UNDERSTANDING PATIENT-CENTRICITY:
A BEGINNER’S GUIDE

This guide highlights key resources for people interested in learning more about ways to engage patients as partners in biomedical research, medical product development, regulatory decision-making, and healthcare delivery.

The resources highlighted here – and many more – are available online at FasterCures’ Patient Engagement Resource Library:

http://www.fastercures.org/programs/patients-count/patient-engagement-library/
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From passengers to co-pilots: Patient roles expand

Margaret Anderson* and K. Kimberly McCleary*

The premier position of medical research on the U.S. national policy agenda offers an unprecedented opportunity to advance the science of patient input and marks a turning point in the evolution of patient engagement.

For most of history, patients have been the passive recipients of medical care with little or no role in research. Even as research subjects, patients were not required to give informed consent prior to adoption of the Nuremberg Code in 1947. Since then, patient participation has expanded dramatically, and today, opportunities abound to serve as active partners in defining and prioritizing research questions and solutions. As digital strategist Leonard Kish declared in 2012, “If patient engagement were a drug, it would be the blockbuster drug of the century and malpractice not to use it” (1).

Patient engagement offers the promise of advancing more personal and efficacious medical products faster than the typical ~15-year discovery-to-market timeline (2). Here, we explore the early foundations of patient engagement (table S1), where it occurs in the drug-development pipeline, the power of recent policy initiatives, and prospects for success in improving health outcomes.

FROM SIDELINES TO CENTER COURT

Early in the last century, patients began to mobilize to accelerate research for particular conditions. The March of Dimes, founded by President Franklin D. Roosevelt in 1938 to expand polio research, is one of the first examples of philanthropy directed at finding treatments and cures. Research supported by individuals through the March of Dimes led to development of the “iron lung” and a successful vaccine. Until recently, this case was an outlier, considering that until the 1973 Patient Bill of Rights was adopted by the American Hospital Association, patients did not necessarily expect to be told their diagnosis, much less have a voice in determining their care plan.

Even in recent years, patients didn’t always express their own preferences and expectations for care, deferring to choices the doctor deemed best.

The HIV/AIDS movement catapulted patient needs to the forefront of research and created the force for change that dramatically altered regulatory approval processes at the U.S. Food and Drug Administration (FDA), funding formulas and emphasis at the U.S. National Institutes of Health (NIH), and the path forward for disease organizations. People affected by HIV rallied together and created a movement that demanded change and got results (3): from the creation of Gay Men’s Health Crisis in New York in 1982 and the AIDS Coalition to Unleash Power in 1987, to the National Institute of Allergy and Infectious Diseases’ (NIAID’s) formation of the largest HIV clinical trials network in the world, to protests at both NIH and FDA, to passage of the Ryan White Comprehensive AIDS Resources Emergency Act in 1990.

The HIV/AIDS model continues to provide a roadmap followed by other patient communities, demonstrating that it is not enough to question the status quo; you have to do the hard work of presenting well-founded alternatives. As Anthony Fauci, director of NIAID, noted at a FasterCures event in 2011, “If you really want to shake cages you have to be persistent. This is very different than coming to a meeting once a year. We knew the HIV/AIDS activists weren’t going away.”

Today, the role of patients as partners permeates the R&D landscape, extending far beyond the traditional model of funding basic science through donations. Spurred on by the increase of entrepreneurial philanthropy and the proliferation of technology that connects and empowers patient communities, patient influence on decision-making is increasing. In particular, the venture philanthropy drug-development model pioneered by the Cystic Fibrosis Foundation—which led to the codevelopment, with Vertex Pharmaceuticals, of Kalydeco, the first disease-modifying treatment aimed at the genetic cause of cystic fibrosis—is gaining steam and altering the landscape of disease research and cross-sector collaboration.
The U.S. federal government recently initiated a series of efforts to more formally incorporate patient input into its decision-making processes. Efforts and entities have jumpstarted activities across the medical products industry to elicit and include patient perspectives along the full range of clinical development, such as the Patient-Centered Outcomes Research Institute (PCORI), established through the Affordable Care Act in 2010; the Patient-Focused Drug Development initiative at the FDA, mandated under the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2012; and a Patient Preference Initiative launched by the FDA’s Center for Devices and Radiologic Health (CDRH) in 2013.

POLICY PROSPECTS CONVERGE

The past year has ushered in a “perfect storm” of policy initiatives in biomedical research and opportunities for patient engagement. In April 2014, the chairman of the U.S. House of Representatives Energy and Commerce Committee, Fred Upton, partnered with Rep. Diana DeGette to launch the 21st Century Cures Initiative with a series of hearings and roundtable discussions around the country. These listening sessions solicited unprecedented public input about how Congress could help “accelerate the discovery, development, and delivery of promising new therapies and cures for patients and maintain our nation’s standing as the biomedical-innovation capital of the world” (4). In recognition of the committee’s patient-centered emphasis, Title 1 of the first draft of proposals—released on 27 January 2015—was titled “Putting patients first by incorporating their perspectives into the regulatory process and addressing unmet medical needs” (5). The proposals also include patient representatives in nearly every council, panel, advisory board, and body that would be created under the act.

Two days later, a companion effort was announced in the U.S. Senate under the Health, Education, Labor, and Pensions Committee entitled “Innovation for healthier Americans: Identifying opportunities for meaningful reform to our nation’s medical product discovery and development” (6). It highlighted disease registries sponsored by nonprofit organizations as a “way for patients with a specific disease to signal their potential willingness to participate in research on that disease” and public-private partnerships as a means to “bring academia, government, patients, industry, and others together to solve complex scientific and process questions about medical product development.”

The next day, the executive branch added its voice to the chorus when U.S. President Barack Obama announced the Precision Medicine Initiative, a “moon shot” type project that includes the building of a cohort of 1 million engaged participants to contribute data and insights over many years, enabling researchers to better understand how genomic variations and other health factors affect disease development. The president’s invitation outlined a collaborative approach to identifying superior treatments and prevention strategies: “In order for us to realize [the Initiative’s] potential, I’m asking more hospitals and researchers and privacy experts to join us in this effort. I’m asking entrepreneurs and nonprofits to help us create tools that give patients the chance to get involved as well. Because we want every American ultimately to be able to securely access and analyze their own health data, so that they can make the best decisions for themselves and for their families.”

Negotiations for the sixth authorization of PDUFA will begin this fall among the FDA, Congress, and the biopharmaceutical industry. For the second time, patient representatives will have an active role in the process, although not quite full negotiating status, because user fees are paid by industry to FDA with oversight from Congress. Most recognize that patients’ influence and the open dialogue among stakeholders under the 21st Century Cures initiative has served as a dress rehearsal—in particular, these new actors are given opportunities to contribute to the hashing out of ideas, alignment of goals, and vetting of approaches to meeting those goals.

For example, FasterCures, the Biotechnology Industry Organization, and Eli Lilly & Co. developed independent yet complementary proposals for Congress as part of 21st Century Cures to authorize a public-private partnership dedicated to developing tools and methods to support science-based approaches for collecting patient input. The bipartisan discussion draft includes such a body, the “Council for 21st Century Cures,” whose mandate is to “accelerate the discovery, development, and delivery in the United States of innovative cures, treatments, and preventive measures for patients” (7).

THE SCIENCE OF PATIENT INPUT

Accompanying acceptance of the need to integrate patient perspectives is an increase in the demand for research-based methods and tools to measure the effectiveness of incorporating patient input into the system and, ultimately, its impact on patient health. What began as an extension of patient advocacy has evolved into an emerging scientific discipline aimed at understanding and incorporating patient needs into the processes of developing, regulating, and delivering new therapies.

A compelling “call to action” authored by thought leaders from international patient organizations and pharmaceutical companies describes the gap that must be closed: “Despite the increasing number and scope of patient-involvement initiatives, there is no accepted master framework for systematic patient involvement in industry-led medicines research and development, regulatory review, or market access decisions…. It is essential that all stakeholders participate to drive adoption and implementation of the framework and to ensure that patients and their needs are embedded at the heart of medicines development and lifecycle management” (8). Meetings convened in the first quarter of 2015 by the Clinical Trials Transformation Initiative, National Health Council, University of Maryland’s Center of Excellence for Regulatory Science Innovation, and PCORI have provided opportunities to share emerging practices and lessons learned.

