, and clinicians making use of any digital technology including smartphones, tablets, texting, calling, video conferencing, specialized applications (apps) or monitoring devices to deliver patient care, monitor outcomes, and/or conduct research. Digital health may include the use of devices and apps to conduct real-time monitoring of patient vital signs; to collect digital social and behavioral information; to gather patient-reported data, such as quality of life measures, on a regular basis; to deliver that information to care providers and/or researchers; and to provide care directly through telemedicine apps. While digital health may supplement or supplant other forms of healthcare in high resource countries, it is becoming particularly important in resource-strapped settings, where digital health options can surmount shortfalls in traditional healthcare delivery. This chapter explores ways in which registries may be able to take advantage of digital health technologies, with a particular focus on the strengths and limitations of these technologies to collect patient-generated health data, a discussion on how they are currently being used, and where it is anticipated that they will be of value in the future.

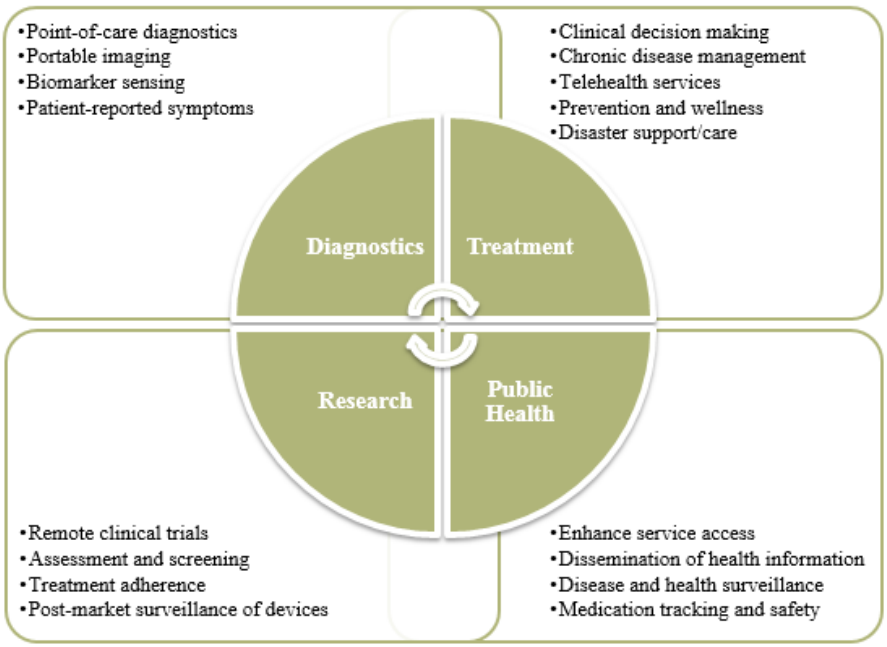
Introduction

The term 'digital health' refers to technologies that can receive and transmit electronic data that can be used, directly or indirectly, to monitor or enhance health or coordinate healthcare services. Digital health includes a wide range of different technologies that can be used in healthcare including categories such as mobile health (mHealth), health information technology (IT), wearable devices, telehealth and telemedicine, and personalized medicine.[1] Other terms such as mHealth, eHealth, social media, and the medically-related Internet of Things[2] are sometimes used interchangeably because there are no globally agreed upon definitions. For the purposes of this chapter, we use the term "digital health" to broadly encompass various terms including, but not limited to, mHealth, eHealth, social media, and the Internet of Things.

Major advances have been made in the last decade in low-cost, real-time technologies to assess disease, movement, images, behavior, social interactions, environmental toxins, hormones, and other physiological variables. These advances are due to increased computational sophistication, as well as reductions in the size and power requirements of digital technologies. As shown in Figure 1, these technologies provide the potential to advance diagnostics, treatment, public health, and research. Social media's impact in healthcare has also significantly grown and while there have been increases in published research using social media, best use cases are not yet clear and policies are still being developed.[3] Despite all of this growth in digital health, the collective understanding of how these components, devices, and technologies work has remained fragmented.[3]

This chapter examines the role of digital health technologies and their use in patient registries. It also reviews recent advances with a look towards where the use of these novel technologies may provide value to the future of healthcare research.

Figure 1. Spectrum of Application Areas for Digital Health Technologies



The Rise of Digital Health

While computing and the Internet have been a part of research for decades, the use of digital technologies for health research is much more recent. Dr. Topol and colleagues present the growth of digital health technologies in table below.[4]

Table 1. Expanding Use of Digital Health Technologies

Use of Technology	2010	2015	2020
World Population, billion	6.8	7.2	7.6
Number connected			
Devices, billion	12.5	25	50
Devices per person	1.8	3.5	6.6
Number of smartphone subscriptions, billion	0.5	3.0	6.1
Number of sensors	20 million	10 billion	1 trillion

Adapted from JAMA 2015[4]

The table above demonstrates significant growth in the use of digital technologies over the past five years and predicts accelerated use of various digital technologies over the next five years.[4] However, smart phones and sensors are only one small part of the digital technology field.[5] Additional sensors, either worn on the body, implanted in the body, or embedded in the skin are provide access to data on a wide range of biological, physiological, and behavioral variables and expected to grow in use exponentially. Due to rapid adoption of these sensors and mobile devices, it is now feasible for researchers to assess activity, location, images, behaviors, social interactions, environmental toxins, and physiological variables in real time.[6]

By enabling participants to conduct many of these measurements remotely, the number of assessments within a study can increase without greatly increasing costs. Sensors can identify environmental exposure (e.g., indoor smoke), location (e.g., via GPS), physical activity (e.g., via accelerometry), sleep, social interactions (e.g., via microphones and cameras and use of built in communications such as email and SMS), images and visual stimuli (e.g., via smart eyeglasses), and electronic exposure (e.g., via social media data). Assessment of physiology such as blood pressure, heart rate, blood oxygen and respiration can now be done via mobile units with high enough quality that some of these devices have been approved by the United States (US) Food and Drug Administration (FDA) for use in hospital settings.[7] Others, such as the camera on the smart phone, can be used for less accurate, potentially valuable measurement of heart rate in real time.

The integration of sensors into a “smartwatch” or “activity band” has made sensors convenient and wearable for long durations. These devices have been initially developed to monitor physical activity and some physiological signals (e.g., heart rate), although the quality of their measurements remains unknown. In the near future, commercial device manufacturers (e.g., Apple and Samsung) promise to monitor pulse rate, hydration levels, glucose levels, and blood

pressure, in addition to physical activity and sleep behavior. The quality of these commercial measures remains to be seen and validation with standardized measures will need to be actively pursued by the research community.[5] The challenge, however, is that by the time a study is completed to demonstrate validity, the device may have been updated with new technology and the validation may no longer be current for that device.

The use of the internet, whether it is accessed on a stationary computer or through smartphones and tablets, also allows for faster and more direct assessment, intervention, and distribution of information. The data that can be collected include not only those collected in conventional surveys, but also data collected by sensors in the device, such as cameras and microphones. Data such as time on the page and number of clicks to get to information are also a part of the digital health environment. Fixed sensors, whether designed for health (such as Bluetooth enabled scales), or developed for other uses (e.g., the Kinect gaming sensor or movement sensors) can also be employed as a part of the digital health ecosystem. Although a newer area of research, examples of this work abound in smart homes, which use both stationary and mobile sensors to measure the activities in the home and to make inferences about health and disease.[8, 9] As more devices in our lives get connected to the internet every day, such as our socks, beds, refrigerators, ovens, televisions, toothbrushes, scales, and thermostats, the possibilities expand for contribution to research. This new industry is attracting the attention of healthcare, as identified in books by leaders such as Dr. Joseph Kevdar and Dr. Eric Topol.[10, 11]

These data, especially when combined across different technologies, have the potential to yield new insights into factors that lead to disease. They also have the potential to be analyzed and used in real-time to prompt changes in behaviors that can reduce health risks, reduce harmful environmental exposures, or optimize health outcomes. Indeed, this new area of digital health research has the potential to be a transformative force as it is based on the continuous input and assessment process and may scale more cost efficiently than other types of research. It can ensure that important biological, social, behavioral, and environmental data are used to understand the determinants of health and to improve health outcomes. Importantly many of these data can be collected with minimal patient burden (e.g., the fixed sensors embedded in smart homes) or in real-world environments.

Utilization of Digital Health in Clinical Research

Smartphones have become an important way for patients to acquire healthcare information. In fact, in 2013, 38 percent of users in the United States considered their phones to be an "essential" tool for obtaining this information.[12] Many stakeholders (clinicians, administrators, professional colleges, academic institutions, ministries of health, pharmaceutical companies, among others) believe that mobile and wearable health technologies can be leveraged to improve health outcomes at lower costs.[3, 13] These devices are considered strongly influential to the patients who use them.[12]

Patient-Reported Data

There are many types of mobile health technologies available today. The first discussed in this chapter are patient-reported data which are captured through a mobile, internet-connected device and collected in a clinical study or registry. The term patient-reported data is used in this chapter

to encompass information captured directly from the patient, person, citizen, individual, and/or self or other terms that could be used to represent the participant in the study. When the data collected is based on validated measurements of patient outcomes, it is called Patient Reported Outcomes or PRO.

A device equipped with PRO capabilities typically has software that captures structured queries and specially designed assessments, as well as free text or audio narratives from patients. In addition to this, PRO systems can use web-based software and telephones. These questionnaires can be in the form of text messages, interactive voice response, or in the use of an app.[14] PROs can be synchronized with wearable devices as well. The most notable benefit from these types of tools are the large amount of data that can be collected from patients without requiring many visits to a healthcare facility.[14]

PROs are used widely in research and by a variety of stakeholders in healthcare. The use of PROs extends from a routine office visit to a clinical trial. As an example, The Patient Centered Outcome Research Institute has invested millions in establishing the National Patient-Centered Clinical Research Network, PCORnet, with a goal of working with patients, researchers, clinicians, and health systems leaders to build and run a network that conducts research addressing the real world needs of patients and those who care for them.[15] As part of the network, outcomes including patient reported outcomes are collected that are considered clinically meaningful and measured from structured questionnaires as well as from mobile apps and devices.

Many companies have created their own PRO web-based systems to use within clinical trials and prospective observational studies. Additionally, patients who are willing to use this technology are also more willing to share their information in general.[14] Utilizing mobile technology for PRO collection offers the following additional benefits: ease of use, better connectivity, the option to work offline, integrations with other apps and devices, direct connection to an electronic data capturing system, ability to custom-design software according to a researcher's needs, ease of distribution, and a relatively smaller learning curve.[14] In addition, data from PROs and mobile apps are collected in real-time, providing clinicians, and often users, with the ability to analyze results as they come in and respond to issues as soon as they arise.[16] Moreover, data collection does not have to have a definite end date and capabilities exist for importing the collected data into an electronic health record system.[16]

Vital Signs

The capabilities of digital health technologies are constantly expanding. With recent advancements, there are now opportunities to use digital technology to monitor a range of vital signs, including glucometers to track blood sugar and devices to track heart function.[17, 18] This enables the collection of clinical information outside of the traditional healthcare settings and thus far has achieved good initial uptake.[19] The two major factors that have been driving the adoption of remote monitoring systems are a growing elderly population with associated disabilities and chronic diseases as well as dwindling traditional healthcare resources.[8]

There has also been a shift in healthcare to focus more on a person-centered approach with an emphasis on early detection and prevention of disorders. For the elderly and those with chronic

diseases, digital health technologies could make it possible to extend care to the home, enhance chronic disease management, allow for rehabilitation supervision, and curb unnecessary re-hospitalization (saving many resources). Most remote monitoring has been developed with the capability to monitor several different vital signs including electrocardiogram, heart rate, respiratory rate, blood pressure, blood glucose, etc. Some also include the ability to record information from an accelerometer and gyroscope for posture and activity, electrodermal activity sensors to try to assess emotional status, and ambient sensors to record information on the general context of a user (location, temperature, humidity, etc.). All of these data points combined with activity trackers (discussed below) can provide clinicians with the user's physiological state continuously and in real-time.[19]

Lastly, digital health technologies as part of a multimodal approach to remotely monitor patients has been shown to improve health and quality of life.[19] DeLuca et al, through a randomized controlled trial, found that using digital health properly to monitor patients living in a nursing home and responding accordingly and in a timely manner to any concerning changes, improved the health of the elderly. They also found that the use of these devices in conjunction with psychological counseling improved quality of life, reduced healthcare service access, hospitalization and all associated costs.[20] There are many cloud-based systems that use two or more wearable devices to measure data directly from patients and use a mobile app for recording of PROs.[21] The resulting data registry can then be mapped to the patients' clinical records.[21]

Activity tracking

Many digital health technologies are focused on consumer-facing technologies.[17] Individuals are using mobile health apps, wristband activity trackers, and athletic sneakers that all collect information from a users' day-to-day activities.[17] The types of activities that these devices track include: sleep patterns, emotions, surrounding conditions, and level and type of physical activity, among others. Most of these technologies are adopted outside of the healthcare setting, although some hypothesize that this consumer data could be harnessed to improve patient health outcomes and providers' clinical success. Patients who spend more time on self-care lower costs for everyone within the healthcare system. Effective self-care allows for prevention of avoidable visits to the emergency department and physician offices, and reduces the chance for lengthy hospitalizations. An unfortunate reality of these devices, however, is that there is a barrier to use them among those who would benefit the most.[19] This is often due to their cost, as well as implementation and designs that require too much investment from people who are low in resources (e.g., time, money, technology, or social support).[19]

There is a shift of focus in this industry to work with researchers and developers to generate user-friendly tools, use data from these devices, and incorporate the information in a patient's electronic health record to enhance the quality, availability, and utility of patient-generated data.[19] There are limited opportunities to collect data from all patients' observations of daily living, and these social, behavioral, and preventative self-care measurements are often missed in traditional office visits without this kind of technology.[17] Wang et al. found that there was an increase in activity among overweight and obese adults that were using a wearable fitness monitor that gave instant feedback on performance through a mobile app with detailed summaries of activity levels.[18] This adds support to the belief that there could be far-reaching applications for activity trackers and a new way in which to tackle major public health issues.

To make this kind of remote monitoring a success there will continue to be a need for advancement of more user-friendly devices that provide information when and where people want it, as well as automatic algorithms for online data interpretation, event(s) classification, and identification of invalid data. Advances in user-friendly, meaningful analytics will also be necessary to process the data in real-time and to make meaningful inferences from the data by all stakeholders involved.[19]

Education

Patient education is incredibly important and the cornerstone of many public health initiatives. Due to the sheer volume of individuals interacting through digital technologies such as social media, such a platform could be a useful tool for patient education. Social media works similarly to traditional educational methods in that specific platforms are more effective in communicating with specific audiences. Facebook is considered a suitable channel for education of individuals aged 30 to 50 years; this communication channel is also appropriate for pediatric and elderly patient populations since their caregivers are likely to be in this age group.[22] Instagram has the youngest users and therefore would be suitable for messaging directly to teenagers and young adults.[22]

Some have concern that social media is only used by certain age groups; however, the number of US adults using social networking sites has increased from 8 to 72 percent from 2008-2013, and the number of US adults aged 50-64 years using social media increased from 7 to 60 percent from 2005-2013.[23] The increase in utilization demonstrates that social media can indeed be a useful tool for sharing information with a variety of patient populations and could lower the costs associated with patient education campaigns.

