Guide To Patient Involvement In Rare Disease Therapy Development

A PUBLICATION OF THE RARE DISEASE PFDD COMPENDIUM WORKSHOP SERIES

HOSTED BY:

EVERYLIFE FOUNDATION FOR RARE DISEASES

Bio Biotechnology Innovation Organization

PUTTING PATIENTS FIRST NATIONAL HEALTH COUNCIL

PhRMA RESEARCH • PROGRESS • HOPE

AN INTRODUCTION

From the Initiative Leadership Committee

"In many cases, developing a treatment for a rare disease can be especially hard and presents unique challenges. Each success is the end of a long uphill climb. It requires the concerted efforts of stakeholders, including scientists, product developers, regulators, policy makers and of course, the energy and organization of patient advocacy groups."

– Former FDA Commissioner Scott Gottlieb,
11th Annual FDA Rare Disease Day, 2018

During the annual EveryLife Community Congress meeting in December of 2019, members reflected on the shifting medical product development landscape. Seated in the room were leaders from the patient advocacy community and biopharmaceutical partners who together had spent the prior 18 months leaning into policy efforts that yielded the Patient Experience Data (PED) provisions within the 21st Century Cures Act and the expanded Patient-Focused Drug Development (PFDD) momentum of the Prescription Drug User Fee Act (PDUFA) VI.

The collective goal was that these policy efforts and the U.S. Food and Drug Administration (FDA) Guidances arising from these landmark bills would serve as a navigation tool to ease the "uphill climb" of therapy development.

But one very important question remained. How would these Guidances – the regulatory navigation tools – apply to therapy development for *rare diseases?*

While comprehensive and forward leaning, the Guidances being developed and published were not yet specific to rare disease.

So we – the EveryLife Foundation for Rare Diseases – joined with the Biotechnology Innovation Organization (BIO), National Health Council, Pharmaceutical Research and Manufacturers of America (PhRMA) and an expert Steering Committee to lead a concerted effort that harnessed the energy and expertise of patient advocacy groups, scientists, product developers, regulators and other stakeholders. Collectively, nearly 100 experts have come together to assess all available Guidances through the lens of our rare disease community. And together we set out to develop a navigational resource for patient advocates, sponsors and all within our rare disease ecosystem that we hope will serve to make new territory seem more familiar, ease the climb and ensure the success for which we each strive.

The PFDD Guidance Compendium Workshop Series was convened to examine distinct phases of the medical product development process, from early-stage research through post-market integration into healthcare practice. For each of four workshops, subject matter experts examined relevant Guidances and resources. They identified case studies within the rare disease ecosystem and other experts willing to share their experience to inform our understanding of emerging best practices and confirm existing gaps. FDA leaders from across the agency provided input and feedback at the midpoint of the Workshop Series and on a late-stage draft of this Guide.

The product of our collective effort is this "Guide to Patient Involvement in Rare Disease Therapy Development." We hope it serves as a companion to the Guidances and expanding library of resources it references as a go-to navigational tool specific to rare diseases. We hope you will read it, reference it and share it with your partners. Ultimately, we hope it inspires more confident engagement among stakeholders and that it yields collaborative efforts to address the unmet needs of rare disease patients around the globe.

With deep gratitude to all who have contributed to this effort and the movement it reflects,

Annie Kennedy, EveryLife Foundation for Rare Diseases

Eric Gascho, National Health Council

Danielle Friend, Biotechnology Innovation Organization (through Aug. 7, 2021)

Victoria Dohnal, Biotechnology Innovation Organization (from Aug. 10, 2021-Nov. 17, 2021)

Katherine Donigan, Biotechnology Innovation Organization (from Nov. 22, 2021)

Maria Apostolaros, Pharmaceutical Research and Manufacturers of America

Christine Harhaj, Pharmaceutical Research and Manufacturers of America

Kim McCleary, Kith Collective

Samantha Mayberry, Kith Collective

TABLE OF CONTENTS

The EveryLife Foundation for Rare Diseases proudly presents the Guide to Patient Involvement in Rare Disease Therapy Development. This Guide is the final product of a year-long initiative. See page 24 for a complete listing of Leadership and Steering Committee members and initiative sponsors.

THIS INITIATIVE BY THE NUMBERS

23 Leadership and Steering Committee Members

88 TOTAL
Subject Matter Experts
- 8 Academia
- 40 Industry
- 28 Patient Advocacy Organizations
- 5 Payer Organizations
- 7 Other

20 FDA Guidances

12 Hours of Workshops

8 Cross-Cutting Topics and Sets of Action Steps

4 Workshop Summaries

112 Resources Linked in This Guide

FDA'S LEADERSHIP IN PATIENT-FOCUSED THERAPY DEVELOPMENT

Patient advocacy was forever transformed by the urgency of the early years of the HIV/AIDS crisis. At the time, patients mostly gathered to fund academic research and/or support one another in the model of self-help groups. But HIV/AIDS movement leaders recognized their lives depended on becoming experts on the fast-changing science of the virus and being strategic about policy. Among the changes that occurred as a result of their collective activism was passage of the first Prescription Drug User Fee Act (PDUFA) in 1992. This important legislation created a new funding mechanism to expand staffing at the U.S. Food and Drug Administration (FDA) as a means to speed review of and access to pharmaceutical products – including promising therapies to treat HIV. PDUFA also provided a vehicle for key agency stakeholders, patients and consumers to assess and influence FDA programs through its reauthorization every five years in light of evolving science.

Another change resulting from HIV/AIDS activism was recognition by FDA of the value of patient perspectives in regulatory decision-making. From the appointment of the first person with HIV to an FDA Advisory Committee in 1993, to establishment of the Patient Representative Program (2001), to encouraging patients to report medical product problems through MedWatch (2008), opportunities for patients and caregivers to be heard and engage with agency staff gradually evolved.

Introduction of Patient-Focused Drug Development

In 2012, the fifth reauthorization of PDUFA (PDUFA-V) was passed. Patient advocates and trade organization and industry representatives worked with FDA in the years prior to create a new way for patient communities to inform FDA staff, sponsors and the public about the impacts of their conditions and expectations for care options. This program, titled the "Patient-Focused Drug Development (PFDD) initiative," provided for 20 public meetings to showcase patient perspectives in specific disease areas outside a specific product approval decision. The first of those meetings was held in April 2013 on myalgic encephalomyelitis/chronic fatigue syndrome; narcolepsy was the subject of the first PFDD meeting dedicated to a rare disease in September 2013. The "Voice of the Patient" reports issued following each meeting are publicly available on the agency's website as an enduring resource. By the end of PDUFA V, FDA had convened 24 disease-specific PFDD meetings. *[#1]*

Initially these meetings were considered to be a modest starting point, however, FDA and others quickly recognized the unique contribution the discussions provided and the value of hearing directly from patients and caregivers about how symptoms affect their lives and the treatment benefits that matter most to them. The program was expanded to enable patient advocacy organizations to host meetings in collaboration with FDA, called "Externally-led Patient-Focused Drug Development meetings." To-date there have been a total of approximately 80 meetings, roughly half of which have been dedicated to rare diseases. *[#2-3]*

Another new effort in PDUFA-V was the development of FDA Benefit-Risk Framework, a formal and more transparent means to document the regulator's benefit-risk assessment during the review of an application for marketing authorization of a new drug or biologic. (See figure below – Benefit-Risk Integrated Assessment.) PFDD meetings inform the top two rows of the benefit-risk framework by providing a better understanding of the context and burdens of the condition and treatment burdens and needs from a patient and community perspective. *[#4]*

Deepened Commitment and Expanded Expectations

PDUFA-VI was signed into law in 2017, shortly after passage of landmark health legislation called the 21st Century Cures Act that codified PFDD as a part of FDA's mission, created a new category of "patient experience data (PED)" and issued new reporting requirements for FDA. *[#5-6]* (See figure on next page – PED Table.) In PDUFA-VI, FDA committed to issue a series of four methodological regulatory guidances and a glossary of terms to help foster PFDD and use of PED. *[#7-8]* Links to these and other important guidances are included in the Resources listed in each section of this Guide.