For medical devices and biologics, the call to action was answered by the FDA’s CDRH and Center for Biologics Evaluation and Research on 13 May 2015, with a draft guidance entitled “Patient preference information—Submission, review in PMAs, HDE applications, and de novo requests, and inclusion in device labeling” (9). The guidance outlines “qualities” of patient preference information acceptable for regulatory purposes and directions for submitting such data to the agency. On the same date, the Medical Device Innovation Consortium (MDIC), a public-private partnership, released its “Framework and catalog of methods for incorporating information on patient preferences regarding benefit and risk into the regulatory assessments of new medical technologies” (10). The catalog captures methods of assessing patient preference that are adapted from health economics, outcomes research, epidemiology, social sciences, and marketing sciences. Although compiled for medical technology development, the catalog is expected to be highly transferable to the development of pharmaceuticals and biologics as well.
For drugs, the groundwork has been laid by researchers who participated in early organized efforts to develop structured assessment of benefits and risks, including the Benefit-Risk Assessment Team convened by the Pharmaceutical Research and Manufacturers of America, the Centre for Innovation in Regulatory Sciences, and special interest groups within the International Society for Pharmacoeconomics and Outcomes Research. FasterCures’s Benefit-Risk Advisory Council comprises many of these experts along with patient leaders and provided the faculty for a one-day “benefit-risk boot camp” on this topic in September 2014.

On a parallel track, patient organizations have piloted new approaches to meet the demand for data that supplement personal testimony and participation of individual advocates as patient representatives in decision-making bodies. Parent Project Muscular Dystrophy (PPMD) demonstrated leadership in sponsoring a benefit-risk-preference study among parents of boys with the rare but fatal form of muscular dystrophy known as Duchenne. PPMD published the results, held a policy forum that attracted 17 FDA officials, and organized a community-based drafting of a regulatory guidance for drug development. The FDA opened a public docket to receive comments on PPMD’s guidance document and is expected to issue its version in coming weeks. Other patient organizations are following PPMD’s model—seeking academic partners, building patient registries, and educating their patient communities about new opportunities to reshape treatment pipelines and care delivery.

ACCOUNTABILITY ALL AROUND

To fulfill the prediction that patient engagement will be the blockbuster drug of the century, we offer five observations to guide the path forward:

• There is a need to expand the capacity of all participants—industry, academia, government, and patient organizations—to engage patients in biomedical research, medical product development, regulatory decision-making, and health care delivery. We must understand the full range of patient experiences and expectations across a representative cross section of individuals with a particular diagnosis or collection of conditions.
• Developing appropriate, scalable, sustainable methods and practices will require collaboration, experimentation, coordination, and transparency. Multiple types of expertise will be needed, and adoption will be highly iterative and require extreme focus on the goal: improved patient outcomes.
• It’s too early to tout emerging practices as being “best,” and standards are likely to change rapidly. This may challenge resources and introduce new sources of uncertainty, especially at first. We may all need to tolerate more turbulence in the ascent, with our seatbelts fastened, before we reach a comfortable cruising altitude.
• Different diseases, disease communities, stages of disease, and stages of life might warrant distinct approaches to patient engagement and integration of patient input. The role of the caregiver and family members is clear in pediatric disorders, disabilities, and conditions associated with aging such as Alzheimer’s disease; individuals who surround the patients also should be factored into our understanding of unmet medical needs in mental-health conditions such as addiction and schizophrenia.
• Patients are found not only in conventional settings, such as disease-specific foundations and clinics, but also living their lives as members of social media networks and local community organizations. We need to rethink and expand the settings in which we recruit and equip individuals to be informed participants in research and care activities. This will take time to implement.

Medical products and interventions that begin with a solid understanding of patient needs and expectations promise better outcomes for the individual, families, communities, our nation, and global health. More than 75 years ago, patient engagement contributed to arresting the polio epidemic. The HIV/AIDS activists charted a path forward for the way patients can engage in all aspects of research and delivery of care under stunningly difficult circumstances. With advances in the tools we have for conducting science and communication, think of the potential we have to capitalize on the blockbuster that is patient engagement. The possibilities are endless.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/7/291/291fs25/DC1

Table S1. Patient engagement timeline.

REFERENCES AND NOTES

10. MDIC patient-centered benefit-risk project report: A framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology (MDIC, St. Louis Park, Minnesota, 2015).

10.1126/scitranslmed.aac6023

Patient Group Engagement Across the Clinical Trial Continuum

Building a model to evaluate impact

<table>
<thead>
<tr>
<th>Pre-Discovery</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2/3</th>
<th>FDA review &amp; approval</th>
<th>PAS/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interest of research question to patient community</td>
<td>• Network recruitment / outreach</td>
<td>• Direct funding and fund raising for trial operations support</td>
<td>• Direct funding and fund raising for research or product development</td>
<td>• Serve on FDA advisory committees</td>
<td>• Serve on post-market surveillance initiatives</td>
</tr>
<tr>
<td>• Provide data on unmet need and therapeutic burden</td>
<td>• Direct funding and fund raising for research or product development</td>
<td>• Network recruitment / outreach</td>
<td>• Infrastructure support</td>
<td>• Provide testimony at FDA hearings</td>
<td>• Provide feedback on how the patient community views results</td>
</tr>
<tr>
<td>• Direct funding and fund raising for research or product development</td>
<td>• Direct funding and fund raising for research or product development</td>
<td>• Network recruitment / outreach</td>
<td>• Provide input on study design (barriers to participation)</td>
<td>• Feedback on meaningful clinical endpoints</td>
<td>• Help return study results to participants</td>
</tr>
<tr>
<td>• Understanding mechanisms of action relevant to disease and symptom burden</td>
<td>• Support trial awareness and recruitment</td>
<td>• Peer advocate during informed consent procedure</td>
<td>• Support trial awareness and recruitment</td>
<td>• Co-present results</td>
<td>• Write newsletter articles or blog about results</td>
</tr>
</tbody>
</table>

*Adapted from Parkinson’s Disease Foundation materials for CTTI’s Patient Groups & Clinical Trials Project
A LIFECYCLE APPROACH TO FDA’S STRUCTURED BENEFIT-RISK ASSESSMENT FRAMEWORK

This White Paper was developed by the Structured Benefit-Risk Working Group of the Biotechnology Industry Organization (BIO). The paper identifies considerations for biopharmaceutical companies who choose to use FDA’s Structured Benefit-Risk Assessment Framework earlier and more broadly throughout a product’s lifecycle as a mechanism to both solicit patient perspectives on areas of unmet medical need and assess patient preferences, and to align with FDA on key benefit-risk considerations.
Opportunities for Structured Benefit/Risk Assessment during Drug Development

Assess patient group views on:
1. Analysis of Condition
2. Treatment Options

Share clinical data confidentially with patient groups and seek feedback on:
3. Benefit
4. Risk
5. Risk Management

Provide Advisory Committee Members with sB/R in briefing document to frame the meeting

Phase 1
- Pre-IND Mtg
- Align with FDA on Condition & Treatment Options

Phase 2
- EoP1 Mtg
- Sponsor submits sB/R to FDA align on B/R considerations

Phase 3
- EoP2 Mtg
- Sponsor submits sB/R with NDA/BLA

FDA Review
- Pre-NDA
- Late-Cycle Mtg

Phase 4
- FDA Posts Final sB/R
The PCORI Engagement Rubric: Promising Practices for Partnering in Research

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Advisory Panel on Patient Engagement (2013 inaugural panel):
Tandrea S. Hilliard, PhD, MPH4
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ABSTRACT

PURPOSE Engaging patients, caregivers, and other health care stakeholders as partners in planning, conducting, and disseminating research is a promising way to improve clinical decision making and outcomes. Many researchers, patients, and other stakeholders, however, lack clarity about when and how to engage as partners within the clinical research process. To address the need for guidance on creating meaningful stakeholder partnerships in patient-centered clinical comparative effectiveness research, the Patient-Centered Outcomes Research Institute (PCORI) developed the PCORI Engagement Rubric (Rubric).

METHODS PCORI developed the Rubric drawing from a synthesis of the literature, a qualitative study with patients, a targeted review of engagement plans from PCORI-funded project applications, and a moderated discussion and review with PCORI’s Advisory Panel on Patient Engagement.

RESULTS The Rubric provides a framework for operationalizing engagement to incorporate patients and other stakeholders in all phases of research. It includes: principles of engagement; definitions of stakeholder types; key considerations for planning, conducting, and disseminating engaged research; potential engagement activities; and examples of promising practices from PCORI-funded projects.

CONCLUSIONS PCORI designed the Rubric to illustrate opportunities for engagement to researchers interested in applying for PCORI funding and to patients and other stakeholders interested in greater involvement in research. By encouraging PCORI applicants, awardees, and others to apply the rubric, PCORI hopes to shift the research paradigm from one of conducting research on patients as subjects to a pursuit carried out in collaboration with patients and other stakeholders to better reflect the values, preferences, and outcomes that matter to the patient community.