Aside from traditional social media sources, there are stakeholders in healthcare that are attempting to build custom mobile technologies for the purpose of patient education. Certain stakeholders have begun to develop digital health technologies intended to educate patients including those who are involved in clinical trials. Their hope is to expand these tools for general use around the globe, creating versions that support multiple languages and countries. Some pharmaceutical companies, for example, have used this type of global educational solution in their clinical trials.[21]

Mobile Research Systems

Mobile research systems hold great potential to reduce costs and patient burden, increase efficiency, and facilitate recruitment while curbing loss to follow-up.[24] Some experts believe that this technology will increase public awareness of clinical trials and encourage more partnerships between the current stakeholders in healthcare and crowdsourcing organizations.[25] Still, users and researchers alike have expressed concerns about devices and apps, including device failure, user error, data integration, site preparedness, poor quality of data, potential for selection or user bias, and the need to coordinate with several different "help desks" if they were to encounter issues with any of the platforms.[21, 26] Moreover, these types of devices and apps require the use of a smartphone and an Internet connection to transmit data, which is subject to third-party carrier charges.[16] The requirement of keeping up with messaging protocols, updating new versions of hardware/software versions, the need for backward-compatible "hybrid" solutions,

evaluating the content validity of questions and answers during transition into a mobile app (especially for informed consent), and how to properly present a survey question are also important considerations.[16, 27]

Apple's ResearchKit is one example of a platform that allows researchers to build their own data collection apps that will interact with other apps in order to record health information from a multitude of sources. The perceived benefit of these systems solutions is their ability to give researchers access to a global, existing population while providing researchers with secure and HIPAA compliant data-collection options.[24] Recently, Google has announced a similar system, called Research Stack.[28] In addition, NIH has funded Health ePeople, a mobile registry designed to support mHealth research and clinical trials across a diverse population base.[29]

Examples and Case Studies of Digital Health Uses in Global Patient Registries

Globally, mobile health technologies are being used to perform disease and pharmacovigilance surveillance. Recently, in Cambodia, mobile phone-based, short message service (SMS) text messages were used to conduct pharmacovigilance on 17 different vaccines.[30] Their intention was to provide a timely and efficient pharmacovigilance platform to a developing country that would otherwise not have such a system. There is high unmet need for such a system because of the higher risk for patients in developing countries to be subjected to illegal and counterfeit drugs and vaccines.

Developed nations such as Australia have also used similar technologies with SMS text messages to monitor adverse events following immunization.[31] The conclusions drawn from this study were that active surveillance of adverse events following immunizations using SMS has the capacity to complement existing passive reporting systems and has the potential to identify emerging safety signals more rapidly. See Case Study 1 for additional information on how SMS is being used in Australia to monitor adverse events post immunization.

In the United States, surveillance systems for communicable diseases such as influenza are tracked through a "Flu Near You" (FNY) mobile health program. FNY prompts users every Monday to report symptoms of influenza-like illness experienced during the previous week. Throughout the 2013-2014 season, 336,933 reports were submitted showing potential to serve as a viable complement to existing outpatient, hospital-based, and laboratory surveillance systems.[32] Additional information on FNY is provided in Case Study 2.

Many researchers and clinical programs are using mobile technology to provide clinical information to patients, to send out reminders for clinic visits, and also to collect data from patients remotely.[13, 33] SMS clinic visit reminders have been shown to increase the uptake of prenatal care in resource limited settings such as Zanzibar (Case Study 3).[33] Wearable health sensors are also used to collect relevant data from patients. The benefits of wearable health sensors are that they collect both self-reported data and high quality structured data that can be used to evaluate the safety and efficacy of a trial.[13] Utilizing automated data collection should generate a more comprehensive database, allowing for more thorough analysis of side effects and other long-term issues that may arise. Given that these data can be collected from the patient while they are at home, these digital technologies should significantly reduce cost over time and reduce patient burden. This technology could also amass a larger pool of data that can be

analyzed more thoroughly for signs of side effects and other long-term problems. With the increase in FDA approved health-sensors, the need for technology that can evaluate and that can integrate with these data should be prioritized to ensure that these data are being used to their full potential.[13]

A unique tool that could be used along with other digital technologies was recently developed to allow patients to record short videos and send them to their medical team via a mobile device.[34] This tool has the potential to allow for a more in-depth understanding of patient preferences regarding a drug's benefits and risks while better informing their healthcare providers to aid in the decision making process. Since patients use the tool to record free-form videos, patients can provide unrestricted comments to medical teams at the press of a button. The tool allows for the medical team to respond to patient videos as well, potentially enhancing the patient-doctor relationship.[34]

However, confidentiality of patient data is paramount and must be considered when designing any sort of digital health technology. The level of risk is typically commensurate with how sensitive the information being collected is and how large the data files are.[35] Some systems require the collaboration of several outside contract organizations, including access to the data, which introduces additional concerns about security and confidentiality and complicates questions around responsibility of the data.[24, 26]

Case Example 1. Active Safety Vaccine Surveillance with mHealth Technology [31]

Description: To evaluate the performance of an active surveillance system (called SmartVax) that utilizes mHealth technology with SMS text messages for adverse event monitoring following immunization.

Time Period: November 2011 – June 2013; **Location:** Australia; **Number of Patients:** 3,281

Challenge: The existing surveillance system in Australia that was used to capture all of the adverse events experienced by individuals following administration of influenza vaccines was passive. However, the Illawarra Medical Centre administers more than 2,000 vaccinations annually and captures a wealth of documentation in a patients' electronic medical record, including mobile phone numbers. Therefore, the Illawarra Medical Centre sought a new digital health solution to extract vaccination data from the clinic's existing commercially available practice management software.

Proposed Solution: Utilize SmartVax, an active surveillance system, to send consenting patients (who had received an influenza vaccination and provided a mobile telephone number) an SMS text message within the following seven days. SMS replies were automatically written back into the SmartVax tool and linked to the patients' vaccination data in real-time. If a patient experienced a reaction or if the patient did not respond, then the clinic staff would telephone within 24-hours of the SMS message.

Results: Of the 3,281 vaccinated patients, 2,342 patients, more than 70%, responded by SMS and 264 reported possible adverse events following immunization. Active surveillance has the capacity to complement existing passive reporting systems and could enhance rapid identification of emerging safety signals.

Key Point: In many countries post-licensure monitoring of vaccine safety relies largely on passive surveillance the constraints of which are well recognized. These limitations may be overcome by active surveillance using a digital health technology.

Case Example 2. Digital Health Technology to Monitor New Cases of Influenza [32]

Description: Flu Near You (FNY) is a participatory disease surveillance system for volunteer reports of influenza-like illness symptoms created through a collaboration between the American Public Health Association, HealthMap of Boston Children's Hospital and the Skoll Global Threats Fund.

Time Period: 2012 – 2014; **Location:** United States and Canada; **Number of Patients:** 40,000

Challenge: Public health surveillance has been limited by the capacity of public health authorities to conduct case and contact tracing because of the reliance on data provided primarily by the medical system. Mobile health technologies are now making it possible to enable the public to actively be part of the public health surveillance system.

Proposed Solution: Flu Near You is a website and mobile app that allows participants in the US and Canada to report their health information using a weekly survey that is presented through a reminder system. The data are then published to a website which offers an interface to compare its data with data from the Centers for Disease Control and Prevention Sentinel Influenza Network and Google Flu. The mission is to collect and freely share this information in an open, timely manner with the general public and key stakeholders to increase awareness and insights about flu activity.

Results: More than 61,000 participants submitted at least one report during the 2012–2013 season with 327,773 influenza cases reported and 40,000 participants submitted at least one report during the 2013–2014 season, with 336,933 influenza reports. With increased participation, FNY has the potential to complement traditional and existing surveillance systems. FNY offers advantages in the areas of speed, sensitivity and scalability.

Key Point: FNY was able to engage thousands of participants in reporting their health status within North America giving valuable information on the incidence of influenza that can be shared with the public and stakeholders to influence important public health initiatives. This mobile health technology also has the ability to be configured to detect a wide variety of syndromes and contribute to public health preparedness.

Case Example 3: SMS Text Reminders to Improve Prenatal Care Uptake [33]

Description: To describe the association between a mobile phone intervention and prenatal care visits in a resource-limited setting.

Time Period: March 2009-March 2010; **Location:** Zanzibar, Africa; **Study Design:** Cluster-randomized controlled trial; **Number of Patients:** 2,550 pregnant women (1,311 interventions and 1,239 controls)

Challenge: A great proportion of stillbirths occur in low-income countries, many of them due to preventable causes related to poor maternal health. Inadequate prenatal care is also associated with poor pregnancy outcomes. Women in low-income countries are often unable to make informed choices in relation to their health due to the lack of relevant and high quality prenatal care in Sub-Saharan Arica.

Proposed Solution: The first ever cluster-randomized controlled trial to assess the use of a mobile phone intervention to improve access to essential reproductive health services in Zanzibar. With primary healthcare facilities in Zanzibar as the unit of randomization, 2250 pregnant women who attended prenatal care at selected primary healthcare facilities were included in this study and followed until 42 days after delivery. Primary health care facilities in 6 districts (24 facilities total) were randomized to either the mobile phone intervention or standard care. The intervention consisted of a unidirectional text message and mobile phone voucher system providing the possibility of two-way communication between mothers and providers. The aim of the SMS component was to provide simple health education and appointment reminders. The control group received standard to care. Primary outcomes included the attendance at four or more antenatal care visits during pregnancy.

Results: Those receiving the mobile phone intervention were more likely to attend prenatal visits. 44% of women in the intervention group received four or more prenatal care visits versus 31% in the control group. Using simple text messaging, women in the intervention group had more than twice as likely to attend four or more prenatal visits (OR, 2.39; 95% CI, 1.03-5.55).

Key Point: Mobile health technologies can be utilized for increased uptake of prenatal care in resource limited settings such as Zanzibar.

Advantages of Using Digital Health in Patient Registries

"Fast", "cost-effective", "large-scale", "transparent", "the ability to have patient-generated internet data in real-time", and "general usefulness" are all common phrases used to describe the strengths of digital technologies.[36-39] Much of the data captured from digital technologies are often available in real-time, allowing researchers and healthcare providers to quickly grasp epidemiological insights such as disease prevalence, as well as impact of medical interventions.[40]

Passive Monitoring and Social Listening

Few researchers and companies are actively soliciting healthcare data from digital health technologies (such as adverse event [AE] reports), but a majority are passively monitoring. Many of these entities are using a combination of automated and manual processes to identify individual case safety reports. For example, social listening, the manual or automated collection of patient-generated data that is unsolicited and available publicly or with permission, enables a stakeholder to capture a large amount of patient-generated data.[39] Digital health apps and social listening sites have been used to determine where to host a clinical trial or launch a product.[41] In spite of the early uptake of social listening by some, many are unaware of social media's ability to reduce the burden of data collection on all parties, and how to attenuate and mitigate their associated risks.[41]

Patients first-hand experiences and perspectives provide a valuable data source that can be used to improve the care they receive.[42] The widespread use of social media provides registry stakeholders with the ability to listen to a larger population than those typically included in traditional research studies.[37, 38] The innovative use of this new technology, as well as the rapid uptake, may allow industry, academia, healthcare providers and others to better understand the patient communities they are serving.[21]

Social listening can be performed manually or through automated tools that filter and/or classify information acquired from social media, and provide end-users with the resulting data, either in verbatim form or in aggregate. Automated data processes typically employ normalization, text-matching, and natural language processing techniques to collect and filter data.[36] Best analytical practices include the use of both automated and manual data collection and processing to clean and curate the data.[43]

When considering the evaluation of social media data, analytical processes should include the following qualities: central, comprehensive management of "topic tags" through a robust taxonomy that includes slang terms; ability to restrict by language and country with the option to

"listen" to countries that speak in other languages; manual aggregation and curation of the data; dashboards with filter and comparison options for visualization of analyses; sentiment analyses (refers to the use of natural language processing, text analysis and computational linguistics to identify and extract subjective information in source materials), demographic information; identification of influencers and important topics; historical data for retrospective analyses; and the ability to filter appropriate terms such as personally identifying information (PII) from the data.[43] Social media vendors who provide these services should be able to meet software and accountability standards required for any type of research or investigational purpose.[43]

Certain social media platforms are better for specific uses and/or populations. Each form of social media has demographic characteristics associated with it and, as in all technology, the people who employ a given platform changes over time. Facebook is most useful for specific medical conditions, peer-to-peer support, fundraising, and sharing research amongst researchers and healthcare providers.[3] Twitter is most useful for the hashtag (#) feature, which acts as a folder system and allows for the collection of posts referring to one topic or event.[3] This is often used for group conversations and could be used to identify conversations amongst specific patient populations.[44] Twitter has also had success in facilitating patient-provider conversations.[3]

Some physicians deliberately decide to connect with their patients on social media; however, most have reflected that they are wary of doing so.[45] In spite of this concern, a survey of physicians as well as an analysis of impact of the internet on physician consultations resulted in positive comments outweighing negative comments by 2:1.[46] Social-media savvy clinical practices do exist; however, closed social media platforms are most often used to allow patients to be actively involved in their own care coordination, track their clinical progress and have greater access to their physicians.[46] The motive for physicians to engage on social media is to provide information to their patient population in hopes that this information will lead to improved patient outcomes.[47] Patients also find it helpful to be able to ask their physician general questions about where to find information on a particular topic of concern and could do this through a social media platform.[47] Some online patient communities (i.e. PatientsLikeMe, MyHealthTeams, MediGuard, etc.) also provide solutions for patients to communicate and partner together. These communities are often engaged in the healthcare industry through data-sharing partnerships to improve products, services and care for patients.[48]

Initial pilot studies on the impact of crowd-sourced research protocol designs indicate that patient participation has increased, and provider burden has been partially alleviated.[43] While the data available are limited, the majority of surveyed companies believe that input from social media communities could improve the feedback they receive on clinical trial protocol design feasibility, protocol procedures and scheduling, and case report form design.[43] Many companies (including Transparency Life Sciences and Genomera) currently use social media for development, planning and study design through the use of crowdsourcing techniques to engage patients.[43]

Greater Access to Minority Populations via Mobile Devices

Another advantage of the increased use of mobile technologies is that it has shown potential for overcoming the digital divide previously identified in the digital health space. The digital divide refers to the chasm between those with regular access and ability to use digital technologies, such

as the internet and those lacking such access. Past studies describe the realities of inequities in digital access by race and income and describe fears of the 1990's that the internet would not scale economically to encompass users of all demographics. These studies indicated minorities, low income families, and individuals living in rural areas were less likely to have telephone access and household computer access compared with whites living in urban areas and those with household incomes of greater than $75,000 annually. However, past barriers to information access such as costs of laptop and desktop devices and broadband access have been circumvented by the smart phone. In lower income groups, smart phones provide regular access to communication and information with fewer cost and access constraints than traditional broadband services.

Research on population level data of ownership and access to mobile technology show tremendous uptake of smart phone technologies across the country for all Americans, as 91% of the adult US population now own a cellular phone with over half having a smart phone as of For example, although African-Americans trail Caucasians by 12% when considering broadband access to the internet, both groups now show parallel rates of mobile platform ownership.[49-54] Ownership of cellphones in Latinos has also increased now to roughly 86%.[53] Pew research reports also indicate Latinos are more likely than Caucasians to use their mobile devices for accessing the internet.[53] New data demonstrating the increased use of smart phones for health specific information underscores the potential for mHealth to capitalize on the narrowing digital divide to reduce health inequities.[49, 52] Roughly 62% of all smartphone owners have used their phone to look up information concerning health conditions.[52] Roughly 35% of African-Americans and 38% of Latinos regularly use mobile platforms to access health related information, compared to 27% of Caucasians.[50] Minority groups are not only more likely to own mobile phones, and specifically smart phones, but they are also more likely than Caucasians to use their device for health specific information.