The latest reauthorization of PDUFA is in process as this Guide goes to press. As drafted, PDUFA-VII extends the agency's commitment to PFDD with a focus on staff training about PFDD and development of guidance for the collection and application of patient preference information (PPI), along with many other provisions. *[#9]*

In addition to meeting legislative requirements related to PFDD, FDA has created additional opportunities to interact directly with patients. *[#10-14]* Key to progress has been FDA leaders' visible and vocal testimony about the merits of patient-focused development for the full-range of therapeutics – drugs, biologics, medical devices and cell- and gene-based therapies. For example, an editorial published

BENEFIT-RISK INTEGRATED ASSESSMENT

FDA and others quickly recognized the unique contribution the discussions (from PFDD meetings) provided and the value of hearing directly from patients and caregivers about how symptoms affect their lives and the treatment benefits that matter most to them.

Benefit-Risk Dimensions

DIMENSION	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
Analysis of Condition		
Current Treatment		
Benefit		
Risk and Risk Management		

FDA's structured benefit-risk assessment framework

Example of FDA's Patient Experience Data Table included in review documents for approved New Drug Applications (NDAs), Biologics Licensing Applications (BLAs) and supplemental applications

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			**Section of review where discussed, if applicable**
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

in the Journal of the American Medical Association (JAMA) in 2015 by then soon-to-be FDA commissioner Dr. Robert Califf and FDA co-authors states, "FDA seeks to directly involve patients throughout the lifecycle of medical product development. Although patients today have a greater say in which FDA-regulated products are included in their own care, these new approaches will help to ensure that patient perspectives also have an effect on which medical products are developed and cleared or approved for the market." *[#15]*

Global Momentum for Patient Involvement

FDA's prominent role in fostering patient-focused therapy development has encouraged other countries' regulators to build this into their programs as well. *[#16]* In 2020, the Assembly of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) endorsed "development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both regulated industry and regulatory authorities." Comments received by ICH reflect wide support for the development of this guidance. *[#17-18]*

Patients and advocates around the world are getting involved in therapy development. The full promise of this new transformative movement lies ahead, in the form of high-quality patient experience data that is used across the lifecycle to inform decisions and medical products that truly align with patients' unmet needs and prioritized outcomes. Continued leadership by FDA and other global health authorities will be instrumental in achieving that goal for all patients, including millions worldwide who live with one or more rare diseases.

Resources

1. FDA-led Patient-Focused Drug Development (PFDD) Public Meetings (FDA-CDER)
2. Externally-led Patient-Focused Drug Development Meetings (FDA-CDER)
3. External Resources and Information Related to Patients' Experience ("Voice of the Patient" reports from externally-led PFDD meetings)
4. Enhancing Benefit-Risk Assessment in Regulatory Decision-Making (FDA-CDER)
5. 21st Century Cures Act (U.S. Congress)
6. Assessment of the Use of Patient Experience Data in Regulatory Decision-Making (Eastern Research Group for FDA-CDER)
7. PFDD Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision-Making (FDA-CDER)
8. PFDD Glossary (FDA-CDER)
9. PDUFA-VII Reauthorization Performance Goals and Procedures (FDA-CDER)
10. FDA Patient Engagement
11. FDA-Center for Biologics Evaluation and Research (CBER) Patient Engagement Program
12. FDA-Center for Drug Evaluation and Research (CDER) Patient-Focused Drug Development
13. FDA-Center for Devices and Radiologic Health (CDRH) Patient Science and Engagement Program
14. Rare Diseases at FDA (includes links to rare disease programs for CBER, CDER and CDRH)
15. Engaging Patients Across the Spectrum of Medical Product Development: View from the US Food and Drug Administration. JAMA. 2015;314(23):2499-2500.
16. FDA/EMA Patient Engagement Cluster
17. ICH Reflection Paper on Proposed ICH Guideline Work to Advance Patient Focused Drug Development
18. ICH Summary Report of Comments Received on the Proposed ICH Guideline Work

GETTING STARTED *How to Use This Guide*

Discovery, development and delivery of a new medical product is a complex, lengthy and resource-intensive undertaking that requires many different skill sets to execute well at every step along the way. In 2021, FDA approved 50 novel drugs and biologics (combined) and 44 innovative medical devices and technologies. Yet, for every medical product that succeeds to the approval stage, thousands of possible therapies don't progress. A substantial portion is abandoned in early phases of research, before the compound or technology is ever tested in a human being. Even those that advance to clinical trials face formidable odds.

A Unifying Approach

Over the past 10 years there has been growing recognition that early and continuous integration of patient perspectives is essential to enhance the chances of success for the development of new therapies. This Guide is intended to help all the stakeholders involved in developing new therapies for rare diseases to better understand how patient perspectives can be elicited and applied to leverage opportunities and mitigate challenges. The Guide takes an agnostic approach to the type of therapy, although different types may have variations in regulatory requirements and pathways to gain approval. Demonstrating that the benefits outweigh the risks for the intended patient population is a unifying objective for development of drugs, biologics, gene- and cell-based therapies and medical devices (which include many types of lab tests, durable medical equipment and digital therapies). Rare disease patients depend on all these types of medical products to manage their care – often in combination.

Informing Action by Different Stakeholders

The next part of this Guide is organized into eight topics. Each topic includes introductory information to help frame that subject in the context of patient-focused therapy development for rare diseases. Several of the topics are relevant across all stages of development. The challenges and opportunities described within each one might change and evolve over time as more knowledge and experience is gained. For example, the approval of a new therapy may warrant a reassessment of the unmet needs of a community in the context of that approval.

Because patient advocacy organizations and sponsors are responsible for conducting many of the activities that can lead to patient-focused therapy development, considerations for each are highlighted within each topic. The term "sponsor" is used throughout the Guide to represent any responsible party overseeing clinical research, including biopharmaceutical companies, medical device companies, academic research institutions, government agencies and other entities. "Opportunities for Collective Action" provide additional areas for collaboration, often in concert with other stakeholders. Resources provide more detailed information for further exploration, including examples of materials or programs developed by rare disease patient advocacy organizations. Note that many of the FDA guidances are relevant to multiple topics; each resource is listed just once, and the resource number is used to cite it elsewhere. Consider all the resources listed and linked to be potentially useful across all the topics and at any stage of development.

Stage-by-Stage Direction

Part two of the Guide is the Appendix, with summaries of each of the four workshops that were organized by stage of development. The BIO Framework below inspired the workshop series structure, and it is a useful reference tool as well. Please view both parts of the Guide as companions. This two-part complementary structure anticipates some readers will consult the Guide to get a broad orientation to patient-focused therapy development, while others may use it to find tips that address specific challenges. It is designed to be an evergreen resource to return to often as work progresses.