INTRODUCTION

Engaging patients and other stakeholders as partners in research increasingly is recognized as a promising approach to generate evidence that is trusted, meaningful, and useful to clinicians, patients, and their families when making health care decisions. The evidence base for stakeholder engagement in clinical research is growing; it shows that engagement is associated with increased recruitment and retention of study populations; more patient-centered and culturally appropriate methods; and greater relevance of research questions and outcome measures.1,3

The Patient-Centered Outcomes Research Institute: Fostering Engaged Research

The Patient-Centered Outcomes Research Institute (PCORI), authorized and funded in the 2010 Patient Protection and Affordable Care Act, funds comparative clinical effectiveness research for the purpose of generating evidence that helps patients and their health care providers better understand their diagnostic and treatment options and make more informed clinical decisions.4 Active and sustained engagement of patients and other...
stakeholders in setting research priorities, reviewing research applications for funding, designing, conducting, and disseminating research, and evaluating PCORI’s progress are all central to PCORI’s mission.

PCORI is deeply committed to patient-centeredness and patient, caregiver, and other stakeholder engagement as organizing principles guiding its governance and operations. These commitments build on the rich history of partnership between traditional powerholders (eg, government officials, scientific, or health professionals) and the intended beneficiaries of programs and services to better understand and address key issues facing communities.5,6

Community-oriented approaches to conducting health research emerged from seminal movements such as the use of “action research,” developed by Kurt Lewin in the 1940s, and its derivatives: participatory action research and community-based participatory research. These approaches were critical in advancing the role of patients and communities from “subjects” or “objects” of research to empowered “co-experts” throughout the research process.7-10 The active inclusion of empowered participants in the generation of evidence and determination of actions for change drives participatory action research and community-based participatory research approaches.11 By illustrating the potential of patient and other stakeholder involvement to improve the relevance and use of research to guide patient-centered care, these movements helped lay the foundation for PCORI’s efforts to advance research partnerships.12,13

Since its earliest application cycles, PCORI provided guidance and resources to support researchers in conducting scientifically rigorous patient-centered and stakeholder-engaged research (Figure 1). The “PCORI Methodology Standards” specify expectations for patient-centeredness and 10 other topic areas to assist researchers in developing methodologically rigorous clinical effectiveness research.14 PCORI’s “Merit Review Criteria” for research applications also serves as a resource for researchers and reviewers in assessing, among other things, each project’s patient-centeredness and engagement plans.15

During PCORI’s earliest funding cycles, however, many researchers interested in applying for PCORI funding expressed uncertainty about how to operationalize engagement of patient and stakeholder partners as referenced in the Methodology Standards and review criteria. Similarly, patients and other stakeholders were seeking clarity on their role as partners in patient-centered clinical effectiveness research. Using adult learning principles, PCORI developed a framework for operationalizing stakeholder engagement in research that highlights promising and innovative examples from its funded projects. This article describes the development of the framework, hereafter called the PCORI Engagement Rubric (Rubric), and its intended application in research practice.

**APPROACH TO DEVELOPING THE RUBRIC**

**PCORI’s Early Foundational Work That Informed the Rubric’s Development**

PCORI’s early efforts to define and advance understanding of patient and other stakeholder engagement in research focused on guiding principles, which laid the groundwork for the development of the Rubric. In 2011, PCORI commissioned 2 systematic literature reviews to synthesize the evidence of how to engage patients in research and identify the benefits, harms, and barriers associated with engagement. In addition, PCORI funded a qualitative study using focus groups of patients from hard-to-reach populations (ie, those that typically do not participate in research due to cultural, socioeconomic, physical, or cognitive barriers) and interviews with clinicians or others caring for these patients.1,2,16 This work led to suggestions for 10 standards for engaging hard-to-reach patient populations.

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**Figure 1. PCORI guidance for patient-centeredness and engagement in research.**

**PCORI’s Methodology Standards: Patient-Centeredness (PC)**
- PC1. Stakeholder Representation: Engage people representing the population of interest and other relevant stakeholder in ways that are appropriate and necessary in a given research context.
- PC2. Study Participant Representation: Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants.
- PC3. Patient-reported Outcomes: Use patient-reported outcomes when patients or people at risk of a condition are the best source of information.
- PC4. Dissemination and Implementation: Support patient involvement in dissemination and implementation of study results.

**PCORI’s Merit Review Criteria**
- Patient-centeredness: Applications should demonstrate that the study focuses on improving patient-centered outcomes and employs a patient-centered research design (i.e., one that is informed or endorsed by patients).
- Patient and stakeholder engagement: Applications should demonstrate the engagement of relevant stakeholders (eg, patients, caregivers, clinicians, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, policy makers, and training institutions) in the conduct of the study.

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Note: The criteria have been refined over time. This figure reflects the PCORI criteria as of publication of this manuscript.
and the establishment of Patient Centered Outcomes Research (PCOR) Engagement Principles to guide its funded research (Figure 2).

**Phases of Development**

The Rubric was developed in 2013 following an evidence-driven, iterative consensus-building process falling roughly into 3 phases. The first phase consisted of a targeted review of research applications to identify exemplary patient engagement practices to guide development of a draft Rubric. Phase 2 included moderated small-group discussions with PCORI’s Advisory Panel on Patient Engagement to review and refine the draft Rubric. The Advisory Panel on Patient Engagement is a standing panel comprised of 21 patient, caregiver, patient advocate, industry, clinician, and researcher representatives created to ensure the highest standards of engagement and a culture of patient-centeredness in all aspects of PCORI’s work. In the final development phase, PCORI senior engagement staff reviewed the Advisory Panel’s recommendations, then refined the Rubric and obtained feedback from PCORI leadership. On an ongoing basis, PCORI updates the Rubric as advancements in engagement practices are identified.

**Targeted Review of Engagement Plans**

PCORI staff conducted a targeted review of all 150 funded research project applications from PCORI’s first 3 award cycles to identify applications with novel and promising engagement activities that could potentially direct the study to be more patient-centered. PCORI’s early focus in developing the Rubric was on engagement of patients, family members, caregivers, and their advocacy organizations. Of particular interest were engagement practices that exemplified the PCOR Engagement Principles. Two senior engagement experts (S.S. and S.S.) developed an abstraction template for the review and independently categorized the engagement plans by research focus area, engagement activities, research phase(s), stakeholder characteristics, and potential effects of engagement activities on the study. The engagement experts then met to review and reach consensus on the data and collaboratively classify the collected engagement activities within themes, which provided the structure for the initial framework. Subsequently, PCORI mapped each engagement activity in the draft Rubric back to the PCORI Methodology Standards and the PCOR Engagement Principles to ensure consistency.

**Moderated Working Group Discussion with Advisory Panel**

PCORI staff shared the initial draft with the Advisory Panel on Patient Engagement during in-person moderated working group discussions. PCORI facilitators led the discussions. PCORI divided the Advisory Panel into 7 breakout groups, each with diverse representation. Using the Rubric as a guide, each group evaluated engagement plans from the same 3 research project applications based on their perceptions of the meaningfulness of the proposed engagement activities. In doing so, the Advisory Panel assessed the Rubric itself, as well as its potential for integration into the merit review process. PCORI engagement experts jointly reviewed the discussion notes from the 7 breakout groups and debriefing notes and then summarized salient themes and patterns related to the Advisory Panel’s perceptions of the Rubric. PCORI then revised the Rubric by: (1) separating descriptions of engagement practices that exemplified the PCOR Engagement Principles under a set of “global principles” instead of sprinkling examples throughout the Rubric; (2) categorizing engagement activities into 3 broad categories of study phases (ie, planning, conduct, and dissemination); and (3) including as many concrete examples as possible of engagement activities from successful projects to illustrate ways to engage stakeholders throughout the 3 study phases.

**PCORI Internal Expert Review and Ongoing Revisions**

PCORI’s scientific program directors then reviewed the revised Rubric and recommended specific changes, including that prescriptive language be modified. PCORI’s Board Committee on Outreach, Engagement and Communication approved the Rubric and supported

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**Figure 2. PCOR engagement principles.**

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reciprocal relationships</td>
<td>Including patient and stakeholder partners as key personnel, roles and decision making are defined collaboratively</td>
</tr>
<tr>
<td>Partnerships</td>
<td>Fair compensation, reasonable and thoughtful requests for time, committed to diversity across all activities, committed to cultural competence</td>
</tr>
<tr>
<td>Co-learning</td>
<td>Reciprocal relationships, researchers help patients and other stakeholders to understand the research process, patient advocate, industry, clinician, and researcher representatives</td>
</tr>
<tr>
<td>Inclusive decision making</td>
<td>Information is readily shared, commitment to open and honest communication</td>
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**Researchers help patients and other stakeholders to understand the research process**

**Team learning about patient-centeredness and stakeholder engagement**

**Patient-centeredness and stakeholder engagement incorporated into research process**

**Transparency-Honesty-Trust**

- Inclusive decision making
- Information is readily shared
- Commitment to open and honest communication
highlighting engagement practices from PCORI-funded projects (See Figure 3 for selected excerpts).