Reduced Time and Potential for Increased Retention and Long-Term Follow-Up of Patients

It is estimated that digital health technologies are being used to recruit patients in only 11% of all industry clinical trials.[55] In spite of the low uptake of use for patient recruitment, several successes have been reported. One study reported being able to recruit enough patients for their entire trial in less than a month, a task that would have taken years to complete through traditional channels.[56] While the authors admitted that this particular situation was a "perfect-storm" of circumstances, the usefulness of digital technologies for participant recruitment added to the success.[56] Many of the stakeholders facilitating clinical trials are now attempting to use digital health technologies for patient recruitment whether they are taking on the task themselves or partnering with a third party.[25, 42, 57]

While digital health technologies have proven useful for patient recruitment, it is not considered a worthwhile tool to screen for eligibility.[58] Determining eligibility requires the need to validate data with confidential patient information that is often not readily accessible. Moreover, many digital health technology users are concerned about privacy in public forums and will refrain from discussing the type of medical information that would be needed to determine eligibility.[59]

Current Limitations and Challenges to Using Digital Health in Patient Registries

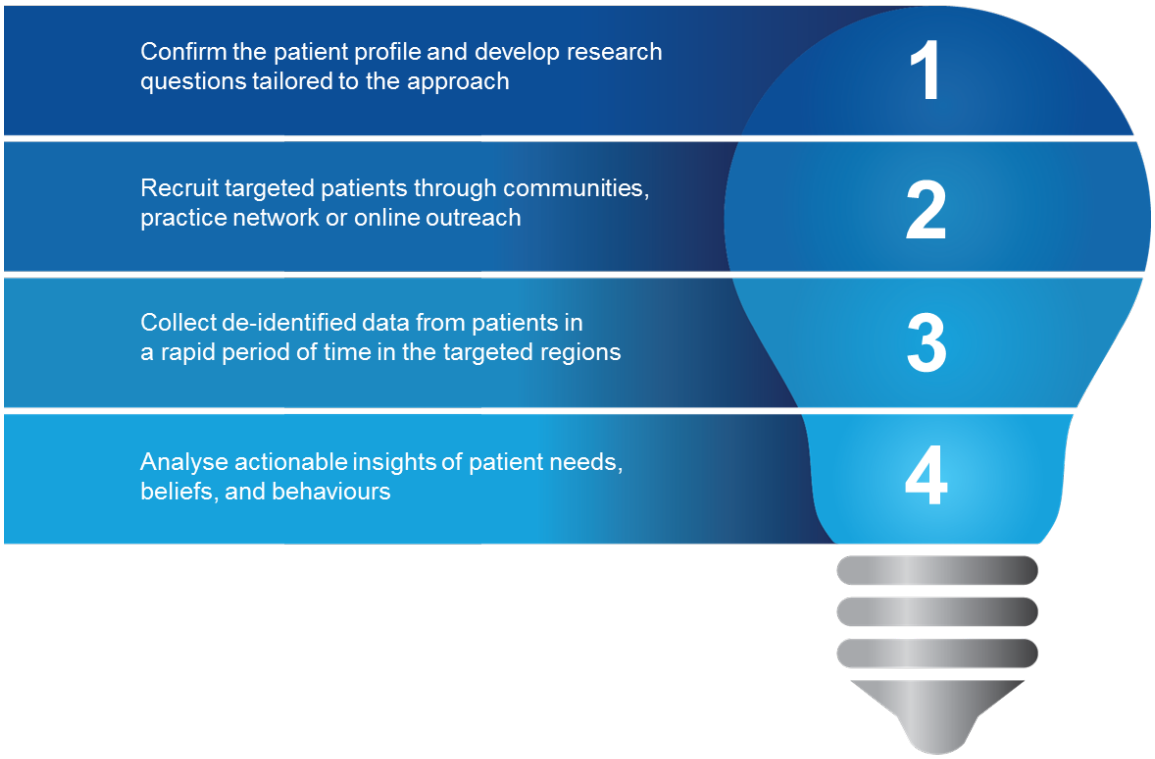
Although there are many advantages to digital health approaches, there are also current limitations and challenges to its implementation in registries.

Including Patient Insights on Digital Health Approaches in the Registry Design Process

To effectively implement a digital health approach or device, it is imperative to understand the patients' perspective on their preferred device or solution. Therefore, engaging with people in the targeted population directly is important to gather data and develop insights that would influence the registry design process.[60] This movement towards capturing patient insights in the registry development process is beginning to gain traction, but is not widely used when designing registries that intend to integrate digital health technologies.

The process, costs and timeline in gaining patient feedback, confirming the key research insights and revising the registries' digital health implementation strategy are additive to current design processes that many researchers employ today. Although they add more work, this patient insight driven approach is critical to enabling the successful integration of digital health technologies into registries (See Figure 2). These approaches may also be effective in enhancing recruitment and engagement in non-digital strategies.

Figure 2. Process for Collecting Patient Insights to Impact Registry Design



In an effort to incorporate digital health approaches, it may be important to evaluate the following questions in the early phases of registry design:

How does the user view the problem? What do they see as the problem?

Is the user willing to try a digital health approach? What are their interests and comfort with technology?

Is the planned digital health approach intuitive to use or require additional education?

What aspects of the digital health approach were not understood or caused concerns with the user?

Does the digital health approach provide additional value and/or features for the user beyond collecting data?

What would motivate and encourage the user to continue engaging with the digital health approach over the course of the study?

What aspects of the digital health approach would make the user not want to engage?

Using an iterative design that incorporates user insights and experts in developing user-centered designs as an institutional part of the process before integrating digital health approaches may continue to influence better registry designs and improved data collection.

Communicating to Patients through Digital Technologies

There are many concerns when it comes to communicating with patients via digital technologies. Patient communication risks may be mitigated by providing non-specific information to patients, rather than recommendations that may mention a specific product/treatment/drug. Engaging patients on social media can provide a public service and comfort to patients and their caregivers.[61] However, physicians who use social media to communicate with patients on registries should be aware of potential privacy and confidentiality violations.[3]

While it is worth noting that the number of these violations committed by physicians is relatively low, Grajaless et al. suggest that physicians abide by four guidelines for risk mitigation during social media interactions: 1) maintain professionalism at all times; 2) be authentic, have fun, and do not be afraid; 3) ask for help; and 4) focus, grab attention, engage, and take action.[3] These guidelines provide a basic framework for best practices that can protect physicians, as well as researchers encouraging their medical staff to use social media platforms for patient engagement. Without oversight, there is the risk that patients (as a result of misinformation) could self-diagnose, and/or use a drug or treatment inappropriately.[3] By using best practices and risk mitigation strategies for digital health approaches, potential issues with communication to patients on social media can be mitigated.

The Longitudinal Nature of Registries Presents Challenges Due to the Speed of New Technology

As many registries are developed for long-term, multi-year, longitudinal engagement with patients, a challenge to launching these registries with digital health approaches is that the

technologies will continue to rapidly update and enhance over time. This challenge requires research teams to add ongoing responsibilities to the project's scope including, but not limited to:

Planning or "future-proofing" proactively to pre-determine what enhancements to a specific digital health approach would require a registry wide upgrade (i.e., if a specific wearable releases a new version with a new data collection endpoint vital to a study endpoint, the actions the study team would need to implement to move forward)

Researching and maintaining deep insight on digital health product updates (i.e., manufacture upgrades, automated programming interface (API) revisions, data element additions, new device versions, etc.)

Educating and training registry stakeholders continuously for new features, improvements or upgrades (i.e., downloading a new version of a mHealth app, etc.)

Planning for replacing digital health devices (i.e., wearable bands that may wear down, or be broken or lost during multi-year, hard usage, etc.), and

Managing upgraded bring your own device (BYOD) solutions (i.e., the patient upgrades their personal wearable or smartphone)

Changing Digital Health Approaches from an "Additive" Solution to a "Primary" Solution

Many of the digital health innovations today are simply being added to registries. This can increase the complexity and cost of the program, which is the opposite effect of what these solutions were intended to achieve and ultimately makes the uptake of these solutions more challenging. Using these approaches as primary solutions, integrated within broader registry operations, is a challenge. This challenge is overcome by designing registries that employ digital health approaches to replace standard processes (i.e., the way patients are recruited, data are collected, or support is provided to enhance long-term engagement).

To move these solutions from simply additive to "primary" components of registries, it will be important to understand the answers to these questions in the early phases of registry design:

If we use this digital health approach, is there another method of data collection that we can remove from the registry design?

What data from the digital health approach is considered "validated" and to what extent can it be used for use in research and/or regulatory-based submissions?

Can we revise our standard registry schedule of events to decrease interventions or data collection time points with the use of this approach?

What data from the digital health approach can be used in supporting a primary or secondary endpoint in the registry?

What positive effects (i.e., patient engagement, long-term retention, reduced readmissions, etc.) can this approach provide in addition to data collection?

How will the data or impact of the digital health approach be shared with the patient's physicians, regulatory agencies, or payers?

How will this approach interface or connect (i.e., via API) with other systems and applications utilized in the registry?

Where best can the training on use of this approach be deployed best to patients, physicians and researchers involved?

How do we measure the return on investment and what are the key performance indicators (KPIs) for this approach?

Where globally can this specific solution be conducted from a regulatory/ethics committee, data privacy, cultural relevance and digital enablement perspective?

Integration of a Digital Health Approach within the Study Operations

Establishing a digital health approach early in the registry development process is critical to building an integration strategy that takes into account the real-world use of the approach. Integration can be documented and achieved with inclusion in the following project assets:

Project plan – the digital health approach details and pro-active strategy should be included within all relevant projects plans including, but not limited to the project timeline, communication plan, stakeholders training plan, recruitment/retention plan, customer support plan (covering both the patient and the researchers), resource plan, and statistical analysis plan.

Architectural plan – this plan should detail how data from the digital health approach will be integrated and interface with other study systems, securely transferred/maintained and validated for specific use in the registry.

A worksheet is provided at the end of the chapter to assist with determining which digital health approach should be used in a registry. It is intended to serve as a guide in the decision making process and is not comprehensive of all study issues that should be evaluated prior to the use of a digital health approach or device within a registry.

A Look at the Future of Digital Health

The convergence of emerging, digital health technologies promises a paradigm shift in the world of healthcare. The technologies are the enablers, as the intention in many nations is to focus much more on the patient. Jeremy Hunt, Health Secretary in the UK gave a speech in July 2015, entitled "Making Healthcare More Human-Centred and Not System-Centred" in which he states that "the transition to patient power will dominate healthcare for the next 25 years."[62]

Our bodies generate data 24 hours per day, seven days per week, and generally those data are only captured by registries in routine healthcare visits. Although data captured at healthcare visits and entered into electronic medical records are generally some of the best healthcare

information available today, with the expert provider as the intermediary creating the data entry, there remains a huge gap in understanding what happens to the patient outside of these visits. Patient-generated health information can help fill in these gaps. Some may find it hard to imagine a future where useful data can be captured from outside traditional healthcare settings. However, many leaders have bold visions of the future, and are making changes to their organizations today, to prepare for that future.

Kathleen Frisbee, co-director of Connected Health at the Veterans Health Administration Office of Information and Analytics, gave a keynote in May 2014 and mentioned, patient-generated data "is going to be the thing that transforms health care. We predict that patient-generated data will be much larger in volume than electronic health care records."[63] Patrick Vallance, Head of GlaxoSmithKline Research and Development, delivered a talk in March 2014 entitled, "Horizon Scanning: Looking Ahead to 2025" and when mentioning sensors in the context of drug safety, cites a future which involves, "Instant feedback in terms of surveillance of medicines post-launch, with various sensing devices/monitors, as well as listening to patients in real-time, much more than we are able to do at the moment."[64]

The sources of health data in the future may be different from the sources that exist today. One new player is IBM, who has set up a brand new division, called Watson Health.[65] They are positioning themselves not just as a leading health data broker, but seek to provide solutions to researchers that could offer new insights by integrating clinical data with external data such as Twitter. [65] If the data that are being generated by patients outside of the healthcare system are controlled by patients, then it may be that the organizations that patients trust the most are the ones that have access to the most amount of health data. Startups such as DataCoup, have emerged to allow consumers to be paid for sharing their personal data.[66] A Self-Generated Health Information Exchange developed at the University of North Carolina at Chapel Hill in partnership with RTI International and Promantus, Inc. further demonstrates this trend towards providing individual control of personal digital health information.[67] The continued success of observational research hinges on the ability to access comprehensive, representative and accurate data on populations.

Since data are increasingly viewed as an asset, a potential threat is the availability of individual level data, particularly if some individuals refuse to share their data or will only share it at the right price. In a report from the Institute for the Future examining the outlook for the Information Economy, researchers predict that "Institutions and individuals will engage in a dynamic information economy by buying and selling, donating or trading personal information in exchange for monetary or social gain." The report envisions a world where a person's wearable device "could routinely prompt its users to consider sharing their health data with a non-profit medical research group, or sell it to a pharmaceutical company."[68]

As sensor technology improves, we are likely to see sensors embedded in devices above and beyond the activity trackers and smart watches that appear to be cutting edge at present. For example, sensors in flexible bioelectronics, such as smart bandages or smart strips that could be easily affixed and removed from the human body. The NIH has initiated a challenge for a wearable alcohol biosensor that would be able to monitor blood alcohol levels in real time.

To better understand medication non adherence, there are new developments such as pill boxes with sensors that can track when a patient opened the box as well as containers and syringes that illuminate brighter and brighter as a reminder system. Going a step further, Proteus Digital Health has developed an ingestible sensor that can measure medication adherence patterns.[69] In 2015, they partnered with Otsuka pharmaceuticals and submitted a sensor embedded version of the antidepressant, Abilify for FDA approval.[70]

Some technology companies anticipate that this is just the beginning. In Japan, Softbank's CEO Masayoshi Son envisions, "Each individual, on average, will have more than 1,000 devices that are connected to the internet by 2040."[71] His vision includes the chair in our living room being a healthcare device, capturing and transmitting data about our health. His company has partnered with Aldebaran, and in 2015, launched the world's first companion robot, Pepper, that reads and responds to human emotions.[72] Given Japan's aging population, one obvious use case for Pepper is to use the robot's sensors to collect data on elderly patients, perhaps even monitoring and helping dementia patients in their own home.[73] In 2016, more of these consumer friendly robots are likely to enter the market, with Jibo from the US and Buddy from France.[74, 75]

Sensors could become ubiquitous in measuring health data, perhaps even monitoring our health during our daily commutes. Even though Ford Motor Company has halted research into installing heart rate sensors in car seats, could data collected from car journeys be of medical value one day? In Beijing, China a pilot project added sensors to straps in buses that are held on to by commuters during rush hour.[76] What about getting a physical as you shop in the supermarket? Project H, a research project in the Netherlands is evaluating a shopping cart that can capture data such as heart rate, one-lead ECG, and SpO2 from the person pushing the cart around the supermarket.[77] In addition to capturing health data more often, it may even be an opportunity to collect data from those who rarely interact with the healthcare system. Also, with regard to food, what if people wanting to track their calorie intake could do so simply by taking a picture of their meal using their smartphone? One of Google's research projects, Im2Calories, is working towards making that a reality.[78]

One of the major drivers behind collecting all of this data is the need to improve health outcomes, to keep patients out of the hospital through remote monitoring, and to reduce costs. Some insurers and employers are also interested in these new sources of data to help them manage risk. Perhaps an airline wants to track sleep data of their pilots to reduce the risk of pilot error in a flight due to fatigue? Insurers who want to calculate risk in real-time may make access to patient generated health data a prerequisite for obtaining health/life insurance, or at least to lower the cost of this insurance.[79]

Researchers need to be mindful that as more data have been collected, concerns about privacy have also grown. One of the recent examples of when privacy concerns impacted progress, despite good intentions from researchers, is the "care.data" project, intended to improve the health of the UK National Health Service.[80] A public backlash in 2013 led to the project being delayed, and has undermined trust.[81] In the future, as more patient-generated health data are captured, shared and analyzed, there may be further backlash from consumers. If some of this data collection is made mandatory by employers and insurers, there is a chance that some consumers uncomfortable with 24/7 monitoring could try to falsify data.