Bio Biotechnology Innovation Organization

Framework for the Use of Patient Experience Data Throughout the Product Lifecycle

		Clinical Development				
Current Meeting Opportunities	Critical Path Innovation Meetings	Pre-IND Meetings Other Type A , B, or C Meetings Critical Path Innovation Meetings INTERACT Meetings (CBER)	EoP1 Meetings Other Type A, B, or C Meetings	EoP2 Meetings Other Type A, B, or C Meetings	Pre-NDA/BLA Meetings Other Type A, B or C Meetings	Mid-cycle Communication Late Cycle Meetings Advisory Committee Meetings	Other Type B or C Meetings
Product Stage	Research & Discovery	Preclinical Development	Phase I	Phase 2	Phase 3	Health Authority Review and Marketing Authorization	Postmarketing
Examples of Patient Experience Data Applicable to the Product Lifecycle	• Experience on current treatments • Unmet medical need • Disease familiarization	• Treatment burden • Patient input on protocol designs • Clinical trial burden • Disease burden • Natural history study • Identification of clinical outcome assessments	• Patient preference for treatment • Patient benefit-risk acceptability • Treatment burden • Patient input on protocol designs • Clinical trial burden • Disease burden • Natural history study • Validating clinical outcome assessments • Patient reported outcomes • Quality of life			• Patient risk tolerance • Clinical outcome assessments	• Patient outcome in clinical practice • Clinical outcome assessments • Development of patient support applications
Relevant Decisions made During this Phase of the Product Lifecycle	• Product design adaptation	• Product design (i.e., type of device, how to take the medicine, etc.) • Protocol design (i.e. meaningful endpoints) • Clinical trial participation • Understanding the feasibility of trial participation	• Treatment arm selection • Subpopulation identification • Risk mitigation • Benefit-risk assessment • Clinical outcome Assessment Identification • Clinical trial design • Personalized medicine/biomarker • To inform the development of drug development tools • Eligibility for expedited programs			• Structured benefit-risk assessment • Subpopulation identification • Labeling optimization • Discussion at Advisory Committee meetings • Labeling	• Label/indication expansion • Shared decision making • Personalized medicine/ biomarkers • Quality of care/adherence (i.e., label clarification, physician counseling) • Risk management • Value frameworks

8 Cross-Cutting Topics and Sets of Action Steps

- Building Relationships That Last
- Documenting Patient Experience
- Defining Unmet Needs
- Determining and Measuring Outcomes That Matter Most
- Preparing for Clinical Trials
- Conducting Representative Clinical Trials and Preparing for Product Launch
- Reporting What You've Learned
- Demonstrating Value

BUILDING RELATIONSHIPS THAT LAST

The expanding practice of patient-focused therapy development in rare disease has provided new and increased opportunities for patient advocacy organizations and sponsors to collaborate.

Yet, these relationships have unique characteristics and may be unfamiliar – if not uncomfortable – at least at first. One party or the other may have limited experience with the "world" that the other inhabits. After all, patient advocacy organizations and biopharmaceutical companies are very different entities, although both may be dedicated to improving and extending patients' lives. That shared goal is an important one and can be a touchstone to guide interactions.

Acknowledging challenges each may perceive or encounter in establishing and maintaining a productive relationship can help smooth the path. There might be concerns about conflicts of interest or not having adequate processes in place to interact smoothly. Patient advocacy organizations' hesitation may stem from limited understanding of the therapy development process and an appropriate way to inform it. They may also have limited staff to dedicate or be wary based on prior experiences with industry where mutual benefit was not achieved.

Timing of outreach can be an issue for sponsors. They may be hesitant to engage patients early in product development to avoid raising premature hopes. They may be reluctant to approach an advocacy organization for the first time in later development stages of a program, fearing criticism for not having engaged sooner. There might also be concerns about perceptions of appearing promotional and the potential disclosure of sensitive information all along the way.

Actions for Patient Advocacy Leaders to Consider

GET THE LAY OF THE LAND

- Learn about the process of therapy development to become a knowledgeable partner. *[#19]* Establish relationships with experienced advocacy leaders and learn from them.
- Recognize that not every development program will succeed. Those that do may not gain approval (or access) at the same time in every country. Educate your community about the process and help manage expectations.
- Understand that you may not have access to as much information or as soon as you would like. FDA cannot disclose information about its confidential interactions with companies; however, companies can determine what and when to share, subject to regulations by the Securities Exchange Commission and other entities and according to internal policies.

PREPARE YOUR ORGANIZATION

- Inventory the assets your organization and community have to offer. *[#20]* Think about ways to help de-risk the intensive process of developing a new therapy for a rare disease.
- Work with your Board and other advisors to proactively develop guidelines that clarify the types of activities your organization will and will not engage in with sponsors. *[#21-22]* Define a process to manage requests.
- Map out PFDD-related roles appropriate for organization staff and how best to involve community members, including patients, caregivers and other family members. Building a roster of research-ready community participants may require up-front investment in planning, communication and training, yet it may also enhance interest in engaging patients.

CONVENE COMPETITORS

- If multiple companies are actively developing new therapies, consider hosting a pre-competitive forum to identify common challenges and shared solutions. *[#23]*
- If multiple patient organizations serve your community, consider how to optimize leadership and resources across organizations, coordinate efforts, avoid unnecessary duplication and manage differences.

There are many reasons to work together to form and foster productive, lasting relationships. They are the foundation for achieving the promise of patient-focused therapy development.

Actions for Sponsors to Consider

GET THE LAY OF THE LAND

- Take time to learn about the various patient advocacy organizations (formal and informal), their missions, key programs, existing resources and staffing levels prior to reaching out or making specific requests. Be sensitive to the demands on time, especially for those in volunteer roles.
- Meet patients and advocacy leaders where they are and help build their knowledge base and confidence in participating in therapy development.

PREPARE INTERNAL PROCESSES

- Educate legal and compliance staff about new expectations arising from patient-focused therapy development and work with them to establish internal processes to support meaningful interactions with patients and advocates.
- Avoid using contracts or memoranda that were written with a different stakeholder in mind. Make sure agreements are written in plain language and are appropriate to the type of engagement.
- Become familiar with fair market rates for compensating patients, caregivers and advocates who engage in research-related activities and strive to meet or exceed them. *[#24]*
- Identify internal silos that may inhibit cross-functional learning across the product life-cycle and plan to overcome them.

BEGIN EARLY AND STAY OPEN

- Identify when (at what stage) patient involvement is critical for your development program and engage patients early enough that patient involvement can inform thinking, planning and decisions and not be a "check a box" activity.
- Consider the benefits of engaging patients for their perspectives, ideas and problem-solving skills in addition to answering specific questions about a protocol or plain language summary. Leave time in engagements for organic, bi-directional learning.
- Build in feedback loops to share information with participants about how their input was or was not utilized.

Collective Opportunities

- Approach engagement as a long-term relationship with mutual benefits, not a one-off transaction. Be as transparent as possible about goals and project status. *[#25-26]*
- Start small – discussion-based interactions can provide durable and useful information and can provide the chance for parties to gain more comfort and experience with one another.
- Designate single points of contact to cultivate relationships, share updates and direct requests.
- Proactively provide timely updates to foster understanding and trust, especially regarding changes of key personnel and material changes to programs of shared interest.
- As relationships mature and build value, explore readiness of both parties to participate in joint meetings with regulators about topics where patient perspectives may be illuminating.
- Maintain an active dialogue about what the next phase of development might present as opportunities for interaction. Avoid assumptions about the level of preparedness, especially as a novel therapy approaches marketing approval and transitions to being a commercial product.
- Identify opportunities to provide (and accept) "in kind" technical support based on the different types of expertise each party may have to offer.
- Break down barriers between stakeholders to expand opportunities for co-learning and interaction, for instance by hosting scientific and community meetings at the same time and location with overlapping sessions.
- Follow best practices for disclosure of financial support given and received.
- Recognize that some stakeholders may discount or disallow data and/or evidence developed by patient advocacy organizations that report industry funding among their revenue sources. Actively participate in multi-stakeholder efforts to educate about the merits of – and appropriate guardrails for – close collaboration between advocacy organizations and sponsors in PFDD, especially as you gain more experience and have case studies that illustrate the benefits.

Resources

19. Online Education About Drug Development (Friends of Cancer Research)
20. Research Partnership Maturity Model for Patient Organizations (FasterCures)
21. Standards of Excellence for Voluntary Health Agencies (National Health Council)
22. Sample: Corporate Relations Policy (TSC Alliance)
23. Sample: Precompetitive Forum (Amyloidosis Forum)
24. Fair-Market Value Calculator (National Health Council)
25. Guiding Principles for Interaction with Patient Advocacy Organizations (BIO)
26. Principles on Interactions with Patient Organizations (PhRMA)

DOCUMENTING PATIENT EXPERIENCE

In 2016, through the 21st Century Cures Act, Congress ratified the value of "patient experience data" (PED) in the structured assessment of benefits and risks to inform regulatory decision-making.