The Rubric defines 2 groups expected to be contributing members of the research team. “Patient partners” include patients (ie, individuals with the lived experience of conditions under study), their family members and caregivers, and organizations that represent patients and caregivers. “Stakeholder partners” include clinicians, researchers, purchasers, payers, health care industry, hospitals and health care systems, policy makers, and training institutions.

The vignettes from PCORI-funded projects corresponding to the engagement activities provide examples of how stakeholders have contributed to improving the efficiency, relevance, and patient-centeredness of the research and more effectively disseminating the findings to those who would benefit. The key considerations section of the Rubric addresses things like the need to financially compensate patients and other stakeholder partners, provide bi-directional training opportunities to engaged research teams, and clearly define roles and decision-making authority for patients and other stakeholder partners.

**DISCUSSION**

The Engagement Rubric was first incorporated into PCORI’s spring 2014 cycle of funding announcements and has since become a cornerstone for guidance on
engagement across the organization. The Engagement Rubric is not intended to be comprehensive or prescriptive. Instead, it provides a practical resource that distills and prioritizes information from promising practices intended to systematically bring stakeholders into the research process in the most impactful way. The Rubric defines and embraces patient, caregiver, and stakeholder engagement as occurring from generation of potential research questions to dissemination of research results and guides applicants in proposal writing and patients and other stakeholders interested in partnering in PCOR. Researchers, patients, and other stakeholder partners can work together, using the PCOR Engagement Principles as a guiding beacon, to determine which of the activities, as well as any additional innovative approaches, best fit their projects given the population or condition to be studied, the nature of past research and incorporation of patient and other stakeholder views into that work, and the gaps to be addressed by the work. The Rubric can also be helpful for evaluating applications for research funding, developing PCOR training materials, and monitoring and supporting research teams in successfully executing their engagement plans.

Limitations of the Rubric
As the Rubric evolves, it is both catalyzing and capturing nascent practices and lessons learned. As such, several limitations should be noted. First, while extensively grounded in literature and evolving practice, the Rubric was developed primarily based on engagement practices applied in PCORI-funded projects. As a result, it is not yet representative of patients and other stakeholder engagement practices in all PCOR studies or in other engaged research. Additionally, more research is needed to document the effects of these engagement practices on how studies are carried out. Second, the Rubric is oriented toward researcher-driven research in that it primarily reflects engagement from the perspective of researchers who are leading the research team, creating partnerships with patients and other stakeholders, and seeking PCORI funding, rather than the perspectives of patients or other stakeholders who are initiating and driving the research and seeking partnerships with researchers, such as in the Patient-Powered Research Networks. Finally, the current Rubric does not address the “pre-engagement” phase of research—the relationship-building efforts that lay the foundation for partnered work on a specific research project.

Implications for the Future
The Engagement Rubric is a living document that will evolve as practices for patient, caregiver, and other stakeholder engagement in research advance. The Rubric is based on the premise that stakeholder input is important at key stages in the process to produce research that matters and evidence that will be applied by patients, families, clinicians, and payers and other relevant stakeholders. The value of the Rubric lies in its influence on the research community to embrace all stakeholders as true partners whose involvement is essential in the research process. PCORI is planning to evaluate researchers’ as well as patient and stakeholder partners’ use of the Rubric and how it is influencing their approach to engaged research. PCORI is also actively investigating how engagement practices are affecting study design and processes (eg, research questions, outcomes selected, recruitment rates, research relevance and quality) and ultimately, the uptake of study findings and impact of those findings on quality health decisions, health care, and health outcomes. PCORI will use what is learned to improve the Rubric and related resources and to help to build a stronger science of patient and other stakeholder engagement. Through this integration of pioneering engagement practices with the stakeholder engagement evidence base and its application to PCORI funded projects, PCORI hopes to shift the paradigm of research from one of conducting research on patients as subjects to a pursuit carried out in collaboration with patients and other stakeholders to better reflect the values, preferences, and outcomes that matter to the patient community.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/content/15/2/165.

Key words: patient-centered; patient outcomes; patient engagement

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References


Key Considerations in Developing & Integrating Patient Perspectives in Drug Development:

Examination of the Duchenne Case Study
Whether to Conduct a Patient Preference Study?

Experts agree that it is important to weigh multiple factors in deciding whether to conduct a patient preference study, especially given that these projects are significant undertakings that require time and resources in order to be successfully executed. It is crucial to determine whether the patient preference study is, in fact, the right approach.

The MDIC Framework Report includes a “core set” of factors to evaluate in considering whether a patient preference study might be useful in different situations. Though this project focused on the device arena, many experts see these considerations, listed below, as potentially relevant more broadly to drugs and biologics.

- **Preference sensitive situations**, defined as “those in which there are multiple [treatment] options and the decision of which option to pursue depends upon the particular preferences of the decision maker.” These situations occur when there are multiple options available to the patient and either no option is clearly superior over a plausible range of preferences and/or the evidence supporting one option over others is considerably uncertain.

- **Situations in which patients, because of their direct, personal experience with the disease, might have differing perspectives** from those of other stakeholders (including providers, regulators, drug developers, and even other patients within their disease community). For example, the MDIC Framework Report cites situations in which patients’ experiences with a therapy are “highly subjective (e.g. pain, fatigue, nausea, paresthesia, itch, depression), or when the impact on quality of life is an important outcome measure.”

- **Situations in which assessing benefit-risk is especially challenging**, including those involving time lags between when patients experience benefits and harms, harms or side effects that are very different from those experienced previously, and harms or side effects that patients would not accept no matter what the potential benefit.

- **Situations involving regulatory novelty**, generally in the rare disease setting, where key stakeholders have little or no previous experience with a condition or treatment approach. Patient groups, drug developers, and even the regulators themselves may undertake patient preference studies to better define and understand patients’ benefit-risk tradeoff decisions in an emerging clinical area or
mechanism of treatment action. As noted in the MDIC Framework Report, "[p]atient preference information will be more useful in informing regulatory decisions in clinical areas with which the FDA staff have less familiarity."102

In addition to the above circumstances, which are more directly related to evaluating a patient preference study approach, there are additional factors to consider in deciding whether to pursue such a study, including:

- **Unique characteristics of the relevant patient population, the disease community, and the sponsor’s environment.** Understanding the capabilities and interests of key stakeholders within the community (including patient groups and clinical networks), as well as the resources available to secure a representative group of participants, will help determine whether a particular disease area is "ready" for the community engagement needed to successfully conduct a patient preference study. For instance, it is important to evaluate whether there are active patient groups, registry data, and key stakeholders willing and able to engage in developing the survey and applying the necessary financial resources. A field of research for a disease may be very early in its process and may not be mature enough to launch a full patient preference study. Rather, stakeholders may want to start with collecting more qualitative information via surveys and interviews.103

- **Scientific Issues.** These include ensuring the study can be appropriately representative of the specific patient population to minimize chances for sample bias; reproducibility; ensuring respondents have the capability to fully understand and consider the questions they are being asked; demonstrating that the studies can be predictive of the actual choices patients will make; and considering whether results from studies will be factored into product valuation models.104

- **Process Issues.** These include maintaining objectivity throughout the study, questions about where and how data from these studies can be included in the regulatory review process, and ability to engage the currently limited universe of experts to do the preference study work.105

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**THE VALUE OF PATIENT PREFERENCE INFORMATION AS A FUNCTION OF BENEFIT AND RISK**

- **HIGH BENEFIT/LOW RISK**
  - Patient preference into less needed it significant benefit and limited risk

- **LOW BENEFIT/LOW RISK**
  - Product may only get approved if significant evidence that at least a subset of patients would take the risk for the benefit

- **HIGH BENEFIT/HIGH RISK**
  - Patient preference into helpful to identify a subset of patients willing to take the high risk for the significant benefit

- **LOW BENEFIT/HIGH RISK**
  - Patient preference into might be helpful to show that at least a subset of patients wants the limited benefit

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**Beginner’s Guide to Patient-Centricity**

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CHAPTER 4
When to Conduct a Patient Preference Study?

There are important considerations in determining the optimal time to launch a patient preference study — the “when” within a specific drug development lifecycle. While it is important to engage input from the patient community throughout the drug development continuum, from the point of view of a patient group, the decision about timing for a preference study relates to the readiness of the community and the ability to adequately engage the appropriate patients and/or caregivers in a substantive effort that can yield the type of data being pursued.

**Duchenne Case Study: Laying the Foundation for Launching the Patient Preference Initiative**

PPMD’s decision to undertake patient preference studies was predicated on a strong foundation of engaging with the Duchenne community in a variety of ways. The organization has, over time, utilized a variety of engagement and research approaches to understand the community needs and perspectives. These include interviews, focus groups, and surveys using traditional methods. Each of these approaches has its pros and cons, and depending on the specific situation, one may be more appropriate and feasible than others.