The registry of 2025 could look dramatically different from the registry of today. Some researchers are excited about the concept of digital phenotyping, and Dr. Sachin Jain has stated, "We think many diseases will actually have a phenotype that presents through patient use of technology."[82] No discussion about the future is complete without mentioning advancements in genomic medicine. The 100,000 Genomes project in England is the largest national sequencing project of its kind in the world.[83] It appears that the Australian government is now considering a similar project.[84] South Korea has just launched their largest genome sequencing project with 10,000 patients.[85] From a researcher's perspective, the opportunity to link genome sequence data with electronic patient records and the social and behavioral information from digital health technologies could lead to many new discoveries about the causes of disease. While computable phenotypes using clinical, social, and behavioral data from electronic health records and PROs are possible today, it is the emerging sources of unstructured data outside of healthcare settings, such as Twitter, along with other patient generated data that are making researchers curious about how we might better characterize diseases in this modern era.[86]

Conclusion

Digital Health is a collection of emerging disciplines and technologies that appear to be evolving and converging at an increasingly rapid pace. Indeed, as digital health technologies continue to demonstrate ways to measure health activities and complement or supplement the traditional approaches to collecting health information, opportunities for registries abound. Opportunities provided by utilizing digital health technologies include improved recruitment and retention, reduced burden on researchers, enhanced uptake of technology solutions by the healthcare system, and collection of information that is not routinely captured.

However, there are still considerable risks with privacy, quality, and control of data analysis and communication. As new digital technologies are developed, researchers must acquire new skillsets to navigate their use appropriately. New methods will also be needed to appropriately integrate various sources of information and transform unstructured fields to formats that can be used for evaluating the safety and effectiveness of treatments used in the real world.

Investments are needed now to prepare for the decade of new digital technologies and their use within registries. Digital health technology will not transform clinical practice and healthcare research without being designed with the complex needs of users in mind, as well as the careful assessment and appropriate level of training on the use of these tools by healthcare professionals. Issues related to interoperability of systems, user engagement, measurement validation, regulatory use in studies, meaningful clinical interpretations, privacy and security, among others, will need to be carefully addressed as these new technologies are utilized in clinical medicine and research.[87]

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DIGITAL HEALTH APPROACH CRITERIA WORKSHEET

When determining which digital health approach or device will be utilized in a registry, it is important for the following criteria to be met as a baseline for evaluation. This checklist is intended to serve as a guide in the decision making process and is not comprehensive of all study issues that should be evaluated prior to the use of a digital health approach or device within a registry. If the study team involved is unable to answer the criteria question below or if the response does not hold "significant" impact to the registry, careful consideration should be given to whether or not the approach/device is best suited for use.

PURPOSE

1	What is the key objective for utilizing this digital health approach or device in the study (i.e. what will we accomplish by integrating it into the registry)?	

USABILITY

2 +	Is there a plan for integration of the approach/device in the operations of the registry with the physician and patient?	
3 +	Would a patient utilize the digital health approach or device and see direct benefit/engagement?	
4 +	Who will be providing patients with technical support should something go wrong with the device itself?	

DATA CAPTURE

5	Can the provenance of data captured be verified? Are you willing to accept the risk that data may be from another person who is not the patient?	
6	Could the data collected be stored in one country or would it have to be stored in multiple countries?	
7	Are there any restrictions on where the data could be analyzed (e.g., country restrictions)?	
8	Is there a plan for how the data will be securely captured, stored and analyzed that meets the regulatory requirements in the countries targeted?	

TECHNOLOGY

9 +	Is there an 'open source' technology available to support your needs, or are you restricted to proprietary tools?	
10	How mature is your technology? If the technology changes during the life of the registry, how would that impact the use of the registry?	
11	What is the risk of your technology not being supported in future?	
12	Are there existing standards/methods for using this technology in registries, or would this require development of standards?	

Direct-to-Patient Registry and Other Patient-Centric Designs: White Paper

Draft White Paper for Fourth Edition of
"AHRQ Registries for Evaluating Patient Outcomes: A User's Guide"

Abstract

Enrolling patients directly into a registry and/or collecting information directly from patients can be efficient and effective for many study purposes. Some examples of situations where direct-to-patient registries can be particularly useful are in situations where only a few patients are seen at any one site, when comprehensive exposure or patient-reported outcomes (PROs) are needed, when some questions are sensitive in nature and the respondent may be willing to disclose the information confidentially for study purposes but not to share that information with his or her medical provider, and/or when long-term follow-up is required, especially when patients may not return to the same medical care provider. Here we address direct-to-patient registry designs, identify scenarios in which this approach is most appropriate and discuss challenges, limitations, generalizability and best practices including approaches to mitigating the potential for bias (systematic error) including selection and channeling bias.

Introduction

A direct-to-patient registry design is one in which recruitment and some or all related communication and data collection is conducted directly with the patients, without guidance from a medical care provider trained in registry procedures. Related but different patient centric designs include registries where recruitment may occur through medical care providers but most or all data is collected directly from the patients. Registries using these designs may contact patients directly and acquire data from the patient via Internet, mobile applications, mailed surveys, telephone, face-to-face interview or other means. The key distinguishing feature from traditional patient registries is that most of the data comes directly from the patients.

Collecting data directly from patients is generally done one of three ways:

> Direct enrollment of patients outside of provider care site(s) with follow-up data collected directly from patients.
>
> Direct enrollment and data collection from patients outside of a provider's site, supplemented with existing pharmacy and/or medical data.
>
> Enrollment by a medical provider with some data collected by the site but most other data, such as quality of life and treatment satisfaction, collected directly from the patient.

Reasons to utilize direct-to-patient and patient centric designs depend in large part on the research question, condition being studied, whether patients can be reasonably good and complete reporters about the exposures and outcomes of interest, in situations where recruitment

through medical care providers is particularly challenging, and lastly, when long-term follow-up is needed.

Patients are often willing to provide rich detailed information about their condition which may be important for understanding treatment effectiveness and safety, or lack thereof. When the research questions concern personal habits, exposures or quality of life, for example, patients may be better reporters than medical care providers. For other types of information, patients may be at least equal reporters compared to those providers. Patients can report important aspects of their disease management that may not be known to their medical care provider. One example of this is injection sites and amounts for hemophilia treatments which are self-administered to prevent bleeding episodes. Patients may also feel comfortable reporting confidential information for study purposes, especially with electronic data capture, that they may be unwilling to share honestly with medical care providers, or information that may be sensitive in nature. [2,3] Examples of information that could be important to understanding effect modification or treatment safety include use of non-prescription medications, complementary/alternative medicines and illicit and recreational "drug" use. Another example of information that is best known to patients is sexual activity, which is important to understanding a range of questions from disease transmission to fertility. Patients can also report habits of daily living that may trigger flares of disease activity. They can track and report daily symptom severity, ability to perform activities of daily living, and respiratory symptoms, and as well as monitor transient events, like headache patterns. Direct contact with the patient also allows efficient capture of various other factors that may or may not be recorded in a traditional health record, like characteristics of employment (desk job vs. working outdoors, for example); support systems from family, friends, and other sources; and recreational activities which may be important to contextualize treatment effectiveness and health outcomes.

Direct-to-patient registries can also facilitate recruitment. For example, without being restricted to recruiting through selected health care facilities, recruitment may be targeted to locations where more eligible patients are likely to notice the request for registry recruitment. This approach to recruitment can also be cost-effective, by avoiding the cost of individual site recruitment, contracting and local institutional review committees. For studies of rare conditions where only one or two eligible patients may be identified through a single medical care provider, patients may be more accessible from web sites where they go to seek information about treatment options, from advocacy group networks, or from an online support group. A registry may also seek patients who are being treated at facilities where regular access to health care providers is difficult, or patients who are treated by various processes including telemedicine and other distance-based care.

Recruitment from an established patient network can increase the efficiency of enrollment. Patient advocacy organizations may already have established networks or patient communities that contain members who are eager to participate in research programs and who are likely to complete any studies in which they enroll. One example would be the Cystic Fibrosis Foundation. Patient-Powered Research Networks (PPRNs), established by the Patient-Centered Outcomes Research Institute (PCORI) as authorized by the Affordable Care Act, offer a myriad of patient registries, including Improve Care Now: A Learning System for Children with Crohn's Disease and Ulcerative Colitis[1] and the Multiple Sclerosis Patient Powered Research Network[2] just to name two examples.[3] Patients within these networks/communities share their experiences

with each other and may be interested in participating in clinical trials and observational research. A patient organization may even sponsor a registry among its community members, often referred to as patient-generated registries, which may be used for recruitment in studies organized by others. While the various characteristics that motivate these patients to participate in a study may make them different from other patients with the disease or exposure of interest and researchers must consider the generalizability of results, those motivating factors may not necessarily interfere with any biologic relationships under study and may enhance retention.

Direct contact with patients can increase the capture of long-term follow-up data and minimize loss-to-follow-up, particularly for patients who are unlikely to return to the medical care provider after an initial encounter or treatment, such as after a surgical procedure, medical device implantation or vaccination. In addition, patients may change their place of residence over the course of follow-up in a registry and may receive their care from another facility or provider not participating in the study. Collecting long-term follow-up directly from the patient may decrease attrition due to patient mobility or distance from the initial provider site.[3]

In summary, patient-reported information is often important for evaluating treatment effectiveness and safety as well as treatment heterogeneity and drug interactions, since some combinations of self-care based treatments and/or other patient practices may enhance or impair drug effectiveness, or increase risks that may be mistakenly attributed solely to the prescription medication or other medical intervention. Direct patient enrollment can be a cost-efficient method of achieving a desired study size, and direct patient contact can enhance the likelihood of collecting information about delayed benefits and risks. Thus, patient-reported information collected through direct-to-patient registries and other patient centric designs can be of tremendous value in assessing treatment effectiveness, effect modification and furthering evidence generation to support personalized medicine.

The various types of direct-to-patient registries and other patient centric designs have differing strengths and limitations that warrant consideration. Here we explore the concept of direct-to-patient registries, identify scenarios in which this approach is most appropriate, discuss challenges, limitations and best practices for this registry design, and examine approaches to mitigating the potential for bias introduced by direct-to-patient contact. In addition, ethical considerations associated with direct recruitment and data collection from patients is explored.

Types of Direct-to-Patient Registry Designs

In this section we offer examples of several types of direct-to-patient and other patient centric registries and explain their purpose and approach to patient recruitment, retention, and data collection. In the next section, we address challenges and limitations in the context of design and operational considerations.

Direct-to-Patient Enrollment and Data Collection

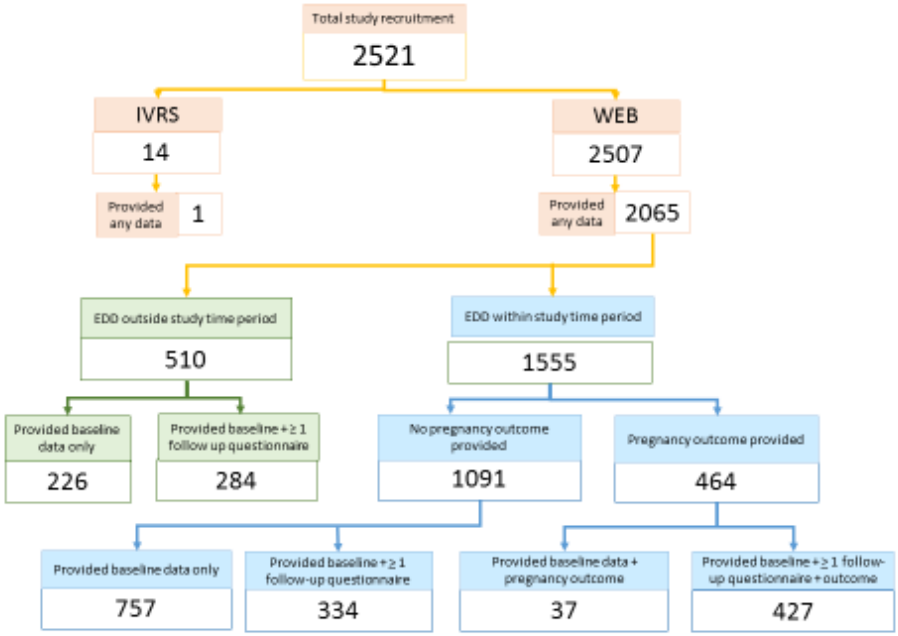
For many conditions, patients can self-identify easily and volunteer to participate in health research studies that are seeking patients with their characteristics, with the caveat that the patient has self-identified as having the condition being studied and this may or may not have been validated. For some conditions, self-identification can be very important because patients may know about their condition and be at high risk for serious consequences, but not have

presented for medical attention. For example, it is important to study fetal exposures in early pregnancy when the risk of teratogenesis is high, yet many women do not present for medical attention until later in pregnancy and are unaware of which exposures may be risky.[4] Not all conditions are as straight forward and easy for patients to self-identify as pregnancy. A limitation of direct-to-patient enrollment is that it assumes that the patient is an accurate, reliable and precise reporter of his or her condition. Depending on the condition and research question, it may be desirable to obtain clinical validation of the enrollment criteria, particularly the diagnosis or condition of interest.

In a recent internet-based pilot study to test new methods of conducting pharmacovigilance (PROTECT), pregnant women were invited to participate in a study of medication use and pregnancy outcomes in four European countries (Denmark, the Netherlands, the United Kingdom and Poland)[5]. Figure 1 shows the process for study recruitment and follow-up. Pregnancy was chosen as the test condition for this project since, if successful, direct-to-patient research could offer an effective way of learning about potentially teratogenic exposures that occur early in pregnancy.

This study showed that women could indeed correctly report most of the prescription medications that they took. In addition, roughly 25% of them reported taking non-prescription medications, some of which were not noted in their electronic health records. Also women reported rich information about personal habits including smoking, alcohol, herbal medications and use of illicit and recreational drugs. They also reported on vaccinations and experience with anesthesia as well as other details not available or easily extractable or linkable from existing databases.[6]

Figure 1: PROTECT Enrollment and Follow-up[6]



EDD = Expected Date of Delivery

Together RA is an example of a direct-to-patient registry that collected both patient-reported information as well as biological specimens. The objective of this pilot program was to study whether a direct-to-patient research approach could be used to complement conventional clinical research methods. A variety of digital approaches were used to promote recruitment including patient communities and social media outreach programs conducted by a large clinical research organization and funded by a pharmaceutical company. Potentially eligible patients with rheumatoid arthritis were invited to access study details, consent to participate, and to be screened for eligibility. The first 1,000 eligible, consenting patients were enrolled in a study that included two web-based surveys. Participants also were required to submit an authorization for medical record release and a saliva sample using a kit that was supplied, including return packaging with paid postage. After receipt of the signed authorization for medical record release, a copy of the patients' medical record was obtained from his or her physician and chart data abstraction was performed.