The Act defines PED as: "Data collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers and drug manufacturers); that are intended to provide information about patients' experiences with a disease or condition, including the impact of such disease or condition, or a related therapy, on patients' lives; and patient preferences with respect to treatment of such disease or condition." *[#5]* This section of the Guide describes types and sources of PED; later sections discuss specific applications of PED.

FDA guidance describes ways PED may enhance medical product development as it is collected via patient registries, natural history studies, clinical trials and patient input on benefits and risks. *[#27-29]* Other types of PED specifically tracked by FDA in the review of applications for marketing approval of a novel therapy are clinical outcome assessments (COAs); qualitative studies (interviews, focus groups, etc.); observational studies; PFDD or other stakeholder meeting summaries and patient preference studies. *[#6]* Data must be of high quality for it to be used in regulatory and other types of decision-making.

Real-world evidence (RWE) obtained from a wide variety of sources are increasingly being used to support therapy development, monitor post-market safety, inform coverage decisions and care guidelines and develop shared decision-making tools. *[#30]* Sources of RWE that might also contain PED include electronic health records (EHRs), insurance claims and billing data, patient-generated data collected by mobile and wearable devices, adverse event reports and care networks.

Actions for Patient Advocacy Leaders to Consider

TAKE STOCK OF DATA-COLLECTION TOOLS

- Inventory the ways you collect data from and about patients and their families. This may be done through research-focused tools like a patient registry or natural history study. *[#31-34]* You may also collect information through surveys, online support communities and customer relationship management (CRM), communications, social media and/or fundraising platforms.
- Develop a profile of how many community members you can reach, where they are located and what you know about them. Assess whether data you collect, manage, store and analyze is sufficient for its intended use and what sources might be of "regulatory quality." *[#30]* Conduct outreach to extend and strengthen bonds and to fill data gaps.
- Consider patient familiarity with, and interest in, the use of mobile and wearable devices to contribute data, including their views about privacy, security, equitable access to technology and potential sources of bias.
- Carefully consider existing data collection burdens on patients and caregivers, and how they can be mitigated or reduced while still addressing important knowledge gaps.

RECOGNIZE THE PERPETUAL NEED FOR PED

- Build a research-ready community that is informed about how their active participation in data-collection efforts can accelerate research, inform access decisions, improve care and attract new partners. Provide regular updates about how patient data are advancing the mission.
- If you don't have a registry or need to upgrade an existing registry, evaluate options for single disease registries and those that house multiple rare disease registries on the same platform. Consider PED needs you and other stakeholders might have over at least the next 3-5 years.
- Establish data governance and access policies in advance so requests are evaluated on an objective basis. Align data privacy, ownership and use provisions with platform and participant consent agreements.
- Submit (or update) your organizational profile on NIH's Genetic and Rare Disease Information Center (GARD) and other rare disease resource listings so researchers, sponsors, payers and others have up-to-date information about your PED capabilities. *[#35]*

Every phase of research, therapy development and delivery to patients requires stakeholders to consistently collect and report relevant, well-specified data about patient experience.

Actions for Sponsors to Consider

INVENTORY DATA SOURCES

- Prior to starting any patient focused-related project, extend the traditional literature review to inform your understanding of the types of PED that is already available (including PFDD meeting reports *[#2-3]*) and include sources of PED collected by patient advocacy organizations, through alliances of related rare diseases and in academic-center networks *[#36]* to leverage existing data sources and avoid duplication of effort.
- Assess the strengths and limitations of each data source with respect to the rare disease of interest. Some data sets may be focused on specific genotypes or contain cross-sectional rather than longitudinal data. There may be other challenges; for example, EHR and claims data may have limited utility unless (or until) the rare disease of interest has a specific International Classification of Diseases (ICD) code in widespread use at points of care.
- Evaluate opportunities to initiate or join pre-competitive efforts to foster a comprehensive and robust data collection system.

FORECAST DATA NEEDS

- Prepare patient advocacy partners for data collection needs well in advance, especially if this is the first therapy for this rare disease. Be as transparent as possible about potential regulatory and market access requirements, especially for therapies in expedited approval pathways, one-time therapies and/or those that may require REMS programs.
- Support capacity building – including education – of partners who have access to patients and caregivers but may not have prior experience or systems to collect data over a 5-10 year time period in a manner that meets regulatory and payer evidentiary standards.
- Avoid establishing registries dedicated to collecting data for a single product – in most cases there will be too few resources, including patient participants, to make such a narrowly focused endeavor sustainable.

Collective Opportunities

- Work collaboratively with as many stakeholders as possible (patient advocates, physicians, academics, sponsors, regulators, HTA/value assessors, payers), from the earliest point to develop a comprehensive data collection system. Design data collection systems based on clear objectives, widely adopted data standards and sound governance. Be inclusive about data sources and types to reflect as great a breadth of patient experience as possible. Ensure that, as much as possible, the system serves a variety of information needs, from safety and efficacy, to value, to clinical and cost effectiveness, to personal meaningfulness.
- For one-time therapies, establish proactive, joint efforts to prepare clinical trial participants and the broader community for the long-term commitment to post-study monitoring and data collection. This may involve discussions about how these requirements affect participants' access to later generation therapies. Site investigators and treating physicians should also be enlisted in the dialogue.
- Balance data collection needs with participant burden to avoid burnout and ensure long-term sustainability.
- Work with regulators to expand opportunities to get input on PED collection efforts early and often in planning and execution stages and to enhance confidence in all PED types, especially those that are not considered as readily as PROs. *[#6]*
- Participate in multistakeholder efforts to better define the evidentiary needs and standards of different stakeholders, streamline data collection and elevate appropriate applications for real world evidence.
- Strive to uphold the FAIR Guiding Principles to improve the Findability, Accessibility, Interoperability and Reuse of data and digital assets. *[#37]*

Resources

27. Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data (FDA-CDER and FDA-CBER)
28. Rare Diseases: Natural History Studies for Drug Development (FDA-CDER and FDA-CBER)
29. eCTD Technical Conformance Guide (FDA-CDER and FDA-CBER; see page 14)
30. Real World Evidence (FDA)
31. Building Smarter Patient Registries (FasterCures)
32. Registries for Evaluating Patient Outcomes (U.S. Agency for Healthcare Research and Quality)
33. Request for Applications: Efficient and Innovative Natural History Studies Addressing Unmet Needs in Rare Diseases (FDA)
34. Rare Diseases Registry Program (RaDaR) (NIH-NCATS)
35. Genetic and Rare Disease Information Center (NIH-NCATS)
36. The National Patient-Centered Clinical Research Network (PCORnet)
37. FAIR Principles (GO FAIR Initiative)

DEFINING UNMET NEEDS

"The concept of unmet medical need" is used to target research, prioritize healthcare resources and advance policy initiatives. It was a driving force behind the 1983 Orphan Drug Act that stimulated therapy development for the 7,000 known rare diseases. *[#38]*

Today the term is also used to characterize aspects of available care that fall short of what patients and their caregivers need to live as fully as possible with a particular disease. An assessment of unmet needs can help avoid dedicating years and millions of dollars to developing and commercializing a product to meet a perceived need that isn't actually relevant to patients and thus, for which there is no market. It can also re-ignite interest in an area where patient-relevant needs are not met.