For example, when PPMD explored the motivations and decision-making of families around clinical trial participation, the organization employed a qualitative interview study followed by a traditional survey. To respond to the FDA’s continued interest in family stories, the group launched a ‘Share your Story’ project to obtain open-ended responses from families.

When PPMD’s leaders focused on the need to quantify meaningful benefit and the tradeoffs families would make for those benefits, they turned to stated preference methods. The activities described above established a rich foundation for the engagement that ultimately drove the development of the preference work’s research aims and survey instrument, as well as providing context for the results of those studies.

From the point of view of a company, there are decision points at every phase of portfolio development that could benefit from quantitative patient input and might specifically justify generating information on trade-off decisions through a patient preference study. For example, as discussed previously in this report, if a company is making internal portfolio decisions among multiple disease settings, having preference information from patients about non-product-specific choices and priorities might be important in choosing where to focus finite resources.

Additionally, there are opportunities for engaging in a patient preference study at various points during the clinical testing of a new drug. If the goal of the preference study is to help shape the clinical trial, then it makes sense to have patient preference information early enough in the process to influence the protocol design. If the goal is to inform the regulatory review of a product it generally makes sense to engage a patient preference study in phase 2 or phase 3 of the development path, although it may not be clear what specific potential harms might be associated with the product or how
much tolerance patients have for risk (and for which patient preferences are sought) until larger studies are underway. However, it is important to account for timing as it is often the case that there is insufficient time to design and conduct a preference study in the period between pivotal trial topline results and a regulatory submission.

**CASE STUDY:**
**COMPANY-LED INITIATIVE #1**

A sponsor company was developing a drug to treat a serious condition. Historically, the primary outcome measure for trials designed to justify approval of therapies for this condition targeted a level of efficacy that was consistent with the level of efficacy expected from older therapies. A new class of products was developed that demonstrated higher levels of efficacy than the standard of care at the time. The sponsor was interested in communicating the higher than anticipated levels of efficacy in product labeling because of the assumption that the additional efficacy would be clinically meaningful to patients and that patients would be willing to accept the incremental risk that may be associated with that additional efficacy. In order to test these two assumptions, a patient study was pursued to assess patients’ benefit-risk tradeoff preferences.

The sponsor initially reviewed the scientific literature and consulted with a leading patient advocacy group to determine if previous studies addressing this question had already been completed. After considering the available data and validating the study question with patient advocates, the sponsor selected a leading academic in the social sciences field to design and implement the study on the company’s behalf. The study was designed in consultation with the sponsor and the patient advocacy group, and then it was implemented by the academic institution.

After the study was enrolled and data analysis was completed, it was found that the data supported the sponsor’s initial assumptions, as well as the company’s labeling proposals. The plan is to publish the results of the study so as to contribute to the body of knowledge in the scientific community.

**Who Should Conduct a Patient Preference Study?**

When the decision is made to utilize a patient preference study approach, an important step is to identify “who” to work with to design and conduct the study and how best to engage the appropriate expertise and partners for the project.

**Organizational Approach: Developing Collaborations and Selecting Partners**

The initiative for conducting a patient preference study can originate from within the patient community itself, inside a company, from academia, or even within a regulatory agency, and the project can be executed individually or via collaborations. In determining whether and what type of collaborations and partnerships might be needed, it is especially important to evaluate the resources needed for the successful
ASSESSING MEANINGFUL PATIENT ENGAGEMENT IN DRUG DEVELOPMENT: A DEFINITION, FRAMEWORK, AND RUBRIC

Deliverables from conference organized by the University of Maryland Center of Excellence in Regulatory Science and Innovation (CERSI), government agencies, academia, and industry to provide a forum for all patient-focused drug development stakeholders to gather for an open dialogue.
**Preparation Phase**
- Understand disease/condition from patient’s perspective; the patient journey; preferences for outcomes, etc.
- Patient registries
- Identify unmet need
- Patient/community/researcher training on effective partnership
- Assess current treatment effectiveness/sub-populations

**Research Questions**
- Develop a research question based on patient interests
- Patients prioritize research questions
- Patients provide feedback on potential indications

**Pre-Clinical Development**
- Gather or develop study tools (PROs, ClinROs, PerROs, ObsROs)
- Patients identify potential barriers for study recruitment/participation
- Plan for who, when, and how patients will be engaged throughout
- Patients’ feedback on study endpoints

**Execution Phase**
- Patients help with recruitment and provide feedback on experiences as participants
- Patients serve on data safety monitoring board (DSMB)

**FDA Approval Process**
- Patients serve on advisory committees, contribute to benefit/risk discussions, and as Patient Representatives

**Communication Phase**
- Patients provide input on Risk Evaluation and Mitigation Strategies (REMS)
- Patients provide feedback on Phase IV studies
- Patients understand how to report adverse events
- Patients provide context for economic information under FDAMA 114
- Patients provide feedback on patient counseling information, MedGuides, Package Inserts, Instructions for Use

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**Feedback from Post-Marketing Studies**
A Proposed Rubric – How do we know the patient has been engaged in drug development?

The meeting discussion captured a range of characteristics that were proposed as to what would constitute sound elements of PFDD. It is difficult for a single or small group of individuals to faithfully represent the patients’ perspectives as a whole. The use of science-based methods for gathering patient perspectives ensures that the data collected are valid and representative. The experiences of patients can be heterogeneous and an individual patient’s perspective may differ from that of other patients and may change with time as personal circumstances and his or her state of disease or condition changes. It is important that patient participation activities capture the range of and subtleties of patients’ perspectives.

These elements were used to formulate the following rubric:

1. **Patients as Partners**: Patients, caregivers, and other relevant people (e.g., people who are at risk for a disease, but do not yet have the disease) are recognized as partners in the drug development process throughout the life cycle.

<table>
<thead>
<tr>
<th>Patient Role</th>
<th>Examples</th>
<th>Engagement Level</th>
</tr>
</thead>
</table>
| Partnership role   | ● Patients provide a priori and continuous consultation on outcomes of importance, study design, etc.  
                  | ● Patients are paid investigators or consultants  
                  | ● Patients have a governance role; patients have “a seat at the table” | High |
| Advisor role       | ● Patients serve as advisory committee members or provide *a priori* consultation on outcomes of importance and study design, but have no leadership role or governance authority | Moderate |
| Reactor            | ● Patient input is collected distally through surveys, focus groups or interviews, but patients are not consulted directly or *a priori* on such things as study design and outcomes of importance  
                  | ● Patients are asked to react to what has been put before them rather than being the origin of the concepts of interest | Low |
| Study subject      | ● Patients are recruited or enrolled as study subjects, but are not asked for input, consultation, or reaction | None |

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2. **Continuous Patient Engagement**: Patient engagement is continuous, throughout the drug development process and product lifecycle; it is not a one-time or sporadic event.

<table>
<thead>
<tr>
<th>Engagement Continuity</th>
<th>Examples</th>
<th>Engagement Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>● Patients are engaged in various ways throughout all phases of research planning, implementation, analysis, write up, and dissemination stages of the life cycle</td>
<td>High</td>
</tr>
<tr>
<td>Sporadic</td>
<td>● Patients are asked for input into research planning, study design or outcomes of importance at several points in time but without coordination or meaningful continuity</td>
<td>Moderate</td>
</tr>
<tr>
<td>One-time</td>
<td>● Patients are only asked for input into research planning, study design or outcomes of importance at one point in time (e.g., early planning or late dissemination) and the study or program proceeds without further patient consultation</td>
<td>Low</td>
</tr>
<tr>
<td>No engagement</td>
<td>● Patients are not asked for input into such aspects as research planning, study design or outcomes of importance</td>
<td>None</td>
</tr>
</tbody>
</table>

3. **Meaningful Patient Engagement**: Patient engagement must be meaningful. That is, it must be a real interaction and dialogue, not a “check-the-box” exercise. Patient input should come from thoughtful dialogue and patients should be able to see how the input they provide is used in the specific studies or in the development processes.

<table>
<thead>
<tr>
<th>Engagement Meaningfulness</th>
<th>Examples</th>
<th>Engagement Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meaningful</td>
<td>● A plan for interaction and dialogue among stakeholders is outlined with clear objectives, why and how the dialogue will take place, the information sought, how it will be used, and how patients will be kept informed throughout  ● A range of engagement methods can be used as deemed appropriate</td>
<td>High</td>
</tr>
<tr>
<td>Partial</td>
<td>● Specific activities for meaningful dialogue are</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
undertaken but are not comprehensive or well-coordinated
● Patient engagement methods are used, but they may not be appropriate or sufficient for the circumstance

Superficial
● Informal conversations with patients take place in which their input and views are sought, but there is no interactive dialogue, formal process, or plan for using the information

No interaction
● No interaction or dialogue is initiated

4. The Right Patients are Engaged: Throughout the process, the target patient population is well represented, and other relevant populations are considered for engagement.