Over the 18 week enrollment period, 22,855 patients visited the study website and 8,142 (36%) attempted to screen for the study. Nineteen percent (n=4,289) completed the screener with a self-reported RA diagnosis. Only 1,421 (6%) met the study enrollment criteria based on self-reported RA diagnosis; previous exposure to an anti-TNFα; age 21-75; Caucasian; and located in any US state except New York or Maryland. One thousand patients proceeded to complete enrollment by consenting to provide medical record release and a DNA saliva sample for genetic analysis. Eighty-two percent (818) of enrollees provided lab data and genotyping was completed for 80% (798). In addition, 59% (591) of patients' medical records were retrieved.[7] Overall, data for all three aspects of this pilot study (PROs, lab data for genetic analysis and medical record review) were completed for 48% of enrolled patients, with collection of medical record data being the most difficult to complete.

Direct-to-Patient Enrollment and Data Collection Supplemented with Existing Data

In some cases, even when direct-to-patient enrollment and data collection is preferable overall, there is still certain clinical information that is best provided by a medical care provider.[8] For example, in a study of birth outcomes, a trained clinician would be better able to provide a clinical description of most birth anomalies than would a patient. When medical care provider input is critical to meeting the study objectives, direct-to-patient registry recruitment can include patient authorization for targeted data collection from the patient's medical record and/or design the study such that medical provider sites may be integrated into the recruitment strategy.

The National Amyotrophic Lateral Sclerosis (ALS) Registry is an example of a registry that collects data in two ways, from existing data and from direct enrollment. The first approach used four existing national administrative databases (maintained by Medicare, Medicaid, the Veterans Health Administration, and the Veterans Benefits Administration) to identify cases of ALS. The second approach used a secure web portal (www.cdc.gov/als) where patients self-enroll after answering six validation questions. These questions were developed by the Veterans Administration and were found to be 93% accurate when reviewed by a neurologist for an ALS diagnosis. The decision to use the national databases was prompted by pilot projects to evaluate the feasibility of identifying ALS cases. An algorithm was developed using ICD9 codes, frequency of visits to neurologists, prescriptions for Riluzole, and death certificates listing ALS

as cause of death to identify cases as either "definite ALS," "possible ALS," or "not ALS." The algorithm has a sensitivity of 87% and specificity of 85%.[9]

When patients enroll directly their self-reported data are linked to existing data. Direct-to-patient enrollment is accomplished via an online portal that also uses data acquired from national administrative sources including the Centers for Medicare and Medicaid Services (CMS) and the Veterans Health Administration. This federally mandated program is used to describe the incidence and prevalence of ALS in the United States, characterize the demographics of those with ALS, and examine potential risk factors that may lead to disease development. Patients are identified using a two-pronged approach: (1) through existing national administrative databases on the basis of services received and (2) using a secure web portal where patients self-enroll after answering six validation questions. A total of 12,187 persons were identified as "definite ALS" across the four national databases and through web portal registration from October 19, 2010–December 31, 2011.[10] The majority of patients (70%) were identified via national databases. This direct-to-patient approach has allowed for the administration and completion of more than 50,000 follow-up surveys to date among all enrollees to better understand potential risk factors and disease etiology.

These surveys represent the largest collection of ALS risk factor data ever assembled and analyses are ongoing. By leveraging existing national administrative databases and using an online secure web portal, the Registry has been able to estimate the first-ever national prevalence of ALS in the US and plans to continue to release future prevalence, incidence, and mortality estimates as subsequent calendar years are analyzed. This ability to follow the patient across changes in medical provider allows for the long-term follow-up needed to provide valuable insights into disease etiology.

The Registry has also developed an email research notification mechanism which alerts eligible patients to potential research studies after the research plans have been reviewed and approved by an Institutional Review Board.[11] Over 96% of enrollees have elected to be notified about research opportunities. To date, 21 studies have used the Registry for recruitment purposes, and researchers report that the ability to connect directly with patients was critical to successful recruitment. Another interesting aspect of this registry is its national biorepository, which is currently being tested through a pilot study. The goal is to have a nationally representative registry that will contain biologic specimens (e.g., blood, tissue) from patients enrolled in the National ALS Registry. As of the date of this writing, the biospecimen study is attempting to collect blood, urine, hair and fingernail clipping samples from 300 people with ALS in their homes. Additional specimen collection includes postmortem specimens of brain, spinal cord, cerebral spinal fluid, and pieces of muscle, skin, and bone from ALS. Data from the biorepository will be paired with the completed surveys in the Registry and hopefully will help researchers learn more about disease pathology and pathways.[12]

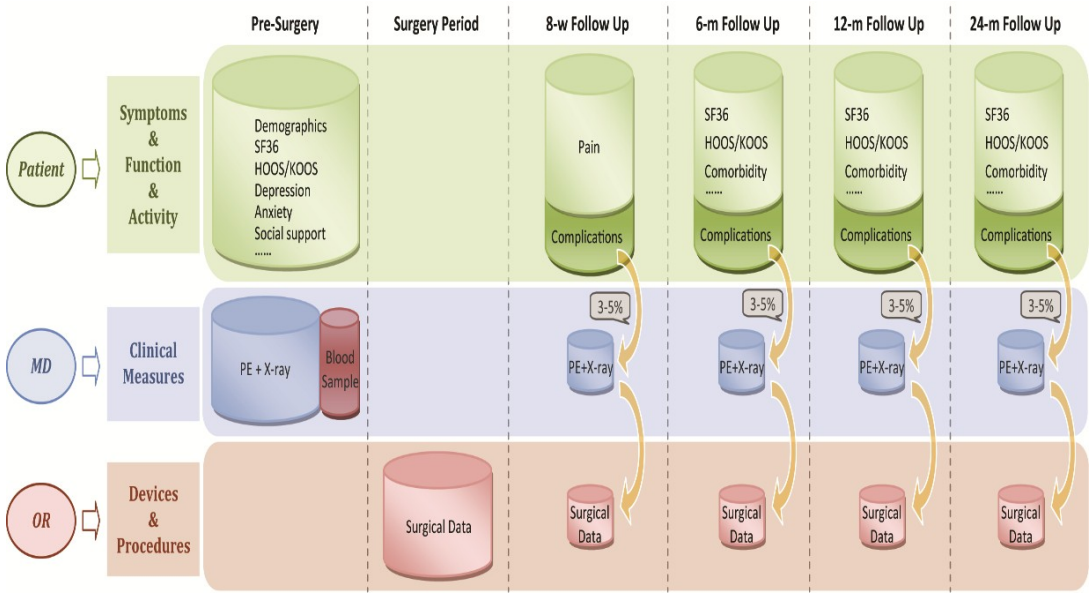
Site-Based Patient Enrollment and Data Collection Supplemented with Patient-Reported Data

In some cases it may also be desirable to identify and enroll patients from medical provider sites but contact them directly for follow-up data. This patient-centric study design is particularly attractive when patients may not return to the original site where they were recruited, thereby

impeding the collection of follow-up data required to achieve the registry objectives. This may occur for example in long-term follow-up after bariatric surgery to evaluate sustained weight loss, evaluation of long-term success after implantation of a medical device, or treatment satisfaction and safety of cosmetic treatments.

The patient-centered Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR) Registry, funded by the Agency for Healthcare Quality and Research, FORCE-TJR uses direct-to-patient data collection supplemented with data obtained from medical chart review. FORCE-TJR is a national registry established from a comparative effectiveness research network of community-based orthopedic offices that are representative of contemporary TJR surgeons and their patients (e.g., 75% are community practices)[13.] The goal of this program, like all quality improvement programs, is to reduce medical errors and adverse events and improve patient outcomes. In addition, FORCE-TJR a research program to develop new knowledge about best TJR surgical practices.[14] A unique feature of FORCE-TJR is that is collects patient-reported outcomes (PRO) before and after joint replacement with a focus on general health, the frequency and severity of joint pain, and the ability to walk or climb stairs and walk distances, before and after the surgery.[15] At the same time that patients complete the PRO, they are also asked to report any visits to an emergency room, hospital admission, or inpatient or ambulatory surgical procedure related to their knee or hip implant during the first six months following TJR surgery. Annual PRO surveys inquire about revision surgeries or any operative procedures related to the implant. The Clinical Data Team investigates all patient-reported events by reviewing the medical records from the facility listed on the report. FORCE-TJR's timeline for data capture is illustrated in Figure 2. This systematic approach to data collection permits estimation of readmission rates within 30 days of discharge from TJR surgery and 90-day complication rates.

Figure 2: FORCE-TJR Data Capture and Timeline



The majority of the FORCE-TJR data are obtained from the patient, particularly through questionnaires summarizing pain and function (Knee Injury and Osteoarthritis Outcome Score

[KOOS], Hip Disability and Osteoarthritis Outcome Score [HOOS]). In addition, patients report key data including medical and musculoskeletal co-morbidities. The ability to capture patient-centric outcomes over long-term follow-up is valuable for surgical procedures and implants since these are often intended to be long-lasting treatments. To obtain these PROs, FORCE-TJR built a centralized information technology system to automate timely distribution of surveys via secure email with an individualized web link or mailed scannable paper, automated reminders, tracking for completion, and personal reminders as needed to assure complete follow-up. This flexibility in method of survey administration based on patient preference is practical with the direct-to-patient design. In fact, thus far FORCE-TJR has collected PROs from more than 85% of the registry patients.

These patient-reported data are then supplemented by EMR information for patients who report post-operative adverse events and surgical data for all patients. Medical chart reviews are conducted through either electronic data capture or manual chart review depending on site capability. In both scenarios a standardized clinical review is performed to apply pre-defined standardized definitions and algorithms for each diagnoses. For example, the diagnosis of infection is not a code from the electronic medical record (EMR). Clinic notes, labs, and treatment records are reviewed to assure standard definitions independent of the data were sent.

Further, CMS administrative data are collected annually and used to validate post-operative events which are reported for patients who are over 65 years of age at the time of surgery which represent 50% of the registry patients.[15] FORCE-TJR submits a "finder file" and CMS returns matched data, recognizing CMS will not be able to provide any data for patients under age 65, since they are not eligible for medical coverage by CMS. Those CMS data are then linked with the PRO data collected annually by FORCE-TJR.[16] Over time, FORCE-TJR patients age and become CMS beneficiaries, so the administrative data will allow for validation of long-term revisions and complications to supplement patient-reported events.

One of the strengths of using patient-reported complications and outcomes data is that it improves complete capture of post-operative events and assures consistent clinical definitions. On average 25% of all readmissions and complications in the 90-day post-TJR period occur at hospitals or emergency rooms other than where the TJR was originally performed. While payer data such as CMS would capture these events, the surgical hospital does not have this information.16 In addition, this approach avoids extensive chart reviews on patients without reported post-operative events and focuses staff effort on those patients who report a suspected complication. Finally, this approach allows FORCE-TJR to use consistent clinical definitions for adverse events which minimizes the impact of varied definitions that result from differing administrative coding practices across hospitals. For example, the definition of "deep vein thrombosis" will vary across hospitals, but centralized registry staff can impose consistent clinical criteria.

FORCE-TJR plans to track patients for decades, even if patients no longer have a relationship with the original surgeon, have moved, or have different insurers/healthcare system. The direct-to-patient approach not only helps FORCE-TJR maintain a relationship over time, but also allows the collection of PROs, revisions and adverse events data much longer than 90 days after surgery, information which is of great interest to patients, surgeons and medical insurers.

Design and Operational Considerations

Generalizability

A strength of patient registries is that they are more generalizable than randomized controlled trials, since registries reflect real-world behavior and practices and have fewer inclusion and exclusion criteria. However, as with any study design, thoughtful selection of the patient population is critical to enhance generalizability and reduce the potential for systematic error (bias). It can be particularly challenging to defend generalizability for direct-to-patient registries, since patients are recruited directly in situations where the underlying sampling frame is unknown. The concern to evaluate the representativeness of any cohort study conducted without benefit of an underlying sample frame is indeed challenging. In these situations, generalizability is addressed in terms of characterizing the population that has been recruited (accessible population) and comparing their demographic and other characteristics with what is known about the target population from other sources, e.g., case series and/or national data. For example, those who participate in Internet studies are often more educated. Also it is not uncommon to find racial and ethnic differences. At the very least, a direct-to-patient registry should report its findings by major subgroups and characteristics of interest, and leave it to others to determine whether the patterns observed in these cohorts are similar to other patient populations of interest. Thus the basic scientific process of replication and confirmation holds true for registries as with other forms of scientific inquiry.

In the PROTECT pregnancy study, there was concern that requiring study participation via the internet would discourage women with low income (and no internet access) from participating, which might bias the results. In an effort to ensure accessibility to women of various social classes and income levels, the study was designed to collect data in two modalities: by Internet or by interactive voice. However, Internet data collection was overwhelmingly the most popular choice, with only one woman completing the baseline pregnancy questionnaire by interactive voice; she subsequently dropped out of the study (see Figure 1). PROTECT study participants were described by age, ethnicity, parity and residence within country, and those characteristics were then compared with known information about each country's population. Although this descriptive approach cannot guarantee that all eligible subjects have been recruited or that the same is truly representative of the target population, it is often sufficient to characterize a population and provide a rigorous study of those participants, even if not 100% complete or representative.[17]

In contrast, consider the FORCE-TJR example where the registry staff monitor surgery logs each week to assure that all TJR patients are referred for invitation to the registry. The operating room schedule was used to identify eligible patients at sites with both phone-based and on-site recruitment. Case identification through operating room schedules avoided the potential bias of surgeons not enrolling more complex cases. In this example, the characteristics of participating patients can be compared to those who do not participate, using the surgery logs to enumerate the entire target population. Further, since FORCE-TJR has a follow-up rate of more than 85% among enrolled patients, reportedly the highest among all joint replacements registries in the US, their data are likely to be less biased than other datasets (http://www.force-tjr.org/overview.html).

Validity

Data collection from patients should be approached differently from data collected from medically trained personnel. First, patients working independently may not have as much patience or persistence in completing a long, detailed questionnaire as they might if someone were present and coaching them. Second, a patient cannot be expected to report exposures and medical events using the same terminology and response choices as a trained medical professional.

For example, in PROTECT, patients were asked if they had various medical conditions (e.g., respiratory conditions) and if they used any medications to treat those conditions. If they answered affirmatively, they were offered a choice of the most common prescription medications for that condition, along with an opportunity to use text entry if they could not find their medication already listed. In many cases, women provided information on their medication use through free text fields even when the medication was available in the prepopulated list, suggesting either that patients did not recall the indication for which a particular medication was prescribed or that they had forgotten to respond to the condition-specific question when it was first mentioned and did not want to look back through all the indications listed to find where their drug belonged. This finding may, of course, have been related to the technology used for this study, and technology advances in data collection may simplify this type of data collection.