The specific unmet needs of individuals with a given disease may be shaped and influenced by a great many things. Age (at the time of disease onset, diagnosis and needs assessment), stage of disease and of life, symptom frequency and severity, impact of the disease on function and well-being, co-occurring health conditions, rate of change of functional status, access and response to standard of care (current treatments) and personal preferences and priorities are just a few influences to account for. Racial, social, cultural, economic and educational factors may influence the lived experience and the needs of the individual as well. *[#39-40]*

Unmet needs are dynamic and require periodic re-assessment, especially when new scientific discoveries are made, care delivery changes or policy advances. While any PFDD-related program should begin with a purposeful evaluation of unmet needs, there should also be a commitment to continuously refining the understanding of the community's needs and priorities over time.

Actions for Patient Advocacy Leaders to Consider

DISCERN AND ARTICULATE PATIENT AND FAMILY PRIORITIES

- Conduct a needs assessment within your community. *[#41-42]* This can be a step in strategic planning or mapping a research or policy agenda, or a stand-alone exercise. Start with a Board discussion, branch out to involve advisory committees and expand to the community as a whole, including making efforts to engage patients and families who may not be connected to the organization. Make use of family conferences and other events to host dialogue sessions.
- Once the range of needs is identified, categorize and prioritize them. Circulate and invite community input to help refine and/or validate the list and ratings of priority.
- Identify the stakeholder groups that would best be positioned to help address priority unmet needs and develop a plan to engage them and enlist their active participation.

TRANSLATE THESE NEEDS TO INFORM THERAPY DEVELOPMENT

- Educate community members about potential roles to inform therapy development and help prepare them to effectively share their lived experience and unmet needs.
- Make use of formal and informal opportunities to educate and update FDA about the burdens of the condition and the community's high-priority unmet needs.
- When appropriate, apply to host a "Listening Session" or externally-led Patient-Focused Drug Development meeting to bring the community's experiences with and expectations for new treatments to the attention of FDA staff, including members of review teams assigned to evaluate disease-specific plans and applications. Work with sponsors to understand any regulatory issues that patient perspectives might inform. These meetings can also serve as an important venue for identifying and developing solutions for a variety of unmet needs. *[#2, #43]*

At every step of patient-focused therapy development, start with a precise understanding of patients' unmet needs.

Actions for Sponsors to Consider

GET ORIENTED TO PATIENT- AND FAMILY-REPORTED NEEDS

- In the earliest stages of research, use observational methods and a comprehensive review of published and gray literature, patient advocacy websites and publications, patient blogs and videos and social media listening to gain an understanding of the range of unmet needs.
- The review of existing resources can also inform what questions to ask and terminology to use when more direct methods of inquiry with patients (interviews, focus groups, advisory boards) are appropriate.
- Identify any discrepancies with the way other informants, including medical and scientific key opinion leaders, characterize unmet needs.

FINE-TUNE UNDERSTANDING

- When conducting interviews, focus groups or patient advisory boards to better understand broad or specific unmet needs at any stage of development, allow for open-ended sharing about needs that exist and individual priorities. Listen, listen, listen. Share back what you heard and how you will apply it.
- Determine whether ethnographic studies would complement other methodologies to learn about patients' experiences and unmet needs.
- Invite patient collaborators to review and help refine a statement of unmet needs that will guide your organization's research and development mission. This allows them to see how their input is used to drive your work.

CONNECT UNMET NEEDS TO PROGRAM PLANS

- Define one or more patient-focused objective(s) the product is designed to address within the target product profile; revisit and refresh as warranted. *[#44]*
- Use the continual assessment of unmet needs to inform whether there might be preference-sensitive aspects of the product under development (such as mode of administration, durability of benefit, etc.). *[#45]*

Collective Opportunities

- Challenge the binary notion that "unmet need" relates solely to whether a rare disease has an approved therapy or not.
- Co-create patient journey maps that describe the path to diagnosis; common misdiagnoses, comorbidities and complications experienced; burdens arising from symptoms and current therapies/standard of care; challenges adjusting to life with a rare disease; progression and changes in function that may affect care decisions; and end-of-life issues.
- Collaborate to clarify the heterogeneity of unmet needs within a particular rare disease and how patient preference studies might be used to quantify various priorities and tradeoffs. *[#46]*
- Assess legacy measures through the lens of patient-defined unmet needs to identify whether novel measures may need to be developed to align with patient-centered benefit-risk assessment.
- As programs move forward, consider the unmet needs that may hamper clinical trials and access to a novel treatment such as the long diagnostic odyssey, absence of genetic test in newborn screening panels, lack of ICD code for the condition, underpowered registry/data collection efforts, limited understanding of the economic burden, etc. Wherever possible, work collaboratively to address these needs to reduce barriers to timely access to new products in the event marketing approval is granted. *[#47-49]*
- Upon approval of a new product, undertake a fresh look at unmet needs – including developing a new understanding of the different unmet needs that may present for treated patients versus those who cannot access treatment, those for whom the treatment is not safe and/or is not effective and those for whom the treatment is not appropriate or acceptable.

Resources

38. Orphan Drug Act (U.S. Congress)
39. Collecting Comprehensive and Representative Input (FDA-CDER and FDA-CBER)
40. Tackling Representativeness (National Health Council)
41. Methods to Identify What Is Important to Patients (FDA-CDER and FDA-CBER)
42. Rubric to Capture the Patient Voice (National Health Council)
43. FDA Patient Listening Sessions (FDA-OPA)
44. Target Product Profile — A Strategic Development Process Tool (FDA-CDER)
45. Patient Preference Information (FDA-CDRH and FDA-CBER)
46. Patient Perspectives on Disease Impact and Treatment Options: A Stratification Tool (National Health Council)
47. Newborn Screening Boot Camp (EveryLife Foundation for Rare Diseases)
48. ICD Code Roadmap Resource Guide (EveryLife Foundation for Rare Diseases)
49. National Economic Burden of Rare Disease Study (EveryLife Foundation for Rare Diseases)

DETERMINING AND MEASURING OUTCOMES THAT MATTER MOST

A crucial element of therapy development is selecting what measurements will be closely monitored during a clinical trial to determine whether a treatment's benefits outweigh its risks.

In rare diseases, outcome measures may include a combination of laboratory measures, imaging tests and clinical outcome assessments (COAs). COAs measure "how a patient survives, feels and functions" and include patient-reported outcomes (PROs), observer-reported outcomes (ObsROs), clinician-reported outcomes (ClinROs) and performance outcomes (PerfOs). *[#50-54]*

Ideally sponsors will select COAs that closely align with outcomes that matter to patients and they would seek to show those outcomes change in ways that are meaningful clinically and to patients. However, it is more common for rare disease outcomes to be selected on the basis of published research, a consensus of treating professionals and/or to "borrow" outcome measures from therapy approvals for clinically adjacent diseases. Deciding whether to utilize a legacy measure or establish a new COA is among the most challenging decisions in rare disease therapy development. The decision takes on added weight in today's access environment since evidence generated in the clinical trial is used by payers and others to determine coverage and reimbursement policies.