<table>
<thead>
<tr>
<th>Right Patients</th>
<th>Examples of Engagement</th>
<th>Engagement Level</th>
</tr>
</thead>
</table>
| Comprehensive | ● A thoughtful effort is made to engage a range of patients (and caregivers) as is required by the disease and other circumstances (e.g., patients with the disease, cured from the disease, at risk for the disease)  
● Patients and patient advocacy groups (large and small) are engaged as per the disease and circumstance  
● When possible the range of patients afflicted are represented (e.g., age, gender, race, geography, socioeconomic status) | High |
| Representative | ● A representative sample of patients is engaged, but may be limited by demographics, region, etc. is not as comprehensive as needed | Moderate |
| Limited        | ● A small number of homogenous patients are engaged  
● A “convenience sample” | Low |
| No patients    | ● No patients included | None |

5. The Right Time to Engage: Engagement happens at the appropriate time(s) throughout the process.

<table>
<thead>
<tr>
<th>Temporality</th>
<th>Examples</th>
<th>Engagement Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate</td>
<td>● A clear rationale is provided for the timing of</td>
<td>High</td>
</tr>
</tbody>
</table>
patient engagement efforts throughout the life cycle
● The timing of engagement is well planned based upon the characteristics of the disease/condition, the engagement goals, or other documented rationale

<table>
<thead>
<tr>
<th>Acceptable</th>
<th>● A rationale is provided for the timing but is not well supported or does not address all relevant stages of the life cycle</th>
<th>Moderate</th>
</tr>
</thead>
</table>
| Poor               | ● Unclear rationale and temporality  
                      ● No clear plan for engagement timing                                                                                  | Low      |
| Inappropriate      | ● Timing is clearly not appropriate given the disease/condition, study design or for other reasons                      | None     |

**Other key discussion points:**

**Challenges to Successful PFDD:**

- The FDA is open to patient advocacy organizations and similar stakeholder groups working collaboratively to lead their own PFDD meetings styled after FDA’s twenty PFDD meetings. However, the FDA has not yet developed formal policy on how “external-led” PFDD meetings might take place.
- The science of patient engagement is still emerging, especially for drug development. Best practices are needed for systematically collecting patient input on their experience of living with a particular disease.
- There is need to identify and test promising patient-engagement methods.
- It is not enough to engage those who are already participating. There is a need to focus on previously missed opportunities to learn from patients and to engage broader patient populations.
- With the help of collaborative partnerships, the Internet and social media information from patients can be captured and used to foster engagement.
- Differences in culture exist and methods for engaging patients may vary internationally.
- A balance has to be attained between the suitability of the engagement method and generation of high-quality evidence.

**Patient Advocacy Role**

- The role of patient advocacy organizations is expanding including collecting information from the patient community and sharing it with industry and research partners.
- Patients want opportunities to participate in the accelerated approval process.
- Patient advocacy organizations are already collaborating to transition the lessons they have learned through their own PFDD meetings into an operational framework for conducting PFDD programs.

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● Patient advocacy groups report that they need to improve harmonization among themselves to avoid duplication and inefficiency in efforts. Aligning efforts and identifying the contributions of advocacy organizations is vital to successful collaboration.

Regulatory Challenges
● Companies face regulatory hurdles, particularly from within their own organization in engaging patients. Many company legal departments approach pre-approval contact with patients conservatively to avoid perceptions of pre-approval promotion.
● As industry aims to solicit guidance from patients on outcomes and preferences, legal and compliance policies can serve as a barrier to meaningful interaction. While these barriers are intended to protect both parties, for companies to meaningfully involve patients. Regulatory guidance is needed for the biopharmaceutical industry to understand how and when they can engage the patient community.

Emerging Payer Role
● Payers are largely underrepresented as stakeholders in “patient-centric” drug development initiatives; in particular, they must be brought into the PFDD dialogue.
● Payers are key decision makers in determining access to biopharmaceuticals and devices for their patient populations. They can contribute to the creation of a unified paradigm or model of patient engagement for continuity between patient engagement in treatment development and patient engagement in healthcare decision making.
● Payer input would be valuable in designing transparent, consistent methodology to ensure that PFDD evidence is useful in real-world decision-making. PFDD can be an avenue to engage patients in the benefit-risk assessment of drugs so payers can better determine how likely their patient population will tolerate, and therefore be more willing to use, a specific treatment.

Future Directions and Opportunities for Collaboration
● All stakeholders (patient community, industry, academic researchers, government, health systems, providers, and payers) must collaborate.
● Methods development is critical to improve the capture of the right information from the right patient populations at the right time in efficient and valid ways and to improve the use of that information in development programs and benefit-risk assessment.
● Tangible incentives, both regulatory and market-based, are needed so that patients, payers, and biopharmaceutical companies benefit from this transformative initiative.
Capturing the Value of Patient Engagement:

Summary of Results of the 2016 Study of Patient-Centric Initiatives in Drug Development

October 31, 2016
COLOR KEY
- **Green**: denotes aspects of patient engagement in place, with efforts begun
- **Yellow**: denotes aspects that are not now in practice but should be implemented in the medical product life cycle for effective and meaningful patient engagement.
Objectives of the Research

- Quantify the impact of patient-centric initiatives using ROE (Return on Engagement) metrics looking at retrospective data
  - Identify metrics from case studies of measurable benefit to drug development from patient involvement
  - Assess patient-centric initiatives to characterize trends and success factors

- Characterize management and organization models that support implementation

- Identify guidances and frameworks to assess standards
Key Insights

- **Companies are developing and gathering metrics**, but there is no comparative analytic data yet that support *specific methods* of patient-centricity.

- **Metrics are broad and not generalizable** across patient-centric initiatives (PCIs).

- **Low cost PCIs generate the highest benefit**; high tech PCIs show lower ROE, possibly due to early adoption costs & implementation complexities.

- When companies engage patients,
  - **Trial performance improves** (faster planning, approval, enrollment; fewer protocol amendments)
  - **Study volunteer feedback is more positive** & Patient Activation Measures (PAM) scores are higher
  - **Internal and external reach improves**, particularly with use of technology
  - **Long-term drug development portfolio improves** as companies can save millions with a small investment
Key Insights (con’t)

- Companies with a **dedicated patient engagement (PE) role** implement and pilot more PCIs.

- **Regulators are embracing patient-centricity** and plan to develop more guidance for industry in the future, but little is available now.

- **Disease organizations are driving guidance development** (e.g., HIV/AIDS, Chronic Fatigue Syndrome, Duchenne Muscular Dystrophy, ALS-coming).

- **Companies are developing their own tools and frameworks**, but these are not widely available for proprietary reasons.

- The most practical and comprehensive resources are coming from outside regulatory agencies (e.g., UNAIDS, EUPATI, CTTI).

- **Mandating patient centricity makes it happen** (PCORI).
Key Insights (con’t)

- The primary barriers to adoption of PCIs are lack of:
  - internal company buy-in (6 of 22 companies)
  - authority to implement them (5 of 22 companies)

- Others barriers include (perceived) lack of sponsor readiness, risk tolerance, staff, time, and budget
  - 13 out of 20 companies responded there is an organizational budget assigned for patient engagement activities.
  - 6 out of 20 companies responded they did not have a budget for these activities.
  - 1 company did not respond.
Summary of Patient-Centric Initiatives

- **Top implemented initiatives** are:
  - Disease specific patient organization landscape analysis tools (10/22)
  - Patient advisory boards (10/22)
  - Professional panels (10/22)

- **Top piloted initiatives** are:
  - End of study surveys (9/22)
  - Use of patient wearable devices (8/22)

- **Top planned initiatives** are:
  - eConsent (11/22)
  - Adaptive trial designs and adaptive licensing (10/22)
  - Establishing patient communities (during and after clinical trials) (10/22)

- Overall, there are more organizational patient-centric activities in the planning stages than those being implemented or piloted.
On the path to a science of patient input

Margaret Anderson* and K. Kimberly McCleary*

It is early days in the creation of a science of patient input. Participants are establishing rigorous methods to better integrate patient perspectives, needs, and priorities throughout biomedical and bioengineering R&D and care delivery to patients. To assess progress and unmet needs, FasterCures tracked more than 70 collaborative initiatives clustered in six categories that are defining and shaping this developing field. No longer is patient engagement a fanciful notion as it was at the start of our journey in 2003, and the rush of activity is welcome and vital.

In the 21st century, market research is a business imperative for most industries. In 2011—decades after Steve Jobs famously said, “A lot of times, people don’t know what they want until you show it to them”—Apple started a market research group that sends anonymous surveys to invited users to find out exactly what they want from their devices. In January 2016, IBM formally launched a company-wide process to shift its culture to focus on users’ needs (1). Health care and the research and development (R&D) of biomedical products have lagged behind other technology sectors in moving toward consumer-centered practices. Now, as a result of multiple cultural influences and pragmatic factors, the mindset of these stakeholders is changing, and the patient’s role is expanding (2). Momentum is building to incorporate patient preferences into the biomedical R&D system so that products and services better align with patient needs, improve individual and public health, and reduce time and spending on unproductive care.