There have been technological advances in how information on adverse drug effects are collected from patients. MyMeds and Me is a good example of a patient-friendly approach that starts with a picture of the full body and asks patients to place the mouse cursor on "where it hurts."[18] From there, it takes them through guided, well-illustrated pictures with the end result being medically coded adverse event data that can be used for regulatory submission to satisfy the pharmacovigilance obligations of pharmaceutical companies who have marketed products. While this is an outstanding example of how patient-friendly information can be translated into medically useful data, it was developed for a large commercial market (for use in call centers that are maintained by all pharmaceutical companies with marketed products), a situation that is far different from an individual set of researchers tackling various problems of public health interest. In the absence of such data collection and coding tools, it is important to ask patients to report information in terms that can be used to screen important medical events of interest, such as hospitalizations or illness requiring expensive medical care or support, and then flag those events for follow-up with medical trained personnel. That type of targeted medical follow-up can be used as an efficient approach to obtain clinical information to support drug benefit and risk assessments.

Many registries use selective validation to assure completeness and accuracy of reporting. For example, in the ALS registry, three state and eight metropolitan-area surveillance projects were funded for this purpose and several reports have been issued, describing results of local projects which can then be compared with national registry data.[19-21] In the case of FORCE-TJR, which supplemented patient-reported data with existing data, various methods were used to validate patient-reported data. For example, operative data about the implant were used to verify that the patient had a primary (or revision), unilateral (or bilateral) total knee or hip replacement procedure. The implant component type and volume support the coded procedure. FORCE-TJR also verified 30 day readmissions and 90 day complications with review of medical records and

CMS administrative data. Medical record review for all patients (CMS and under 65 years) allowed FORCE-TJR to assure consistent event definitions were applied and consistent with national professional practice standards. A yearly review of CMS claims for patients over 65 years of age allows verification of revision surgery and timing, if present.

Nonetheless, it is important to keep in mind that there is no incentive for patients to tell the truth (or the complete truth) beyond altruism. Since patients are not, as a group, trained in the art of observation and reporting, there may be some suspicion that patients will report what they expect the study team would want to hear.

Patient Reimbursement, Recruitment, and Retention

Methods for patient recruitment including reimbursement vary based on the target patient population, study design, budget and timeline considerations. Methods should be carefully selected to ensure timely recruitment of the desired sample size in a manner that supports generalizability and minimizes the potential for selection bias. Ethical considerations require that any reimbursement be appropriate for time-spent and not be considered any inducement to use a particular product not already prescribed by his or her medical care provider (e.g., by providing free drug). Loss to follow-up is another challenge faced by many long-term registries and can lead to bias by selective reporting from patients with favorable (or unfavorable) outcomes, or who are concerned about the health effects of selective exposures, which could increase reporting experience from people who had those exposures.

Reimbursement for Participation

Patients appreciate some consideration for the time and effort required for them to participate in research,[22] particularly non-interventional research like patient registries where they are not receiving benefits as would be available in a clinical trial (e.g., more comprehensive testing, special treatments and/or other procedures that are not part of standard clinical care). Even in non-interventional studies, patients may receive reimbursement for parking or transportation for participation in traditional office-based registries. However, patients are rarely compensated for time spent completing their forms.

In the PROTECT pregnancy study, there was no reimbursement for patient surveys. A small focus group was convened to understand the high loss to follow-up. Pregnant women reported that while they would consider participating in a study like this purely for altruistic reasons, one of the most frequent comments was that some form of modest compensation, preferably a cash payment, would enhance the appeal of participation.

When cash payment s are used, these reimbursements should be nominal, i.e. in the range of $5 - $20 US or country equivalent per assessment, depending on length, user interface and estimated time for completion. The amounts should be clearly noted in the informed consent form, confirm how the reimbursement will be made, and reimburse directly in an electronic formats in order to best maintain patient confidentiality.

Recognition for registry participation can take many forms besides cash payments. FORCE-TJR did not compensate patients, but instead offered small thank you gifts such as sticky notes and

pens with the FORCE-TJR logo at the time of enrollment. In addition, each year the participants receive a newsletter of "lessons learned" to reinforce the value of their participation.

Recruitment & Retention

Done well, there is tremendous value in being able to recruit patients via the internet and using other strategies that support broad recruitment and minimize the need for in-person contact. For example, a Danish study of characteristics that influence fertility and fecundity used an internet-based study approach to recruit women to a study about pregnancy and time to conceive. Internet-based data collection was chosen as the means for data collection because it afforded women privacy to disclose their intent and behavior and did not require them to share this information in any face-to-face contact with an interviewer or health care provider. The "Snart Gravid" ["Soon Pregnant"] pregnancy planning study started recruitment in 2007. These researchers used a popular website in Denmark (same as was used later in the PROTECT study) and 2,368 participants were enrolled in six months. After 54 months of recruitment, 5,920 women were enrolled in the cohort.[23] The TogetherRA example described earlier showed that a large number of RA patients were enrolled in only four months, with the requirement that they not only provide answers to questionnaires but that they also provide a signed release to allow medical record review and provide a saliva sample for genetic analysis. Overall, use of social media and support groups, with or without the use of paid advertisements, can be a useful tool for patient recruitment.[24]

In the PROTECT study,[22] the internet face of the study was a multi-lingual website that explained the study and showed friendly pictures of well-respected country-lead researchers for each country/language combination. Frequently asked questions were addressed and those who were interested were invited to provide informed consent and enroll in the study. Multiple patient outreach methods were utilized, including both low cost (posts on pregnancy e-forums, hyperlinks on pregnancy-related websites, leaflets and posters at community pharmacies and/or obstetric/midwifery units, social media profile on Facebook) and higher cost methods (large digital banners or hyperlinks on pregnancy specific websites, emails to registered users of popular pregnancy-related websites, and paid advertising on a social media site). After initially focusing on low cost methods, higher cost advertising and paid recruitment activities were implemented and determined to be essential to achieving a reasonable study size.[25]

FORCE-TJR used two methods of patient recruitment, and noted that in-person enrollment by office staff during the pre-TJR visit resulted in somewhat higher recruitment levels compared to phone recruitment in the low volume sites, but both were highly successful. On average, in-person enrollment exceeded 90% of all English and Spanish speaking patients (other languages were not available), while phone recruitment to the distributed network averaged 70-75% enrollment. Of note, when patients were invited by the surgeon at the community sites, and accepted the recruiter's phone call, enrollment exceeded 90%. However if the surgeon did not mention the registry, patients were less inclined to answer the call from the central enrollment staff. When patients answered the recruitment call, enrollment exceeded 80%. In summary, at either in-person or phone recruitment has been highly effective for enrolling patients in a registry. Key office procedures associated with high recruitment rates are (1) an invitation from the treating physician and (2) systematic identification of all eligible patients.

Patient motivation is a key factor influencing patient recruitment and retention. In the ALS Registry, the seriousness of the disease and the relatively short expectancy after diagnosis may be sufficient motivation for enrollment. In FORCE-TJR, patients reported that they want to know how they are doing and where they stand regarding pain relief and functional gain after surgery compared to other patients. They may be a highly motivated population since a successful surgical experience may return them to greater mobility and function than before surgery. In addition, the Registry is used to provide feedback to surgeons about the outcomes of specific devices and surgical approaches. The Registry consent/enrollment process emphasizes that their data are shared with the surgeon and are an important part of the Registry program. A newsletter is distributed to patients annually, and it demonstrates how patient data are used to inform new strategies to improving care.

It is important to keep in mind that no matter what reimbursement is used to enhance recruitment and retention, patients are unlikely to complete questionnaires which they find confusing or lengthy. In the PROTECT study, women who completed informed consent but who did not complete the baseline questionnaire were asked for their reasons for not continuing in the study. Seventeen percent (6/34) of patients indicated that the baseline questionnaire was too long. When assessing patient burden, it is important to consider factors that may affect time required for survey completion, including the educational level of the target population, number of comorbidities and medications, and level of detail requested.

Creating Standing Cohorts

The concept of a standing cohort is that a group of patients with a characteristic in common, e.g., a particular disease or condition, are enrolled in a registry with ongoing basic data collection that can be utilized on its own or in combination with linked data or supplementary data collection to address a specific research question. Recruitment from an established patient network or standing cohort, which may contain patients with a particular condition or exposure that are eager to participate in research, can also increase the efficiency of patient recruitment and enrollment. For example, a standing cohort of pregnant women could be created, with rolling admission and study completion after pregnancy has ended. Such a cohort would provide a rich source of information about changes in medication use during pregnancy and pregnancy outcome.

Standing cohorts can also be created from existing networks which have not been created for a specific study purpose. For example, PCORI has launched the National Patient-Centered Clinical Research Network (PCORnet) to increase speed, efficiency, and relevance of clinical research by funding both Clinical Data Research Networks (CDRNs) and Patient Powered Research Networks (PPRN). Currently they have funded 23 PPRNs that are effectively standing cohorts, operated and governed by patients, advocacy organizations, and their clinical research partners. These networks are tasked with enrolling > 0.5% of the US population with the specified condition with a minimum of 50,000 patients for most common conditions. The PPRNs are developing a governance structure and operating policies that engage patient participants to generate and prioritize research questions. These networks are collecting patient-generated health information suitable for research from > 80% of their membership. These research networks are exploring mechanism for patients to obtain electronic health data directly from administrative

claims or electronic health records in addition to standardizing the collection of PROs. PPRNs are in the process of becoming a sustainable national resource.

Standing cohorts can also be created from existing registries. For example, the ALS Registry's outreach program, which gives participants the opportunity to designate that they are interested in hearing about potential research projects, allows the Registry to then create standing cohorts of ALS patients with various characteristics who can then be questioned and followed over time to learn more about treatment and prognosis.

Ethical Considerations

Ethical considerations for direct-to-patient registries are very similar to all other research with the exception that the language used must be clear on its own and not require medical or legal consultation in order to be completed.

Direct-to-Patient Recruitment Material

Ethics review is required of all materials used in patient registries, including any posters, brochures, educational newsletters, and thank you gifts. Recruiting and informational materials must be carefully crafted, taking into consideration variation in the education and reading level of the target population, presentation of information in an assessable way for non-medical personnel, and ensuring that information is presented clearly and concisely. Patient incentives for study participation should be critically examined and thought through as they are often a concern of ethics committees.

Informed Consent for Participation

Informed consent requirements may vary depending on study design and country. A flexible approach to informed consent may be needed, especially when conducting multi-country and multi-stakeholder studies.

For example, even though PROTECT was a fairly benign study in terms of its questions, there was great variability in the response of four Ethical Review Committees (the European equivalent of Institutional Review Boards). The most frequently cited issues of concern to these Ethics Committees related to data protection, which may be different from US-based studies since the European Union has very strict restrictions on "cross-border" sharing of patient data. There was also variability in how Ethics Committees wanted to document informed consent.[5] One Ethics Committee asked to have the informed consent form printed and mailed; others accepted informed consent by voice and/or by e-consent. Moreover, PROTECT was conducted through a public-private partnership, which complicated all aspects of data collection including safeguards for data protection including data transfer, storage, access and overall liability.[5]

In contrast, consider the Informed Consent used by the ALS Registry.[26] This single-page document uses plain language to explain the purpose and importance of this registry, showing that the informed consent document does not have to be a long, detailed document.

The process for managing informed consent is also important. Enrollment in FORCE-TJR requires office staff to provide an information packet to all patients who schedule TJR and to ask

patients to provide their preferred contact telephone number. FORCE-TJR staff then contacts the patient by phone within two days of having mailed the information to review the material and invite participation. This process assures that consistent information is provided prior to obtaining consent to participate and meant that sites do not need to train research staff on site and do not need to worry about a back-up of eligible patients that need to be consented and enrolled. FORCE-TJR also uses the consent process as an opportunity to help patients understand the importance of the program, including the value of long-term follow-up. Patients understand they will be asked about their experience of TJR surgery over time and that the data have the potential to benefit others.

Patient Consent for Access to Medical Records

Confirmation or supplementation of patient-reported information with data from medical records can be critically important to direct-to-patient research. For example, in the PROTECT pregnancy study, it was difficult to interpret patient-reported information about birth defects. In the FORCE-TJR example, a great deal of information was collected about the device and the surgical procedure for the surgeon's records. In the ALS registry, valuable medical information was obtained from health care providers that substantially enriched the value of the patient-reported data.

In studies where patient-reported information need to be supplemented with medical records, patient consent to access medical records is required. Depending on study design, obtaining consent to access medical records at the time of informed consent for the study is the preferred approach, where feasible, due to its efficiency.

In crafting a medical release form, it is important to consider where the data are being requested from (hospital or specialist vs. primary care) and length of access needed (one-time vs. long-term). FORCE-TJR obtains patient consents and medical record releases at the time of enrollment to specifically allow FORCE-TJR to review patients' medical records and obtain CMS utilization data over time. However, hospitals are often slow to respond to approved requests for record access. Medical records office staff may insist that the medical record release is valid for one year only. In this situation (and whenever data are requested for new sites, such as where a patient may go for a revision or for treatment of a complication), FORCE-TJR is required to obtain a new release from the patient, which involves another step and is cumbersome. Fortunately, less than 8 10% of patients report events at each survey so efforts to obtain medical records are focused on these patients.

In some studies, a patient's primary care physician may be asked to obtain other medical data as needed, such as the discharge diagnosis for a hospitalization, or a specialist's report providing additional diagnostic information. Although it may be tempting to simply ask the primary medical care contact for the registry to seek these additional data without any compensation, those type of requests are rarely given priority and this approach is likely to diminish the amount of supplementary data that are made available to for study purposes. It is preferable to provide compensation for this extra collection and reporting using Fair Market Value for time spent.

Conclusions

Direct-to-patient registries and other patient-centric designs are particularly useful for collecting a broader picture of patient exposures and patient perspectives on outcomes than would be available by obtaining data through medical care providers or by searching electronic databases. There are certain scenarios where these designs provide great value and efficiency, including long-term follow-up after one-time events (e.g., surgery or vaccination), events or exposures that occur when patients may not immediately seek medical care (e.g., early pregnancy or dementia), when broad and long-term data are needed to address multiple research questions relating to disease etiology or natural history, or when patient-centered outcomes (e.g., quality of life) are required. Despite known challenges including generalizability and validity, the utility of this registry design lies in collecting data that are only reliably available directly from the patient whose experience is needed to better understand the topic of interest.

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Registry Networks: White Paper

Draft White Paper for Fourth Edition of "AHRQ Registries for Evaluating Patient Outcomes: A User's Guide"

Introduction

Patient registries are "organized systems that use observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."[1] Health reform and value-based payment are driving increased need for standardized performance measurement on a national level.[2] Registries collect standardized, structured data on patient populations that span institutions, geographic areas and track patients over varying periods of time. These characteristics make them well-suited platforms for performance measurement, including patient health outcomes, as well as clinical research.[3-6]

As interest increases in using registry-generated information to improve health care performance and create new knowledge, registry networks have developed to support, engage and connect registry stewards, organizations that rely on registry information and others with an interest in the medical condition, treatments, outcomes, etc. A registry network is a formal community of organizations operating or using information from patient registries to measure and improve patient health outcomes. Registry networks may be general in nature or focused on specific domains. These networks provide a supportive infrastructure that organizes participants to undertake activities related to the specific goals of the network. Although registry networks may be established for different purposes, at a fundamental level they are strategically collaborative groups where organizations and individuals come together to advance their work, generate and share knowledge, and solve shared challenges. Although some patient registries have existed for decades, the demand for registry information is increasing as the number of registries created for quality improvement, research, medical product evaluation, payment and other purposes continues to grow. This trend has underscored the need for information about registry capabilities, as well as the need to support communities that help organizations new to the field benefit from the experience of more established registries. In addition to their knowledge sharing activities, registry networks build a common infrastructure, create new knowledge, and provide a place to learn about the registries and other registry participants and contributors. Additionally, some registry networks provide access to technical infrastructure such as access to combined datasets or metadata, often facilitated by member registry adoption and use of data standards that the network has developed. Overall, registry networks create communities of registry practice that foster learning and professional development.

