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Patient-Reported Outcomes: Design with the End in Mind

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HEALTH

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INTRODUCTION

"What outcomes matter to patients?"

This question is asked at nearly every meeting in biomedical R&D and health care. As *FasterCures* has documented over the years, there is a big change afoot to place patients in the center of medical product discovery, development, and delivery, and we have many tools available to facilitate inclusion of their perspectives. Now is the time to get more specific about how these tools are used to ensure patients' perspectives are kept front and center during decision-making.

Patient-reported outcomes (PROs), and their measurement instruments (PROMs), are one tool that ideally is developed in partnership with patients to capture the outcomes that matter most to them (e.g., fatigue or specific activities of daily living). Patient responses to PROMs can be translated into numerical scores and used in several ways, including to understand treatment effects or compare treatment options. Across R&D and care delivery, many partners (such as patient organizations, clinicians, payers, and more) have a stake in patient-centered PRO development and utilization, each from a different vantage point. Despite differences in viewpoint, all stakeholders agree that PROs have not reached their full potential of delivering benefits to patients. That is why *FasterCures* brought diverse stakeholders together to tackle the issue.

On June 14, 2017, *FasterCures* held a workshop, "Patient-Reported Outcomes: Design with the End in Mind," to convene representatives from patient organizations, regulatory agencies, payers, medical product developers, clinical researchers, and others. We asked this multi-stakeholder group to discuss the PRO-related challenges and opportunities from a broad view across R&D through care delivery, starting with the perspective of patients and patient organizations. From there we identified next steps along the path to making PROs a more potent tool for incorporating patients' perspectives into R&D and care decision-making.

THE POTENTIAL OF PROs

We opened the workshop with a panel of representatives from five patient groups who discussed what PROs could do for their organizations, the patient communities they represent, and themselves as patients and caregivers, and the role that their organizations are playing in advancing how PROs and PROMs are developed and used in patient-centric ways. The major themes were that PROs and PROMs could help them by:

1. ENSURING THE PRODUCT DEVELOPMENT PIPELINE ALIGNS WITH PATIENTS' UNMET MEDICAL NEEDS

The panelists all expressed the hope that patient-centered PROs would be used early in the R&D process as a vehicle to identify and/or develop more and better treatment options to fill unmet medical needs. Patients routinely find themselves in the position of making trade-offs, often very painful ones, related to their care with relatively little information about the outcomes that matter most to them. In early product R&D, PROMs can be used to refine the product pipeline to bring those products forward that have attributes likely to address the unmet needs patients have identified as important to them. In later stage R&D, patient-centered PROMs can be included as endpoints in trials to ensure that information is available at the point-of-care for decision-making (e.g., on the product label). In health care, PROMs can be used to capture information about how existing treatments are meeting patients' medical needs and as part of determining the quality of care. Ideally, the information collected in the health-care context is fed back into product development so that the suite of available treatments present more favorable trade-offs to patients over time.

2. INFORMING BETTER DECISION-MAKING

Patient-centered PRO information can help align R&D and health-

care decisions with what matters to patients and help patients feel and be more in control of their care. Many patients feel that, despite their participation in the development of a PRO or PROM, they lack access to the PRO information at the point-of-care, when it matters most to them. While the potential burden of filling out multiple or lengthy PROMs exists, patients are willing to complete PROMs when they can see the utility for decision-making, particularly as a tool for shared decision-making with their providers.

3. ALIGNING WITH THE PATIENT COMMUNITY

All stakeholders need to develop and deploy patient-centered practices; even patient organizations recognize they have opportunities to do this more effectively. Patient organizations are working to involve a greater number and diversity of their patient community in their research efforts and are in a unique position to pilot innovative approaches to capturing the perspective of patients. These include innovative ways to determine the patient-centeredness of PROs and PROMs. Traditional approaches often use the clinical trial study visit or clinical care appointment, both single points in time, as the setting in which to record symptom expression and often rely on a patient's recall of symptom duration or severity over several weeks or months.

For example, The Michael J. Fox Foundation for Parkinson's Research launched two initiatives to collect PRO data (e.g., symptoms and physical functioning) using Apple's ResearchKit and a web-based platform to launch a clinical study. These innovative approaches capture information directly from patients and caregivers about their daily experiences with Parkinson's disease-related dimensions that matter to them. Patient organizations are valuable partners in defining efficient and effective ways to expand beyond static or retrospective information or data capture, adapt and validate the patient-centeredness of PROMs, and develop use cases for existing and future PROMs.