With its broad network of stakeholders—patient organizations, industry, academia, government, and funding agencies—FasterCures has a distinct vantage point into this landscape of new patient-centered activities; such information is crucial to the creation of a new field: the science of patient input. The goals of this new field are to develop rigorous methods so as to better integrate patient perspectives, needs, and priorities across the translational research continuum. In this Perspective, we summarize and encourage broad use of resources that are available, and we capture a baseline assessment to benchmark growth and identify areas of unmet need. We don’t want a minute wasted on duplicating efforts.

WHO’S ON FIRST?
Through an environmental scan, we tracked more than 70 collaborative initiatives, clustered in six categories, that are further defining and shaping patient-centered practice and policy (Tables 1 and 2). Within these 70 initiatives, nearly 40 discrete supporting entities are assembling resources, providing direction, and tracking milestones. Each entity approaches this field from a different vantage point, which is what makes the efforts so promising: It is natural and essential—that the work required to create the field of patient input be performed through strong collaborations composed of highly interactive, diverse organizations.

FORMING SOLID PLATFORMS: FRAMEWORKS AND MODELS

Some of the first formal efforts to outline the science of patient input borrow, from software development, the use of frameworks to provide a logical structure for organizing information, identifying sources of the information, and suggesting ways it might be used and viewed by distinct parties (3).

Frameworks serve different purposes, with varied approaches and audiences. It is important to be familiar with these frameworks because they lay the groundwork for much of the ongoing and future work in this space. The Clinical Trials Transformation Initiative (CTTI) created perhaps the most recognizable tool, and its work has become a guidepost. CTTI is a public-private partnership supported by the U.S. Food and Drug Administration (FDA) and member pharmaceutical companies and patient organizations and has popularized a visual chevron-based framework that identifies points at which clinical trial sponsors and regulators might engage patients along the R&D continuum for pharmaceuticals (4). A companion framework for medical devices was developed by another public-private partnership, the Medical Device Innovation Consortium (MDIC), which built detailed considerations into an FDA Center for Devices and Radiological Health (CDRH) diagram of places in the total product life cycle of medical devices at which patient-preference information might enhance product development (5).

The Patient-Centered Outcomes Research Institute (PCORI) requires that all its funded investigators partner with patients from the beginning of the application process through completion of the study and dissemination of its results. To guide formation of meaningful engagements with patients, PCORI developed a Patient Engagement Rubric (6) and a compensation framework (7) that now guide applicants, reviewers, and awardees at every step. The engagement principles outlined in the rubric—reciprocal relationships, colearning, partnership, trust, transparency, and honesty—have become the essential characteristics of patient-centeredness in R&D and health-care delivery. These initiatives, like most of the others identified here, use the U.S. regulatory system as a foundation. Composed of industry and patient groups, the Patient-Focused Medicines Development partnership is leading an effort to develop a comprehensive global framework for patient engagement.

Recently, we have seen a surge in frameworks being used by a number of organizations to help define the value of certain drugs and medical products for insurance coverage decisions. Frameworks assessing the value of medicines have been put forward by the American Society for Clinical Oncology, Institute for Clinical and Economic Review, National Comprehensive Cancer Network, and others; however, most efforts to date have...
not incorporated substantial input from patients or patient advocates, so we have not included them among the patient-centered efforts in Table 1 and Table 2. To provide more of a patient perspective, FasterCures and Avalere are partnering to lead a collaborative, multistakeholder process to develop a patient-centered framework for assessing the value of care (www.fastercures.org/reports/view/56).

SOLIDIFYING THE SCIENCE: METHODS AND TOOLKITS
The science of patient input has roots in multiple disciplines. Patient advocacy builds on the principles of political activism and community organizing. On the academic side, this new science is attracting individuals trained in health economics, outcomes research, epidemiology, social sciences, and marketing sciences. As a result, there are language barriers among the sectors. There is even disagreement on whether the term “patient” means only the individual with a diagnosis or is meant to include caregivers, advocates, and patient organization representatives. Several initiatives are starting to develop shared definitions, standards, and methods and are collecting tools such as guidelines, principles, checklists, model provisions, and templates.

Over the past 5 years, PCORI has made a substantial investment through its Methodology Committee to create or endorse cross-cutting standards for patient-centered outcomes research for 11 topic areas, including standards for 47 areas such as patient-centeredness, formulating research questions, and preventing or handling missing data (7). Many of these standards can be applied to other fields beyond comparative effectiveness research.

Research on patient preferences is getting attention in part as a result of the draft guidance issued by CDRH in 2015, which spelled out how patient input might inform benefit-risk assessments in premarket applications for medical devices. To help guide industry and other stakeholders on what methods exist for studying patient preferences and when they might be most appropriately used, the MDIC framework includes a substantial appendix entitled “Catalog of methods for assessing patient preferences for benefits and harms of medical technologies.” This catalog is crucial because many believe that there is only one way to do a patient preference study, and the catalog sorts multiple methods. Similarly, the Biotechnology Innovation Organization (BIO) is working with Parent Project Muscular Dystrophy (PPMD) and a panel of expert reviewers to produce a new resource, “Assessing and integrating patient views into drug development: Patient preference study considerations,” which is due to be released in spring 2016.

Two separate repositories of toolkits aim to help patient organizations standardize some practices and benefit from others’ successes. FasterCures’ TRAIN (The Research Acceleration and Innovation Network) program (8) collects resources from leading venture philanthropy organizations, and Global Genes’ Rare Toolkits (9) is designed for use by rare-disease stakeholders. In addition, FasterCures held a workshop on 17 February 2016 with key thought leaders from patient organizations, industry, government, and academia in order to identify tools that would enhance the science of patient input, and FasterCures will be leading collaborative efforts to prioritize and produce these tools in 2016 and beyond (10).

The National Quality Forum (NQF) announced early this year that it will lead a multi-stakeholder process in 2016 to develop international standards for patient decision aids (11). NQF standards have a potent influence
Table 2. Science of patient input resources with patient data sources and measurement/metrics. Shown is a selected sample; please visit www.fastercures.org/patients-count-resources for a listing of and links to more than 70 resources.

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Conventional approaches—such as patient advisory boards, focus groups, surveys, and structured interviews—continue to be mainstays. Capturing dynamic data about domains of high interest to patients will be key to developing better endpoints and outcome measures and understanding benefit expectations, risk tolerance, and attitudes toward uncertainty.

New initiatives are taking shape to fill the need. For instance, in implementing requirements of the 2012 FDA Safety and Innovation Act, FDA’s Center for Drug Evaluation and Research is conducting a series of 24 patient-focused drug development meetings to be completed by the end of 2017. Each meeting is focused on a particular disease or condition and is structured to hear directly from patients and caregivers about the impact of the disease on their daily lives and goals. These sessions also obtain perspectives on how well available therapies meet patients’ needs. For most of the meetings held so far, patient organizations have voluntarily assisted FDA in publicizing the meeting and helping prepare participants by holding, in advance, educational webinars about FDA’s mission and conducting surveys to collect input from a broad patient population. After each meeting, the agency posts a “Voice of the Patient” report (12) as a resource for FDA review teams, industry, patients, and other interested stakeholders. The program’s success led FDA to announce guidelines and an application process for scaling the model with help from other parties to organize and host meetings with the benefit of participation from relevant FDA staff (13).

These FDA-convened meetings have exposed stakeholders to real-world concerns of patients and have allowed FDA reviewers to engage directly with patients about their symptoms and their impact on daily life. This process showcases how patients have complicated and narrowed lives as a result of living with these conditions, and FDA has witnessed tremendous unmet need in a new and powerful way.

Another new source of patient data are patient registries, the explosion of which was documented by FasterCures in a February 2016 report, “Expanding the science of patient input: Building smarter patient registries” (14). Adaptable and affordable technology platforms offered by organizations such as Genetic Alliance, the National Organization for Rare Disorders, PatientCrossroads, and Unitio have made it feasible for patient organizations of all sizes to launch registries to study the natural history of disease, burden of disease, expectations on the health-care delivery system, and its standards can have far-reaching impact.

ANECDOCTAL TO ACTIONABLE: SOURCES OF PATIENT DATA

The power of the science of patient input lies in the data, but two key challenges are locating sources of relevant and robust patient data and determining how best to apply them. Data can have limitations and tend to be collected at a single point in time. There has already been enormous investment in standardizing, linking, and mining electronic health records (EHRs), and the promise that EHRs hold for research has been deliberated for years. With U.S. President Barack Obama highlighting the centrality of data sharing for the Precision Medicine Initiative, and related announcements by major EHR vendors to develop open data standards, progress is being made. But more work is needed to make EHRs reflect the needs of developers, health-care professionals, and patients.