Therefore, development of a new COA or a set of core outcome measures is best approached through a multistakeholder initiative that involves patients, caregivers, clinicians, academic researchers, sponsors, regulators, payers and outcome assessment experts. Such a forum enables each to contribute a unique perspective and to build awareness of others' viewpoints to enhance outcome selection, tool design, suitable anchoring and the assessment and interpretation of change when the measure is fielded. *[#55-58]*

Actions for Patient Advocacy Leaders to Consider

BECOME FAMILIAR WITH BENEFIT-RISK ASSESSMENT

- Gain an understanding of the ongoing assessment of a medical product's benefits and risks in a therapy development program and ways to bring community perspectives into that assessment. The value of specific benefits and the acceptability of specific risks or potential harms is subjective and depends on whose perspectives are being considered. Patient-focused therapy development factors patients' perspectives and tradeoffs into the formal benefit-risk assessment during development, at regulatory review and in the post-market setting. Benefit-risk is also the centerpiece of shared decision-making conversations between patients and their physicians and individuals and their family members.
- Review the benefit-risk guidances from FDA *[#59-61]* and the case study published by BIO *[#62]* that describe how patient perspectives can factor into the assessment of benefits and risks. Learn how FDA's Benefit-Risk Integrated Assessment is used and how it connects to the Patient-Focused Drug Development Initiative. *(page 4)*
- As a follow-on to an unmet needs assessment *(page 12)*, develop an understanding of the therapy benefits that matter most to patients and what their tolerance for risks might be. This can be a complex undertaking, so start small and engage experienced advisors to help build a more detailed and comprehensive understanding over time. *[#63]* This is an important step toward developing patient-centered outcome measures used in a variety of regulatory, payment and care decisions. It can also be a starting point for developing draft guidance based on the process that FDA has outlined. *[#27, #64]*

INFORM COMMUNITY MEMBERS ABOUT BENEFIT-RISK AND THEIR ROLES

- Educate the community about the concept of benefit-risk assessment. Although each of us makes decisions every day based on tradeoffs of benefits and risks, the terminology might be unfamiliar and the importance of patients' views might be new, as well.

The ultimate rare disease outcome measure is clinically meaningful to patients and caregivers, can be measured in a manner and timeframe that convinces regulators that the therapy is safe and effective, and informs payer decisions to provide timely access.

Actions for Sponsors to Consider

REVIEW REGULATORY EXPECTATIONS

- Pay close attention to FDA guidances on "Methods" *[#41]* and "Fit-for-Purpose COAs" *[#51]* as you undertake research to understand what outcomes matter most to patients. Determine the potential role for caregivers to inform this research, especially if some outcome measures might include observer ratings (outside the clinical setting) or if a caregiver will report as a proxy for the patient. *[#65]*
- Clarify whether and when PED might be useful, including patient preference studies to prioritize various treatment benefits and risks and/or assess the tradeoffs patients (and caregivers) might be willing to make. Review available FDA guidance *[#45]* and published methods. *[#66]*

DETERMINE WHETHER TO USE EXISTING MEASURE(S) OR DEVELOP NOVEL MEASURE(S)

- Assess whether fit-for-purpose measures and instruments already exist, to determine whether new tools need to be developed or can be modified. *[#67]*
- Explore whether a set of measures (rather than a single measure) might better capture the experience of patients with different clinical presentations or at different stages of the disease. Weigh the extent to which response burdens for multiple measures could affect retention and/or data completeness.
- Apply novel measures or outcome sets in disease-monitoring studies and "run-in" studies to establish baseline understanding of the instrument's psychometric properties and performance and inform refinements prior to inclusion in registration trials, if possible.

INVOLVE PATIENT ADVOCATES IN DATA ANALYSIS

- In addition to involving patient advocates in developing outcome measures (see "Collective Opportunities" at right), engage their help to make sense of outcomes data given their familiarity with: dynamic aspects of the disease; challenges participants may have interpreting questions and response choices; relevance of increments of change to patients' lives; problems with recall frames and other confounding aspects of measurement.

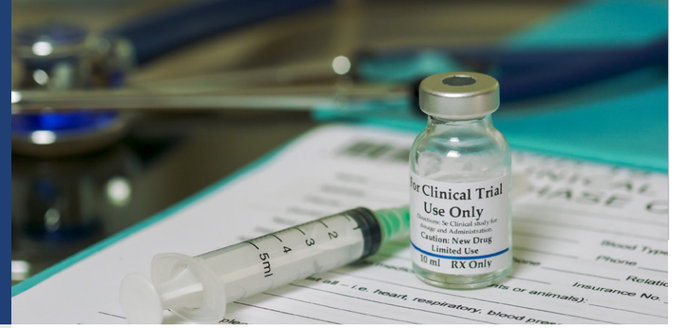
Collective Opportunities

- When developing novel patient-centered outcome measures, work collaboratively with all stakeholders, including clinicians, to understand the dynamics of a selected concept of interest based on lived experience, its variation over time within an individual and across patients and what degree of change would be meaningful, based on the properties and potential benefits of a specific product. Co-develop instruments whenever possible; pilot test them at a minimum. Collaborate during the transition from legacy measures to novel ones.
- Gain a firm shared understanding of what value patients and caregivers assign to slowing progression and ways they might recognize a change in the rate of progression. Identify ways that patients and caregivers might be compensating for functional losses so these can be accounted for in the study. Be sensitive when asking about losses that haven't yet occurred and work together on compassionate and ethical ways to address in assessment tools.
- Engage with other rare disease communities to work on cross-cutting outcome measures. FDA is incentivizing initiatives of this kind through a pilot grant program. *[#55]*

Resources

50. Clinical Outcome Assessment (COA) Compendium (FDA)
51. Incorporating COAs into Endpoints for Regulatory Decision-Making (FDA-CDER and FDA-CBER)
52. PRO Measures: Use in Medical Product Development to Support Labeling Claims (FDA)
53. Principles for Selecting, Developing, Modifying, and Adapting PRO Instruments for Use in Medical Device Evaluation (FDA-CDRH and FDA-CBER)
54. Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments (FDA-CDER and FDA-CBER)
55. Pilot Grant Program: Standard Core COAs and Their Related Endpoints (FDA-CDER)
56. Core Outcome Sets Initiative (Green Park Collaborative of the Center for Medical Technology Policy)
57. Sample: Core Outcomes Set: Hemophilia (coreHEM) (Green Park Collaborative)
58. Coming Soon: Patient-Centered Core Impact Sets Blueprint (National Health Council)
59. Benefit-Risk Assessment for New Drug and Biological Products (FDA-CDER and FDA-CBER)
60. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (FDA-CDRH)
61. Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (FDA-CDRH and FDA-CBER)
62. Key Considerations for Developing and Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study (BIO)
63. Sample: Caregiver Preferences Study (Cure Sanfilippo Foundation)
64. Sample: Patient Advocacy Community Developed Guidance (ALS Association)
65. A National Report on Family Caregiver Roles in Medical Product Development (National Alliance for Caregiving)
66. Framework for Integrating Patient Perspective into Medical Device Benefit-Risk Assessments & Catalog of Methods (Medical Device Innovation Consortium)
67. Core Outcome Measures in Effectiveness Trials (COMET Initiative)

PREPARING FOR CLINICAL TRIALS



In guidance, FDA recognizes the unique challenges associated with conducting clinical trials in rare diseases.

FDA encourages sponsors to "Engage early in the drug development process with patient advocacy groups, experts and patients with the disease, and elicit their suggestions for the design of trials, including trial protocols, that participants will be willing to enroll in and support. For a number of rare diseases, there are active patient advocacy groups that are strongly committed to finding new therapies and supporting clinical trials." *[#68-70]*

These are ample reasons to expand interactions between sponsors and advocacy organizations, both as a program approaches the first-in-human study (which in rare disease may involve patients rather than healthy controls) and when planning larger studies later in development. Interactions are especially important for patient communities that have never before experienced clinical trials and in competitive disease areas where patients and families may be choosing between clinical trials.

In addition to providing important input on trial design, advocacy organizations may help identify sites through established clinical networks and support development of patient-centered recruitment materials, including informed consent. They may help educate community members about what it means to participate in clinical trials, prepare patients and caregivers to serve on advisory boards and in other advisory roles and connect interested participants with research opportunities.

Increasingly, patient advocacy leaders are also playing an important role when invited by sponsors to take part in meetings with regulators. They can provide perspectives on patient-centered aspects of trial design and describe what they're doing to foster understanding of and participation in research.