MYTH BUSTERS

MYTH: PROs are by definition patient-centered.

REALITY: Not necessarily. Many PROs were developed with insufficient understanding about what matters to patients and inadequate partnership with patients in measurement development. Groups that develop PROMs should involve patients throughout development and implementation. This is particularly important for ensuring content validity.

MYTH: If patients are reporting on an outcome, it matters to them.

REALITY: Many patients can be compliant with filling out surveys regardless of whether the questions resonate with what is important to them. PROMs can have adequate psychometric properties, be constructed to produce statistically significant information, and even be valid for use in specific contexts, yet still not capture outcomes that are meaningful to patients. Patients should be asked whether PROMs are capturing what matters to them, as opposed to assuming this based on survey response rates.

MYTH: If a PROM is published, it is automatically validated for any use case.

REALITY: Researchers and anyone implementing PROMs can't just plug a published measure into their clinical study or electronic health record; they need to consider context of use and whether it fits their purpose. For example, a PROM that is developed to capture patients' pain and functioning before and after surgery may not capture the type of pain and functioning that matter for patients undergoing chemotherapy. PROMs may require bridging studies to ensure that published measures are appropriate for a different patient population or use case.

THE BIGGEST CHALLENGES TO EFFECTIVE USE OF PROs

Of the many challenges to using PROs that stakeholders identified at our workshop, these categories represent the biggest barriers.

TOO MANY AND NOT ENOUGH PROS

PROs have been used in product development and implementation for decades. There are enough PROMs to warrant entire collections of measures, but many measures in these collections were not developed in partnership with patients. Some argue that there are too many PROMs and find it difficult to figure out which PROM to use, especially as they try to determine if they are patient-centered. Because of this dilemma, others argue that there are not enough patient-centered PROMs, and greater investment in PROM development is needed. For some diseases and conditions, there are simply not enough PROMs that capture the illness dimensions that matter to patients, and new patient-centered PROMs are needed for use with patients with newly identified conditions and rare diseases.

"The ideal would be to find a happy medium between PROs that work at population level and PROs that can be individualized for use in care and treatment."

– Workshop participant

MEASUREMENT MATTERS

In order to use PROMs effectively for decision-making, they must be appropriate for the context and purpose for which they are being used—what the Food and Drug Administration (FDA) refers to as "fit for purpose." For example, PROMs developed to capture side effects of treatment (such as fatigue) in a highly controlled clinical trial that excludes patients with multiple chronic conditions may be inappropriate for use in the context of clinical care where patients with multiple chronic conditions and different sources and types of

fatigue are the norm. The validity of a PROM developed in partnership with a very specific patient population will not necessarily be valid when implemented in a broader patient population—even when the patients are diagnosed with the same primary condition. Another measurement challenge is when patients are not involved in using the PROM information for clinical care decisions, as in a clinical trial context; the outcome may be statistically significant but not clinically meaningful. This disconnect between the contexts in which PROMs are developed and implemented pose significant challenges to maximizing their use for decision-making.

TIME, MONEY, AND UNCERTAINTY

It can take as long as two years to complete the necessary background research for a PROM and seven years or more for it to go through the FDA PRO qualification process. This makes PRO development a significant and risky undertaking within an increasingly expensive and unpredictable biomedical R&D system. The fact that there has been a decrease in the number of new drug applications that include PROs, yet device applications have seen an increase, raises the level of uncertainty;[1] even with significant investments of time and money, there is no guarantee that the PRO will be included in the label.[2] Similarly, integration of PROs in hospital systems requires significant time and money, plus the buy-in of major electronic health record vendors. PROs in the label allow companies to communicate findings to patients and their providers, but this information is only useful if PROs are patient-centered. In the health-care context, there is no guarantee that the PRO information will be understood and used by providers or payers and result in improvements in clinical care or coverage, in part because the PROs might not measure what matters to patients and/or not produce meaningful information that can be used as part of decision-making.