To develop a more holistic picture of the patient journey, new data sources are being identified and leveraged (Table 2). More affordable and prevalent communication and data storage technology has opened up possibilities for patient registries, online data-sharing communities, smart phones, wearable devices, and social media to be used as tools for capturing patient insights longitudinally.
for treatment benefits, and perspectives on tolerable harms and risks. These tools can go a long way to de-risking the science for academia and industry and incenting further study into a particular disease state.

FDA’s Office of Surveillance and Epidemiology is leveraging the insights of nearly 400,000 patients who participate on the health data-sharing platform PatientsLikeMe in order to better understand medication side effects and other potential safety issues with approved medications (15). The National Patient-Centered Clinical Research Network (PCORNet), sponsored by PCORI, links 20 patient-powered registry networks with 13 clinical-data research networks at leading academic medical centers, creating a potent infrastructure to compare patient-reported data with data collected in clinical care settings (16).

Later in 2016, the U.S. National Institutes of Health (NIH) will announce details for amassing a cohort of 1 million research volunteers through the Precision Medicine Initiative (17). It is anticipated that some of the existing infrastructure supported by PCORNet, NIH’s Clinical and Translational Science Awards, and the U.S. Department of Veterans Affairs Million Veteran Program will be tapped to recruit participants, along with direct public outreach in order to achieve a broadly representative cohort.

BUILDING A CULTURE OF ENGAGEMENT: REGULATORY AND LEGISLATIVE ACTIVITIES

In our 2015 article (2), we described a "perfect storm" of policy initiatives that were generating momentum for patient-centered initiatives in government, the private sector, and philanthropies. A year later, these have matured, and new activities are multiplying.

In the U.S. Congress, the 21st Century Cures Act (H.R. 6) sailed through the U.S. House of Representatives with rare bipartisan support, passing by a vote of 344 to 77. The bill contains several provisions that amplify patients’ voices throughout the continuum of discovery, development, and delivery of medical solutions. The Senate is advancing a series of smaller bills that address some of the same issues as H.R. 6. The biomedical ecosystem is encouraged by the dialogues from these efforts and looks forward to seeing what will come of them.

In the Executive Branch, the positive experience with FDA’s Patient-Focused Drug Development initiative has contributed to the agency’s having made a new generation of patient-focused activities among the top priorities for the sixth authorization of the Prescription Drug User Fee Act (18). Industry, represented by BIO and the Pharmaceutical Research and Manufacturers of America (PhRMA), were reportedly in agreement with the high priority attached to advancing patient-focused drug development, although details about the specific accord reached are still being ratified through the approval processes.

The burgeoning science of patient input has advanced a meaningful culture of patient engagement. For example, CDRH’s 2016–2017 Strategic Priorities outline specific milestones such as “by December 31, 2017, 90 percent of CDRH employees will interact with patients as part of their job duties” (19). This is a strong signal to the medical device industry of CDRH’s commitment. Although work remains to define the purpose and means to meet CDRH’s target, we believe it will be a transforming force for the agency and also will spurn new initiatives in industry. CDRH has also championed patient centricity in its negotiations with industry trade organizations over the fourth authorization of the Medical Device User Fee Agreement, but it is not yet clear how well that priority aligns with industry’s top concerns.

Collective success in the science of patient input depends on incorporating new regulatory tools in this field. Unless FDA has capacity both in terms of appropriate methods and expertise to evaluate patient input as well as patient-centered tools and instruments submitted by sponsors, the field might wither. Similarly, industry and patient groups crave more direction from FDA about how it will use the patient input they provide and tools they develop to reflect patients’ priorities. Collaboration and communication are vital.

In that vein, a new opportunity for patient organizations to influence regulatory decision-making arose as a result of pioneering work led by PPMD to assemble a large and diverse multistakeholder group to draft regulatory guidance to submit to FDA. The agency used the comprehensive draft as a template, and a year later issued formal guidance to inform drug development for Duchenne muscular dystrophy (20). This success has spurred similar initiatives, including one to stimulate drug development for amyotrophic lateral sclerosis (ALS) led by the ALS Association and another to define a “safe harbor” for engagement between patients and industry and the means by which the patient perspective can be better integrated in drug development (led by the National Health Council and Genetic Alliance).

MEASURING PROGRESS: METRICS

To maintain momentum, those dedicating human and financial resources to patient input initiatives feel a pressing need to establish metrics and show a return on investment. A cooperative process led by the University of Maryland Center for Excellence in Regulatory Science and Innovation (M-CERSI) proposes a simple system to assess meaningful engagement in drug development; a rubric that scores engagement is used on several dimensions of activity at different points along the development pipeline (24). CTTI is developing tools for training.

As the momentum for the science of patient input builds, we must address the demand for training. Several initiatives have been organized to develop formal curricula and focused professional trainings designed to expand the capacity of stakeholders to participate effectively in advancing the science of patient input.

The most comprehensive of these efforts is the European Patients Academy on Therapeutic Innovation, a consortium of 33 partners funded under the ambitious Innovative Medicines Initiative. Two cycles of an in-depth Patient Expert Training Course conducted over a 14-month period have so far trained about 150 participants (21). An educational toolkit of online materials available in seven languages is intended to reach 12,000 patient advocates across Europe so that they are educated in clinical trial design and health technology assessment.

In the United States, disease-specific programs provide a useful foundation for broader-based efforts sponsored by PCORI through its Ambassador program and FDA’s Patient Representative Program. As a follow-up to its late 2015 call to action (22) for more training resources, Friends of Cancer Research is developing a program to facilitate patient involvement in clinical trial design and benefit-risk decisions. The Reagan-Udall Foundation, with funding support from PCORI, has begun a new program, “Big Data 4 Patients,” which will create a state-of-the-art patient training program (23). Develop Innovate Advance (DIA) has created a competitive Patient Fellowship program as part of its annual convention to expose patient leaders to topics covered at one of the world’s largest gatherings of life science professionals and has designed intensive multiday sessions to foster colearning by life science professionals and patient advocates.
to measure the return on investment of patient engagement in clinical trials, and DIA has partnered with the Tufts Center for the Study of Drug Development to use selected case studies as a basis for quantifying the adoption and impact of patient-centered initiatives. The American Institutes for Research initiated a process early this year to identify measurement principles that are meaningful to patients and their families.

By far, the most advanced measurement system has been developed by PCORI. Its multipart evaluation is designed to assess the overall impact of PCORI, the extent of engagement in research, and the effect of engagement (25). The evaluation system includes visual models, sets of questions, metrics, methods, and sources of data. It incorporates new data collection tools, such as the Ways of Engaging-Engagement Activity Tool (WE-ENACT), in each funded project.

TODAY’S LANDSCAPE AND BEYOND
On the basis of our research, we have noted some overarching trends and unmet needs.

Avoid duplication and make your work easy to find
The long-ignored area of patient engagement has quickly become crowded with activity. However, the useful frameworks, models, rubrics, tools, and guidelines that already exist are often hidden from plain view. If you cannot quickly and easily find resources on your own website, it’s safe to assume that others outside your organization cannot either. Bringing better visibility to one’s completed work and products ready to be used is a low-cost, high-return action step that would help newcomers get started and seasoned practitioners identify where more work is needed. We have created a fully linked version on our website of the resources listed in Tables 1 and 2 to help establish a patient-centricity library.

We need evidence
Even informal efforts can build an evidence base and document what is working and what is not. It is challenging at this stage to know which efforts are demonstrating positive change and can then be scaled and built into standard operating procedures. We are getting better at incorporating real-world success stories into the narrative of patient centricity, but we need more formal ways to document and share experiences. We must also report failures or speed bumps so that we can all learn from them.

Help wanted
Although the initiatives we have described in this article are spread among many different organizations and involve scores of partners, a closer look reveals that a small group of expert trailblazers is at the core of many. There is a shortage of academic researchers prepared to hone techniques and methods for turning the patient experience into usable data. We ignore this at our own collective peril. The ranks of well-informed and available patient and advocate experts are also thin compared with the heavy demand for their participation. These shortages unduly demands on the pioneers and could result in burnout, lack of continuity, and, possibly, insularity. We also need to better integrate physicians and other healthcare professionals into the dialogue.

This is not a one-size-fits-all effort; customization is required
Much of the early experimentation with patient-centered action has been rooted in rare disease communities, where there are tightly linked patient networks and highly creative and agile nonprofit organizations. As best practices are established to gather and convert insights into actionable data, it is likely that we’ll need to tailor practices to the special features of each affected community, taking into account whether the condition is chronic, acute, or terminal; its prevalence or rarity in the population; the stage of scientific understanding about its cause or pathogenesis; and social dimensions such as how connected or dispersed patients are and whether there might be harmony or discord among the groups that serve the patients’ needs.

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