Given their role in a growing registry enterprise, greater awareness of registry networks and how they operate is needed. This chapter begins by describing different kinds of registry networks and providing an overview of major activities. Additional sections then outline how registry networks are formed, including a discussion about funding, sustainability challenges and solutions, and considerations related to international networks.

TYPES OF REGISTRY NETWORKS

Registry networks are formed for different purposes and have varying structures to meet the strategic objectives of their members.[7] Some networks focus on a particular clinical area or patient population, while others are more broad-based and open to a range of clinical domains and purposes. Registry networks may target registries within a particular country, while others are explicitly multinational. Some networks provide technical infrastructure that facilitates linking of registries with each other, while others also include additional data sources (e.g., administrative claims data) that are linked to registry patients to augment the scope of data collected and/or duration of patient follow-up. In such instances this registry network infrastructure becomes the "core" of knowledge networks powered by registries and other health information systems. The different registry network types are described below.

General

General networks of registries admit organizations operating or planning to operate registries and others allied to the registry field, regardless of their specific focus area. As such, these serve as broad-based, multi-stakeholder professional communities of registry practice. They provide a forum for sharing and creating leading practices, facilitate the development of resources for the registry community, and create formal structures for frequent and meaningful interaction between network participants. They offer access to information about participating registries, such as in a catalog or inventory. General networks may also serve as conveners for consensus-building activities, such as the creation of common data standards that facilitate interoperability between registries and other information systems. While they exist for a variety of purposes, general networks share a common mission to accelerate the development and use of registries to improve health and health care. Examples of general registry networks include the National Quality Registry Network (NQRN), a program of the Physician Consortium for Performance Improvement (PCPI®), and the Registry Workgroup hosted by the Council of Medical Specialty Societies (CMSS).

Clinically-Focused

Clinically-focused networks, such as the North American Association of Central Cancer Registries (NAACCR), are formed when the potential benefit as well as the need to coordinate the activities of registries that share a common clinical focus area is recognized. By concentrating resources on specific clinical areas, clinically-focused networks can convene expert working groups and other formal mechanisms that create infrastructure such as data standards, particularly in cooperation with general networks of registries. These networks can also develop performance measures specific to physicians and health care professionals practicing in a particular clinical area.

Clinically-focused networks often create consensus around best clinical practice standards using research and learnings within the clinical objectives of the registry. From there, participating registries are well-positioned to facilitate the sharing of technical, specialty and/or condition-specific professional resources and tools. These registry networks often seek to build a national or international network that can, at least in some aspects, provide specific functionality or capability uniformly across the network. Once combined, the datasets of clinically-focused

networks are an important source of information for benchmarking and other observational research in those areas.

Research

While networks of registries of any type can facilitate research, some networks focus primarily on developing research methods and/or conducting research studies in one or more clinical areas. An example is the TREAT-NMD Neuromuscular Network that provides community and infrastructure to accelerate research and therapy development into neuromuscular diseases, increase collaboration, and improve patient care. Research networks offer centralized support for research, as well as infrastructure that facilitates the exchange and aggregation of data sets. Such networks also provide forums through which researchers can set common agendas and seek funding to address shared priorities. These networks may make their data sets available to researchers both inside and outside of the network, thereby acting as a source of data for the broader research community. These capabilities are additive in that participation by a registry in a research network does not preclude individual registries from conducting their own research. Activities that add to the value of research networks include the ability to create large combined data sets, establish shared governance and other formal structures to ensure that data collected are usable for research, and engage a broader range of stakeholders in and outside of the health care delivery system who may not otherwise contribute to or benefit from the network.

The Medical Device Epidemiology Network (MDEpiNet) is another important example of an entity that, in part, serves a research-oriented registry network. Initiated by the US Food & Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) in 2010, MDEpiNet is a collaborative program through which CDRH and external partners share information and resources to enhance our understanding of the safety and effectiveness of medical devices after they are marketed. Already, more than 40 stakeholder groups including government agencies, manufacturers, patient advocacy groups, universities, health care provider organizations, and other research organizations have become involved in various meetings, exchanges, and workgroups in an effort to develop this new network. One of its main objectives is to foster the development of national and international registries that can be used for medical device postmarketing surveillance activities.[8-10] In particular MDEpiNet has provided a forum for bringing together registry leaders from around the world to form international consortia focused on advancing registry methods and analyzing data generated by existing orthopedic and cardiovascular registry programs. Together, these networks are developing a national/international infrastructure and methodological approaches for conducting robust studies and surveillance to improve the understanding of medical device safety and effectiveness throughout the medical device life cycle.

MAJOR ACTIVITIES OF REGISTRY NETWORKS

Knowledge Sharing

Networks of registries facilitate the creation of communities of registry practice. Before most registry networks were formed, registry leaders learned their trade and solved problems alone or with ad hoc assistance from within their own informal networks. Information is shared and knowledge transferred, but on a limited and ad hoc basis. By forming registry networks, participants at all experience levels benefit by sharing ideas and collaborating on shared work

products. Registry networks frequently convene committees, task forces and working groups. Participants share knowledge using multiple channels with varying levels of formality, including in-person programs, webinars, blogs and on-line chat rooms. These collaborations often result in development of resources such as guides and tools as well as consensus standards for the community supported by the network.

For example, the NQRN is a voluntary network of organizations interested in registries. The NQRN uses a multi-stakeholder model in which organizations operating or planning registries collaborate with users of information from registries, including health plans, health systems, researchers, organizations representing patients and consumers, federal and state government representatives and others. The NQRN's governance helps to ensure that the network facilitates knowledge sharing that is of value to all participants. The NQRN's committees and task forces produce resources and education designed to accelerate the dissemination of leading practices and lessons learned by the network to the broader health care community.

Creating Common Infrastructure

An important purpose for collaboration across registries is to define common data standards. Data standards are essential building blocks for the sharing of data across registries for research, quality improvement and other purposes. While the creation of common data standards is important for all registries, registry networks are well-suited to carry out this work. By convening working groups of registries and other organizations, registry networks can build trust, leading to a desire on the part of registry stakeholders to collaborate by achieving consensus on how to prioritize the data elements and their definitions.[11]

Harmonizing data standards occurs at two levels: the concept to be measured and the selected definition, including the source and timing of measurement. Typically, a harmonization process begins with a discussion of what concepts are most essential for harmonization. For example, a registry collaboration focused on enabling comparisons of risk-adjusted outcome performance might decide only to harmonize select outcome and case-mix concepts, whereas a different collaboration focused on expanding the dataset for medical device tracking might focus instead on harmonizing device technical and identification parameters that improve the comparability of device information across the registries in the network.

Building consensus is an essential element required to achieve data standard harmonization. Individuals representing the various registry stakeholders must be confident that the methodology for evaluating differences in measure concept prioritization and data definition is transparent and impartial. This typically begins with a review of the evidence followed by a presentation of proposals to be voted on by committee members. Often, a Delphi technique with anonymous iterative voting is used to reach consensus above a certain threshold.[12] Some registries have been able to broker this consensus-building directly, while others have worked with third-party facilitators.

Defining data standards must be followed by dissemination and implementation if widespread adoption is to be achieved. Any switch to a new standard invariably means a loss of compatibility with existing data. Stakeholders will only make this investment when the use case of the standards outweighs the loss of continuity in existing data. Even with a strong use case,

strong stakeholder engagement in managing the transition from the old to the new standard is required. Due to their multi-stakeholder membership models and governance structures, generalized registry networks are well-positioned to act as conveners for creating consensus standards that lower barriers to interoperability and information exchange, increasing the usefulness of registry information.

Creating New Knowledge from Registry Networks

Existing registries, along with other health information systems, provide information that is fundamental to the generation of new knowledge. Registry networks bring relevant registry experts and other stakeholders together to discuss evidence gaps, methodologies, data considerations and other challenges. These groups are then well equipped to identify areas where research work is most needed.

As an example, in the medical device setting, a single existing entity rarely has all the elements necessary to provide robust, long-term device evaluation including unique device identifiers (UDIs), operator proficiency, technical procedural information, long-term follow-up and large enough patient cohorts. Deficiencies of any single registry or data source could be overcome if the registry can be linked to one or more additional registries or other data sources that hold data necessary for robust device evaluation.

Creating a Professional Home for Registry Practice

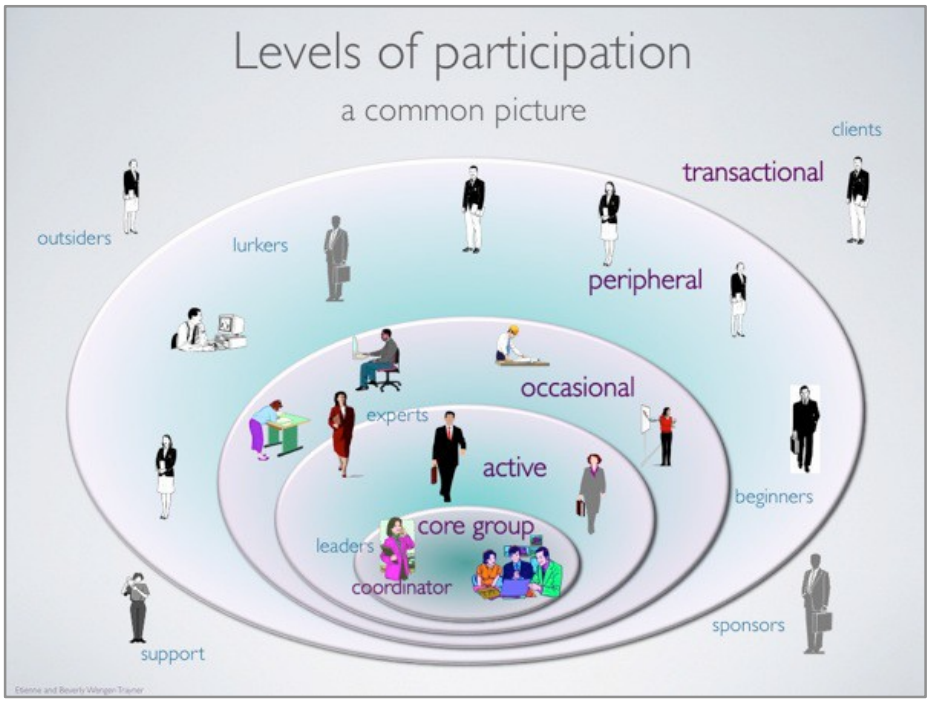
The idea of a "network of registries" described here reflects the broader concept of a community of practice (CoP). Etienne Wenger offers the following definition, "Communities of practice are groups of people who share a concern, a set of problems, or a passion about a topic, and who deepen their knowledge and expertise in this area by interacting on an ongoing basis."[13] In the area of health care practice and research, professional associations often serve as de-facto CoPs for practitioners in a specific clinical field. Practice-based research networks (PBRNs) can also serve this role for primary care providers. The Agency of Health Research and Quality (AHRQ) defines PBRNs as "groups of primary care clinicians and practices working together to answer community-based health care questions and translate research findings into practice."[14]

Communities, or in this case, registry networks, develop their practice by responding to the practical needs of members. These activities commonly take the form of problem solving, articulating and responding to requests for information, seeking out the experiences of one another, reusing assets (e.g., proposals, letters, formulas), discussing developments (e.g., new technologies, regulations, research findings); documenting developments (e.g., case studies, data collection); conducting site visits; mapping knowledge and identifying gaps (e.g., research agenda setting); and coordinating and conducting special projects (e.g., harmonizing data element definitions across registry programs).

While a CoP is typically driven by a core group of people who are passionate and devote time to helping to lead the community, not all the members necessarily participate equally. Multiple levels of participation usually exist, reflecting differences in members' perspectives, needs, and ambitions (Figure 1). Wenger has identified the three key factors for successful CoPs: identification, leadership, and time. Accurately negotiating the domain (i.e., scope) of a CoP allows members to identify with its purpose and also to derive a new identity as a participant in

the CoP. Ensuring that a core group of leaders step up to nurture the community and "take care of logistics" guards against the loss of momentum and member interest. Finally, members are keenly aware of the other priorities that compete for their time, so it is important to ensure a "high value for time" ratio for members.

Figure 1. Levels of Participation in a Community of Practice[15]



In addition to formal knowledge-sharing practices, registry networks provide an organized professional community with benefits that include targeted discussions on leading practices and standards. Social and professional networking, both formal and spontaneous, pave the way for connections that foster mentorship between new and experienced registry stewards and users as well as informed discussions based upon on-the-ground experience at the detailed level that is required to implement successful registry programs. Registries require detailed planning and execution across a number of different areas: technology including data privacy and security; international regulations and ethics, often tailored to multiple countries; deep therapeutic knowledge of study design, feasibility, and operational considerations; and a number of often complex observational study methods specific to collecting and analyzing registry data. Registry networks foster building relationships with registry experts across all of these topics. For those in leadership positions with responsibility for successful implementation, a professional home is a critical component that allows those in a network to have a formal knowledge tree and access to experts who can help shape future of their enterprise, as well as increase awareness among potential community members.

Creating a Registry of Registries

Registry networks often maintain listings of registry programs relevant to their area of focus. The level of detail provided in these listings reflects the network's purpose for the list and resources

available for creating and maintaining it. When establishing a database of registries, there is always a need to balance the comprehensive with the feasible. For example, organizers of the NQRN created its initial list as an Excel spreadsheet to identify possible registries to invite into the network. The NQRN now asks participating programs to send updates to their entry, provide information about the registry's purpose and appropriate contact information. The AHRQ is sponsoring the development of a collaborative web-based registries forum that is paired with another registry list, the Registry of Patient Registries (RoPR). The RoPR focuses on registry programs in the US and promotes collaboration, reduces redundancy and improves transparency in registry research. The RoPR is integrated with ClinicalTrials.gov – the central listing of clinical studies maintained by the National Library of Medicine (NLM).

Condition-specific registry networks can have varying objectives for their registry listings. For example, the goal of NAACCR is to help public health departments meet the needs of federal and state authorities, and its listing is inclusive of all state-based registries in the US and province-based registries in Canada, as well as those of large counties or cities. The TREAT-NMD has positioned itself to conduct distributed research across its multiple major country-based registry programs, chiefly for pharmaceutical companies and academics who want access to data in multiple registries. The International Consortium of Cardiovascular Registries (ICOR) is principally focused on helping its core group of about a dozen national or larger sub-national registry programs share promising practices and work collaboratively on common projects.

These registry listings serve the broader community in multiple ways. They raise awareness of similar research initiatives, enabling direct outreach for knowledge sharing and networking. This can facilitate the use of existing registries as sources of secondary data for additional research questions. While supporting the creation of registries is a key goal of many in this community, researchers are also invested in efficient research spending. When possible, leveraging existing systems is preferred over spending valuable research dollars to create duplicate data systems designed to achieve the same goals.

SETTING UP A REGISTRY NETWORK

The decision to establish a registry network may occur when existing or developing registries or users of registry data (e.g., federal regulators) recognize the need to achieve organizational efficiencies and/or to obtain and analyze data across larger populations than a single registry is able to access. Registry networks may therefore reach across organizational, state, regional, national and international boundaries. Some of the time, it is a regulator, such as the Food and Drug Administration (FDA), that identifies the need for a network of registries and provides startup funds to encourage development, as is the case for the International Consortium of Orthopedic Registries (ICOR) and the International Consortium of Cardiovascular Registries (ICCR). In other instances, a research organization such as the Patient Centered Outcomes Research Institute (PCORI) will launch a network of registries or electronic health records systems (PCORnet) to support its research agenda while also expecting that the network will become self-sustaining over time. In the case of the NQRN, the impetus came from the CMS Administrator, who urged disparate groups (specialty societies, health plans, and payers) to combine their efforts into a single entity.