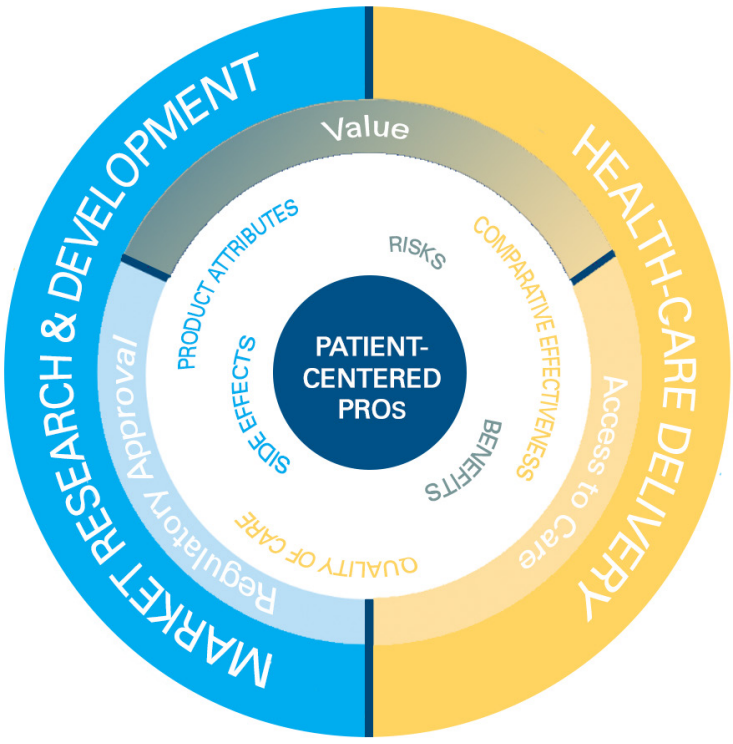
[1] Value and Use of Patient-Reported Outcomes (PROs) in Assessing Effects of Medical Devices. CDRH Strategic Priorities (2016-2017). U.S. Food & Drug Administration.

[2] Gnanasakthy, Ari et al. A Review of Patient-Reported Outcome Labeling in the United States (2011–2015). *Value in Health*, Volume 20, Issue 3, 420-429

IMPLEMENTATION

Despite the widespread introduction of electronic systems in both R&D and clinical care, we are still in a predominantly paper-based world. The same is true for most legacy PROMs, such as those developed more than two decades ago. As the paper-based measures transition to being implemented using a variety of electronic systems—including tablets and voice response systems—there are questions and concerns with these new approaches in that changing the implementation method of the PROM will negatively impact the validity of the information collected. Alternatively, patient organizations are exploring ways to augment legacy PROMs with additional information from patients, so as to preserve the validity of the original measure while integrating other data to enhance the patient-centeredness of the information. Some PROs are being adapted to "gamified" models to keep the participants engaged in data collection; it remains to be seen how these new approaches will square with more traditional implementation.

Figure 1. Building a More Continuous Process for PROs



NEXT STEPS TO ADVANCE PROs

FasterCures has identified three immediate next steps to advance the use of PROs in decision-making across R&D and care delivery. These efforts both build on ongoing activities and initiatives and require new collaborations. *FasterCures* is ready to work across stakeholder groups to move these efforts forward.

1. DRIVE ADOPTION OF PATIENT-CENTERED PROS

There are several existing frameworks, roadmaps, and rubrics of how to integrate patient perspectives into medical product development, clinical research, and health care.

- Recently, the **American Institutes for Research (AIR)** published principles of patient-centered measurement. If these prove to be useful to the field, we should then determine how they can be implemented to assist researchers, PRO development groups, and hospital systems as they evaluate existing PROMs or develop new ones that can be integrated into R&D and care delivery.
- As groups such as the **International Consortium for Health Outcomes Measurement (ICHOM)** move the field toward standardized ways of measuring and reporting patient outcomes, how will these efforts be inclusive of and advance the principles and practices of patient-centered R&D and care delivery?
- The **International Society for Quality of Life (ISOQOL)** has started an annual workshop series, "Measuring What Matters," to tackle specific methodological challenges that prevent PROs from being integrated and used in decision-making, while ensuring the patient-centeredness of the outcomes are preserved.

It is critical that these groups speak with one another and collectively drive adoption of patient-centered PROs, which are impactful only if the results from the PROMs are useful for decision-making by researchers, regulators, providers, payers, and, most certainly, patients.