Actions for Patient Advocacy Leaders to Consider

BE THE "GO-TO" COMMUNITY RESOURCE

- Educate your community about the process of developing new therapies and help set and maintain expectations as the process unfolds. It takes longer and is more uncertain than most people realize; moderate hope tempered with reality. *[#71-74]*
- Produce resources tailored to the needs of patients and families considering whether clinical trial participation is right for them. If multiple types of treatments (drugs, biologics, gene therapies, medical devices) are in development, it may be important to recognize differences between them. Site investigators may need educational support to understand and meet patients'/families' needs during the conduct of trials. *[#75-78]*
- As opportunities for patient/caregiver involvement expand, conduct trainings to help them better understand therapy development and what sponsors might be asking of them.
- Identify individuals who would be good candidates to serve in FDA's Patient Representative program (provide direct input to the agency) *[#79]* and on Institutional Review Boards (protect the welfare of study participants) and Data Safety Monitoring Boards (monitor patient safety during clinical trials).

HOLD FAST TO THE TRUSTED BROKER ROLE

- Track the therapeutic pipeline, making public updates as companies release news about study results and future intentions. *[#80]*
- Stay in communication with sponsors about messaging and questions arising from the community, including practical or perceived barriers to participation that could be addressed.
- Whether there is one company conducting clinical trials or a dozen, remain fixed on the needs of the community and preserve the organization's neutrality and independence. This is a good time to revisit the guidelines described on page 8 to ensure they are appropriate to this stage of engagement.

When an innovative therapy is ready to be tested in clinical trials, opportunities for patient involvement shift into high gear. This is a time where aspirations to be patient-centered can be realized or defeated.

Actions for Sponsors to Consider

INTEGRATE PATIENT INVOLVEMENT EARLY IN PROTOCOL PLANNING

- Don't wait until the final trial protocol is ready for approval to initiate patient engagement. Existing FDA guidance recognizes that patient input on trial design and logistics can help to improve and accelerate clinical study recruitment, enrollment and completion with fewer protocol amendments and better overall data quality, but this isn't possible without early involvement when patient perspectives can truly inform design and other operational plans. Last-minute engagement also risks patient advisors feeling their involvement is a "check-the-box" exercise or for validation.
- Include open-ended opportunities for patient advisors to raise study-related challenges the study team may not have anticipated. This can yield powerful new insights, as well as practical action items.
- Involve a third-party facilitator familiar with the language and terminology of the patient community and the sponsor to "translate" information in both directions, at least in early interactions.

IDENTIFY OTHER WAYS TO INVOLVE PATIENTS

- Review recruitment and informed consent materials with patients and family members and get their input on how and where to present these materials. Ask about visual or cognitive challenges that should be factored into decisions whether to use e-consent.
- Consult patients about digital and app-based tools they use to manage their disease (including symptom, food and activity diaries) before launching development of trial-specific tools. Include user testing at key milestones of the development plan.
- Conduct site simulations to identify challenges patients and families might face in accessing and completing clinic visits and to proactively design site support programs to reduce barriers and burdens.

Collective Opportunities

- Maintain regular check-ins through a single point of contact. As engagement activities expand and potentially involve other functions/departments within each organization, this practice can help reduce the potential for an overwhelming number of requests in either direction and/or non-compliant interactions.
- Address up-front potential challenges to acceptance of placebo-controlled studies, especially for families facing rare diseases with no or limited treatments. This topic is ripe for early discussions that include sponsors, advocacy leaders and regulators, especially if the natural history is not well-documented and/or there is not sufficient evidence from previous treatment studies that could inform the design and conduct of future studies. *[See #68, pages 14-15]*
- Structure engagement activities to facilitate co-learning where the host (whether sponsor or advocacy organization staff) gains a better understanding of community members' perspectives and patient and caregiver participants learn more about therapy development.
- Look for ways to bridge the gap between clinical care and clinical trials as another means to reduce burdens on study participants and families. Share laboratory and imaging test results performed during the study with treating physicians who may require the same information to guide care. Don't overlook the participant's need for other types of specialty care that may not be part of the study; factor it into the protocol so it can be controlled for and coordinated.

Resources

68. Rare Diseases: Common Issues in Drug Development Guidance for Industry (FDA-CDER and FDA-CBER)
69. Enhancing the Diversity of Clinical Trial Populations (FDA-CDER and FDA-CBER; quotation is from page 13)
70. Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations (FDA-CDRH and FDA-CBER)
71. Drug Development and Clinical Trials Process: How New Therapies Are Created and Brought to Patients, A Special Focus on Rare Diseases (BIO)
72. BIO Clinical Trials: The Power of Participation (BIO)
73. Toolkit for Patient-Focused Therapy Development (NIH-NCATS)
74. ClinicalTrials.gov (NIH-NLM)
75. Sample: Clinical Trial Information for Patients/Families (International Pemphigus & Pemphigoid Foundation)
76. Sample: Clinical Trial Information for Patients/Families (including gene therapy) (Friedreich's Ataxia Research Alliance)
77. Sample: Information About Upcoming (first-in-humans) Clinical Trial (Dravet Syndrome Foundation)
78. Sample: Clinical Trial Readiness Materials for Sites (Cure SMA)
79. FDA Patient Representative Program (FDA)
80. Sample: Therapeutic Pipeline Tracker (Angelman Syndrome Foundation)

CONDUCTING REPRESENTATIVE CLINICAL TRIALS & PREPARING FOR PRODUCT LAUNCH

Whether it's scaling from small phase I studies to larger phase II and III studies or overcoming challenges that arise in the conduct of studies, patient involvement can help identify patient-centered solutions.

As FDA guidance acknowledges, "rare diseases often affect small, geographically dispersed patient populations with disease-related travel limitations, thus necessitating special efforts to enroll and retain these participants." *[#69]* Another guidance highlights that patient engagement can be especially helpful when "protocols include lengthier follow-up periods and/or frequent visits to the investigational site." *[#70]*

Clinical trial data informs the ever-evolving assessment of benefits and risks, so this might be an opportune time to quantify how patients weigh particular benefits and tradeoffs with risks for the therapy being studied. *[#81]* Patient preference information (PPI) can also identify how preferences may vary by age, stage of disease, degree of functional impairment and other patient characteristics. PPI may have utility for a sponsor's regulatory, market access and marketing plans and will be informative to patient advocacy organizations as well. *[#45, #82]*

As pivotal trials near completion, promising data may instill confidence to begin pre-launch planning, in which case there is a new agenda for collaboration. Studies may also yield inconclusive data that warrants another clinical trial or other types of follow-on research. It may also become clear that the therapy is not achieving the intended effect or that side effects or long-term risks are excessive. In the event the sponsor discontinues a therapy development program, patient advocates can play an important role in making use of learnings to guide future research.

Actions for Patient Advocacy Leaders to Consider

CONTINUE COMMUNICATING

- Maintain a steady drumbeat about opportunities to participate in clinical research, including outreach to underserved populations. This is an important component of building and maintaining a research-ready community to complete current studies and attract other sponsors to invest in developing new therapies.
- Monitor community dialogue about clinical trials. You may hear feedback that never reaches a sponsor or site staff, particularly from individuals and families that decide not to pursue participation or willing families who perceive or experience barriers.
- Keep sponsors informed about changes in the landscape affecting patients' care-related decisions or perspectives on unmet needs and priority outcomes.
- Educate community members about the phases of clinical trials and periods of relative quiet that may occur following the end of each study. Help prepare for the range of potential outcomes and the year (or more) that it can take for FDA to review a sponsor's application for marketing approval after it is filed.
- In the event a therapy program is put on hold or discontinued, develop a plan to channel community members' disappointment into productive action.

ANTICIPATE CHALLENGES A NEW THERAPY WILL FACE

- Become knowledgeable about the market access environment and network with advocacy leaders who have relevant experience. Form or strengthen connections to payers and value assessors.
- Transition your corporate council to focus on addressing regulatory and access challenges that sponsors may face and that may impede patients' opportunity to benefit from promising therapies.
- Engage medical advisors in advance planning for ways to educate health care professionals about new therapies and identify challenges that may arise in clinical settings.