For each circumstance, it is critically important that the founders of a new registry network agree early on the mission and scope of the new entity. It is also important that a new network not duplicate what is already being done by another network. If a closely related network already exists, potential members are likely to weigh the benefits of joining a new network versus partnering with and expanding the scope of an existing one. This is especially true if the new network will be relying on contributions of volunteer time and other resources during its startup phase. For participants in other networks to be willing to join, they must be confident that the new network will provide value to their organization in a reasonable amount of time in return for participation, in particular a return or outcome that they are unlikely to realize otherwise or elsewhere.

Just as it is important to agree early on what work will be done together through the network, there must also be a shared understanding about what activities will remain outside of the network's scope. For example, network participants may agree to share lessons learned and best practices. Conversely, members may reserve the right to individually advocate on behalf of their registry, organization or providers and patients, even if their position differs from that of other network members. Participants may want the freedom to apply together (all members or a subset thereof) for public or private funding support. Others, especially federal officials and regulators, may limit themselves to an ex-officio or observer role while still participating in and learning from the network.

Governance

Although a voluntary self-governing network of registries, such as the NQRN, has considerable latitude in how it operates, network founders would be wise to solicit input from other stakeholders as they establish initial governance, formulate a strategic plan, and initiate operations. In the absence of existing practices, some networks write a charter, adopt bylaws, and begin to operate with the intent of reviewing initial practices, policies and procedures. Early questions for the founders to consider include whether the members are organizations or individuals, what expertise among advisory board and steering committee members is necessary and desirable to ensure network success, how long members will be asked to serve, and whether decisions will be made by voting or if full consensus will be required. The roles, responsibilities, and terms of officers and other governing body members should be established with succession and continuity in mind. Inaugural board members are often appointed, whereas elections may become the preferred approach once a network has matured.

A network established with private or public funds usually has less latitude as it begins operations than a voluntary network. It is critical that the governing body and professional staff have a clear understanding of the funder's expectations and requirements with respect to membership, accountability, meetings (open or closed), reporting, and other policies and procedures. A network receiving federal funds may elect to operate under the auspices of an umbrella organization such as a university or professional organization that already has the necessary systems and controls in place to ensure compliance with agency requirements. Establishing such systems can be a consuming and complicated task for a fledgling organization.

Membership Rules and Expectations

Registry network founders generally know the individuals or organizations they wish to invite to become members. If a network anticipates a dependence on volunteer time and voluntary financial contributions, the invitation to join must explicitly state those expectations. The founders will be well advised to have done some early "scouting" of potential members and have confidence that those invited will want to join and will be able to fulfill the stated requirements. Organizations may establish different membership categories and accompanying expectations to ensure that there is broad representation across desired stakeholder groups. For example, registry networks may establish lower membership fees or participation expectations for non-profit patient and consumer groups as compared to scientific partners or for-profit enterprises. Within membership categories, fees and expectations may also be based on organizational size, operating budget, and/or provision of non-monetary contributions such as time, space and contributors.

Member Recruitment

A critical role for any network is to recruit members who will contribute in ways that fulfill the mission, goals and objectives of the organization. In the case of a registry network, this may include experts in a clinical domain such as cancer or heart disease, registry operations, patient and consumer engagement, legal matters and other key areas. As a registry network is being formed, it will be important to state the value proposition for each stakeholder group that is recruited. While many individuals and organizations are altruistic, each is likely to be considering the unstated question, "What's in it for me?" Failure to be able to articulate the value proposition for each member may result in a potential member deciding not to join, to only watch from the sidelines, or to adopt a passive approach to membership at a time when action is needed. Additional considerations include desired registry characteristics (e.g., focus, capture rates, data validation strategy).

Staff Support and Succession Planning

The scope, funding, and governance model of a registry network determine whether the organization operates informally using volunteers, hires professional management, or engages an association management company to support operations. The network's scope, size, budget, and funding sources (federal, private, other) determine the degree to which professional managers are needed to support its activities. Just as governing bodies need succession planning, so do managers. The best managers and boards begin succession planning as soon as they begin work. In doing so, they recognize the evolving requirements for network success, develop the habit of identifying talented people, and create opportunities for professional growth for promising professionals they want to recruit or retain.

Infrastructure, Communications, Monitoring Use and Value

As communities, registry networks thrive on communication. Registry networks exist across organizational boundaries and are typically sustained by regular reaffirmation of the goals of the network and progress towards those goals. Registry networks may choose to host conferences or side-meetings alongside existing conferences to build social connections, share updates, and enhance knowledge sharing. Newsletters, webinars, case studies, and blogs can also be used to

sustain the community. Registry networks also benefit from shared work. As exemplified with NQRN, centralized resources within the network, such as project managers, can be invaluable to support cross-network efforts as the priorities of individual members can easily be shifted towards their primary organizational responsibilities. Teleconferencing and videoconferencing technology can effectively enable cross-organizational teams, alongside file sharing and online productively platforms.

Registry network activities may also include creating technical infrastructure for interoperability among the network's registries and with other health data systems. Whether the scope of these activities is restricted to governance, e.g., the convening of working groups to create consensus standards, or includes the formation of a technical infrastructure for information exchange, a network's ability to create infrastructure is dependent on the relationships created and maintained through the communication channels of the network. When technical data-sharing infrastructure is to be built, considerations include network structure (i.e., centralized vs. a distributed data network), and the use of standardized data use and business associate agreements.

Large, more general networks of registries are well-positioned to build technical infrastructure due to their multi-stakeholder membership. These networks can serve as umbrella groups for organizations with specific clinical or other focus areas, enabling the creation of true consensus standards that represent health care as a whole. For example, the International Registry for Health and Lung Transplantation (IRHLT) began in 1983 and now captures longitudinal follow-up data on approximately two-thirds of thoracic transplants across the globe.[16] These data provide clinicians and other stakeholders with a comprehensive view of current clinical practice and associated patient outcomes that can be used to advise best practice. Vendors and other organizations that implement technical standards are motivated to do so when those standards reflect a broad consensus. In the absence of a collaborative network to foster harmonization, organizations typically direct their individual requests of vendors to implement organization-developed standards, which often define the same clinical concepts as other standards do, with minor differences.

FUNDING AND SUSTAINING A REGISTRY NETWORK

Planning for the funding and sustainability of a registry network depends very much on the network's purpose and goals. It is critical to understand early on and continually assess the needs of network participants and other stakeholders so that solicitation efforts and resource utilization are optimized to meet those needs. Although there may be overlap, network funding strategies can be divided into those that respond to a need identified by an external group (market-responsive) and those based on a previously unrecognized or unmet need identified by the founders. In the latter case, the founders may gain the support of funders by educating them and convincing them of that need (market-creation). Sustainability strategies should be expected to evolve as a network matures and has more value to offer to supporters.

Market-responsive funding results when, as examples, a regulatory agency, product manufacturer, health plan or system, patient or consumer group, or a funder of research (public, private, foundation), decides that a registry network will best address a problem that concerns them. A network solution may be preferred or necessary to conduct surveillance across different jurisdictions, geographies or populations, especially if no existing single registry holds enough

data or individual records to address problems such as disease outbreaks, rare diseases, or medical device defects in a timely manner. For example, depending on its goal, scope and robustness, registry networks can be very appealing to regulatory agencies, especially if the network is able to increase power to assess long-term safety and effectiveness data on a broad patient population. Psonet is an international population-based network of registries with psoriasis or psoriatic arthritis patients taking a systemic agent. Funded by the Italian Drug Agency and European Academy of Dermatovenereology, Psonet aims to improve surveillance of psoriasis and psoriatic arthritis in Europe. A common protocol was written to support the collection of a common set of variables to allow for combining data across registries resulting in a larger, more diverse patient population.[17, 18]

Financial support for a registry network can come from a variety of sources, including from specialty societies (e.g., American College of Cardiology, National Cardiovascular Registry and Society for Thoracic Surgery collaboration), health systems (High Value Healthcare Collaborative), research organizations that sponsor comparative effectiveness research (e.g., PCORI, AHRQ), or industry. In these circumstances, the societies or health systems have patient data, but external funding support of a network of data holders is needed to achieve the semantic interoperability necessary for data to be exchanged across systems, aggregated and analyzed. Network sustainability in both instances is possible, although not guaranteed, because participants are responding to an identified market need.

Registry networks may also be created by established registry stewards who are frequently sought out by new registry developers for guidance and solutions to common startup challenges such as vendor selection, privacy and security policies, business associate agreements and the "nuts and bolts" of running a registry. In this instance, new registry developers need to learn, and established stewards seek a more efficient means of sharing leading practices. Such a network, although it may depend greatly on volunteer time and in-kind support, may begin to operate with the support of an organizational sponsor, later soliciting grants, establishing dues, and charging registration fees to support its work. One example of this approach is the NQRN.

Market creation strategies for registry networks are similar to those pursued by individual registries. Once a network is established and its mission and goals have been established, its participants may solicit funding to address research questions that they have identified. A network, if it becomes a platform for data sharing, aggregation and analysis, may receive compensation for providing de-identified aggregated data to parties seeking to meet their business needs without building their own network or data warehouse. It is at this point that a network of registries may itself become sustainable while also contributing to the sustainability of its component registries.

CONSIDERATIONS FOR INTERNATIONAL NETWORKS

Although most registry collaboration to date has been national, a growing number of registries are working across countries to harmonize standards, share data, and contribute to research and development of leading practices. International collaboration offers several advantages: for pharmacovigilance, a pooled international sample can quicken the discovery of problematic drugs or devices; for research, data pooled across multiple countries can lead to more generalizable evidence; and for professional and institutional learning, a broader range of

practice settings can capture higher variation in performance and more opportunity for discovering and analyzing outliers.

International registry networks are not without their challenges. The data harmonization required for surveillance, pooled research, or comparisons must build on consensus that bridges health systems, reimbursement structures, and cultures, often with different stakeholders holding decision-power in each system. A pragmatic approach that starts with the most interested countries and their key decision makers is essential to get started. Beyond harmonization, actual sharing of data is also made more difficult by divergent national rules. Privacy laws, for example, vary by country and sometimes by region, allowing greater or lesser ease global aggregation or de-identified patient-level data. Again, an approach selecting those countries with data privacy laws that are facilitative of international collaboration is suggested. Operationally, running an international registry network is also challenging. Communication, for example, relies more heavily on video and teleconferences that must span a broad range of global time zones and require a single common language or use of simultaneous translation. But most international registry networks have managed to organize regular, typically annual, in-person meetings to facilitate relationship building and counterbalance reliance on virtual meetings, although the cost burden for attendees or funders of these meetings can be significant. Despite these challenges, successful international registry networks have and will continue to develop. We share four examples below.

International Consortium of Orthopedic Registries (ICOR)

The ICOR is a US FDA-sponsored initiative that is quickly evolving into a public-private partnership, with over 30 registries participating worldwide.[19] The purpose of ICOR is to facilitate and enhance inter-registry collaboration by providing of a supportive infrastructure and developing a distributed data network that uses innovative approaches to analyze the data.

Launched in 2011, the ICOR initiative addresses gaps in evidence and data related to medical implants. The network is composed of more than 70 stakeholders and over 30 orthopedic registries, representing 14 nations. ICOR is implementing a worldwide surveillance system and a meaningful UDI system with two important goals: 1) completing demonstration projects of research and surveillance for hip and knee implants, and 2) harmonizing worldwide implant data through creation of an implant library. Numerous papers have been published based on ICOR collaboration.

International Consortium of Cardiovascular Registries (ICCR)

The successes of ICOR are being replicated in cardiac and vascular fields by the International Consortium of Cardiovascular Registries (ICCR) with two major initiatives of MDEpiNet: The International Consortium of Transcatheter Valve Registries (ICTVR) and The International Consortium of Vascular Registries (ICVR).[20]

These two initiatives provide a collaborative platform through which registries and other stakeholders around the world can begin a dialogue, discuss data challenges and develop aggregate level innovative analytic methods for conducting worldwide studies. An additional goal is to work with stakeholders, such as manufacturers and regulators, to improve their understanding of the safety and effectiveness of aortic valves and vascular devices designed to be

implanted percutaneously. For example, the ICTVR and ICVR initiatives are creating one of the largest networks that includes registries and academic centers with the research and clinical capabilities needed to address the most important issues related to cardiovascular device surveillance.

International Medical Device Regulators Forum (IMDRF) Registry Working Group

To address the challenges in international regulatory approaches to registry-based evidence, the International Medical Device Regulators Forum (IMDRF) created the Registry Working Group to develop white papers detailing the essential principles related to: [21]

> Linkage of electronic data from patient, device and outcome registries and related data repositories or identifiers (such as UDIs), including the principles of data access, security, informatics formats, governance and other key areas related to global regulatory applications for medical device evaluation; and
>
> Optimal methodologies for analysis of heterogeneous data sources applied to medical device safety, signal detection, performance and reliability.

The IMDRF's vision is to provide guidance to stakeholders that will enable greater international regulatory collaborations among those that strongly rely on registries and collaborative distributed data consortia.

International Consortium for Health Outcomes Measurement (ICHOM)

ICHOM is another effort that functions partially as a registry network. Its stated goals are to enable value-based health care by defining and driving adoption and reporting of outcome measures that matter to patients.[22] The core of ICHOM's work has been to align registry and institutional outcome measurement efforts internationally around a common set of clinical outcomes and case-mix factors per condition, called "Standard Sets." ICHOM has been successful in producing twelve of these Sets and continues to add more each year. These standards are published in peer-reviewed journals and are openly available for public use without restriction. ICHOM's work has been recognized by the Organization for Economic Cooperation and Development as an example of defining more meaningful outcome measures than those typically collected today.

In addition to defining standards, ICHOM supports implementation of outcomes measurement and has plans to support benchmarking across member institutions internationally. Its work is supported by a variety of public and private partners.

CONCLUSION

Given the increasing use of patient registries as sources of health information,[1,23] the expectations of registry stewards and users of registry information have risen considerably in a relatively short span of time. Registry networks have responded by forming communities of registry practice in the US and internationally.

While registry networks differ in their focus and operational model, all strive to increase the reach and utility of registries through the sharing of knowledge, and in some networks, infrastructure including data standards. Registry networks facilitate knowledge sharing and creation, oversee the development of standards for improved interoperability, and create professional communities of registry practice. Their success hinges upon there being awareness of network activities and resources, and on encouraging all who are interested in registries to get involved and take advantage of what networks of registries have to offer.

When compared to other organizations in health care, such as professional societies, registry networks are still in an early stage of development. Anecdotal evidence, such as steadily rising attendance at registry network conferences suggests that registry networks are providing a valuable service to the patient registry enterprise. Given the increasing number of registries and patient records contained therein, registry networks are in a strong position to promote data exchange and aggregation, develop data standards, lower barriers to registry use, and increase adoption. As registries diversify and increase in numbers, the authors recommend further research to measure the impact registry network activities have on the broad health care improvement objectives.

Ultimately, the strongest argument for these networks comes from the engagement of the users and the resulting strong communities and work product, including research projects facilitated by the networks. Energized participation, international growth and increased reach among networks such as those described in the examples and case studies contained within this chapter illustrate the utility of registry networks to all involved.

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