2. DEFINE THE RETURN ON INVESTMENT

As the novel approaches to PRO development and implementation advance, there remains a need to identify, define, and capture the return on investment across key stakeholders, such as payers, hospital systems, and providers, as well as returns experienced by patients. All stakeholders will look for shorter-term returns on their investment of money, time, and effort in order to maintain the momentum.

- What is the return of upfront investment in integrating PROs in early R&D as opposed to waiting until later phase clinical trials are being launched?
- What are the returns for hospital systems, providers, and patients when PROMs are collected in the context of care, whether through electronic health records or another method?
- What is the benefit to payers, hospital systems, and patients of using PROMs as part of coverage and reimbursement decision-making?
- What is the return on investment of development of fit-for-purpose PROMs as a primary endpoint in a pivotal trial?

Defining these returns may minimize the perceptions of risk and make a case for sustained investment, especially if returns can be both short- and long-term. The **Clinical Trials Transformation Initiative (CTTI)** has defined the return on investment, using net present value, of patient engagement in clinical trials. This is a promising first step, and more efforts like this are needed to demonstrate returns and ensure continued investment in this area.

3. CELEBRATE SUCCESSES

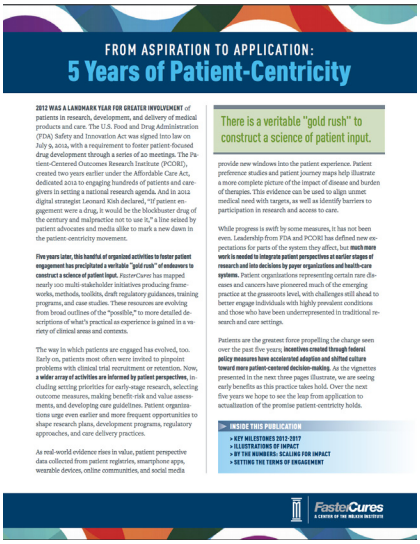
Defining success will help stakeholders benchmark their efforts and to see the end goal. That is why *FasterCures* is looking for case examples of PROMs that have been "successful," which can be defined as those that have been developed to align with concepts

that patients identify as important to them and/or integrated in clinical development in such a way that the results of the PRO are available to patients and their care providers and/or implemented in electronic health records or care delivery to improve the quality of care for patients. We suspect patient- and disease-focused organizations will play a lead or partnership role in initiatives to advance the development and implementation of patient-centered PROs. Therefore, in 2018, *FasterCures* will map these case examples to further identify gaps and champion successes.

CONCLUSION

For too long, patients' unmet medical needs and perspectives have been an afterthought, rather than a starting point, for developing medical products that address their priorities and deliver value to them and health-care systems. By advancing patient-centered PROs in medical product R&D and care delivery and removing or reducing barriers to effective and efficient implementation, the entire ecosystem can have access to better, patient-centered evidence for decision-making.

Learn more with these *FasterCures* resources



REPORT

ONLINE RESOURCE

BLOG

WORKSHOP PARTICIPANTS

We are grateful to the following participants for sharing their time and expertise during our workshop. Affiliations were accurate as of June 14, 2017, when the workshop took place in Washington, D.C.

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ABOUT US

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Dr. Cynthia (Cyndi) Grossman is director, Science of Patient Input at *FasterCures*, a center of the Milken Institute, leading efforts to improve health by expanding opportunities for patients' perspectives to shape the processes by which new therapies are discovered, developed, and delivered. Prior to joining *FasterCures*, Grossman was chief of the HIV Care Engagement and Secondary Prevention Program at the National Institute of Mental Health at the National Institutes of Health (NIH). At NIH, she worked on collaborative efforts to define the social and behavioral scientific agenda for the development and clinical testing of microbicides as HIV prevention and HIV cure-related research. She has spent nearly two decades encouraging research to identify and address the unmet patient needs related to mental health, stigma, and other social determinants of health. Grossman graduated Phi Betta Kappa from Earlham College with a B.A. in psychology and biology and earned her Ph.D. in clinical psychology from the University of Vermont. Grossman has been the recipient of a National Science Foundation Incentives for Excellence Scholarship, an NIH Ruth L. Kirschstein National Research Services Award, and a Postdoctoral Fellowship in Pediatric Psychology at the Warren Alpert Medical School of Brown University.

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