There is a shared opportunity to mobilize patients and families to participate in clinical trials to generate the evidence needed to assess the safety and efficacy of a new therapy and then prepare together for next steps.

Actions for Sponsors to Consider

FACTOR IN FDA RECOMMENDATIONS

- Review FDA's "Enhancing the Diversity of Clinical Trial Populations" guidance *[#69]* that provides strategies to improve enrollment and retention of representative study participants. The following sections are particularly relevant; recommendations specific to rare disease are noted:
  - "Understanding how participants choose whether to participate in a clinical trial allows sponsors to more effectively recruit participants who may be reluctant to enroll." *(page 11)*
  - "Consider diversity when selecting health care providers and study coordinators to assist with clinical trial recruitment, because participants may prefer a health care provider of their same cultural background." *(page 11)*
  - "Consider re-enrolling participants in early-phase trials into later-phase randomized trials when appropriate." [Rare disease-specific] *(page 13)*
  - "Consider a broader pediatric development program early. The arbitrary sequential enrollment of pediatric subgroups by chronological age for some conditions could unnecessarily delay development of medicines for children by limiting the population for study." *(page 7)*
  - "Make available an open-label extension study with broader inclusion criteria after early-phase studies to encourage participation." [Rare disease-specific] *(pages 13-14)*
  - "Remain engaged with communities after the conclusion of the clinical research and share trial updates to continue to strengthen bi-directional relationships with communities." *(pages 10-11)*

STEWARD LEARNINGS FOR OTHER PLANNING PURPOSES

- Make use of what is learned about barriers and burdens specific to a therapy in planning for launch, clinical adoption and market access, including patient support programs that might be warranted to overcome these challenges if marketing approval is granted.

Collective Opportunities

- Understand the implications of the study structure and site visits for families that may have more than one affected family member who desires to participate.
- Work together with clinical experts to re-evaluate eligibility criteria if there is a high rate of screening failure.
- Assess barriers and sources of burden for study participants that might stem from transportation issues, physical and accessibility challenges, child care needs, limited clinic hours, excessive time away from work or school as well as inequities due to racial, ethnic and cultural backgrounds such as access to specialty care and diagnostic and confirmatory tests. Work collaboratively to identify sensible solutions.
- Ensure that direct and indirect costs to participants in a study are fully understood and that reimbursement – in an amount, on a timely basis and in a form easily useful to the participant – is provided.
- Consider the possibly urgent needs of those who are ineligible to participate in a clinical trial and wish to access the therapy. Work together to develop and inform community members about expanded "compassionate" access programs.
- Co-develop a clinical trial exit program to learn about the participant's experience in the trial to improve later phases of study or future programs in the same disease or other adjacent diseases. Determine how best to return information about the study to participants in a manner that honors their contributions and is sensitive to medical and emotional factors related to study participation.
- If safety concerns appear during the study that suggest they could be reduced through specific precautionary communications or actions, enlist patient advisors to develop plans that could evolve into proposed Risk Evaluation and Mitigation Strategies (REMS). *[#83]*
- If a program is discontinued, work collaboratively to identity appropriate ways for placebo/standard-of-care data to benefit the field and patient community.
- In preparation for potential launch, engage patient advisors to help develop and/or review patient-facing materials including product information (including website) and patient support programs.

Resources

81. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (FDA-CDER and FDA-CBER)
82. Sample: Patient Preference Studies & Data Collection (Parent Project Muscular Dystrophy)
83. Risk Evaluation and Mitigation Strategies (REMS) (FDA-CDER)

REPORTING WHAT YOU'VE LEARNED

Communicating what is learned through patient engagement and the collection of patient experience data (PED) is the ultimate cross-cutting topic.

It is relevant at every stage of therapy development and delivery and is vital to every stakeholder. The task has multiple dimensions: individual and organizational learnings, internal and external information needs, immediate and long-term implications, technical and artistic representations, formal and informal reporting. It requires conveying complex information in a clear, cohesive and compelling manner so the recipient understands what was learned and how they can apply it to decision-making, whether the recipient is an FDA reviewer focused on a new drug application or a family caregiver weighing the potential benefits and risks of a new treatment plan. *[#84]*

To do this will require more than expository text, pivot tables and bar charts. Storytelling techniques can help contextualize and provide a companion narrative for data-driven elements. *[#85]* Data visualization tools provide an accessible way to display patterns and trends. Video, infographics and podcasts are potential vehicles to employ, depending on who you are trying to reach and for what purpose. Some settings require structured approaches – such as regulatory filings – while others can integrate more creative methods. Every effort to communicate about patient experience should be grounded in helping uncover meaning and guide action, rather than simply documenting completion of an activity.

Two important best practices to incorporate in reporting are health literacy and the return of results to participants in patient engagement activities and clinical trials. *[#86-88]* Both aim to enhance trust and transparency and contribute to a more informed and engaged public.

Actions for Patient Advocacy Leaders to Consider

REINFORCE THE RETURN ON ENGAGEMENT

Attract and sustain community involvement in efforts to collect and apply PED by regularly reporting back on what is being learned and how it is informing action within the organization and by others. *[#89]*

- Experiment with a variety of formats and channels to share information back with participants in PED efforts. Information overload and survey fatigue can lead to burnout, so balance more comprehensive reporting with visuals and bulleted lists that can be shared through social media. *[#90-95]*
- Ask sponsors who request assistance to recruit individuals for advisory boards, interviews, etc., whether they will report back on what was learned. Posing this question can help shift practice if this is not yet routine for their company.

TRANSLATE UNIQUE INSIGHTS INTO PRODUCTIVE RELATIONSHIPS

- Recognize that your unique vantage point on what matters most to your community members is a vital resource for other stakeholders—if you can translate what you know to inform the kinds of decisions they face. Presenting new PED learnings to sponsors, regulators, payers, academic researchers, clinicians and lawmakers will each require a targeted approach. The better you understand their unique needs and tailor your communications to meet them, the more valuable the information – and your organization's role in collecting it – become.
- Develop relationships with regulators that build over time through your ability to convey and connect them to community perspectives as the therapy pipeline develops. This might start with a listening session or externally-led PFDD meeting but can extend to periodic briefings on new learnings or collaborative interaction to address emerging regulatory issues. *[#2, #43]*

The richness of patient experience data warrants new approaches to derive meaning from it and share it with others. Content collected from multiple sources using a blend of methods deserves novel presentation formats that reach and move intended audiences.

Actions for Sponsors to Consider

DEVELOP PROACTIVE COMMUNICATIONS PROCESSES

- Seize the opportunity to differentiate the way in which your company shares news with advocacy leaders and communities. Create a (compliant) practice of timely and tailored business and community communications (e.g., working with community leaders to provide updates in parallel to shareholder announcements and press releases). *[#96]*
- Recognize that savvy advocacy leaders and community members will monitor the company's website, investor news and records on clinicaltrials.gov for updates. Build trust by communicating regularly with community leaders, even if there isn't news that you're able to share. The effort will go a long way to avoid speculation and dampen misinformation.
- Follow the emerging best practice of reporting back to participants in advisory boards, interviews and formal studies with high-level summaries of what was learned. This may require getting legal and compliance colleagues on board with the rationale, format and timing of feedback.

CONNECT THE PED "DOTS"

- Present PED that has been collected via methodologically sound methods to ensure regulators can utilize the data. Provide a clear narrative about what was learned and how it applies to the filing, strategically linking evidence from multiple studies and engagements.
- Use a similar strategy for linking PED elements to support market access discussions with value assessors, payers and pharmacy benefit managers.
- Utilize this information for marketing plans as well, centering patient-facing product-related information and communications on what has been learned across all the engagements with patients and family members. Pay particular attention to health literacy, cultural considerations (both general and unique to the specific community) and patient-preferred terminology and language to describe their disease. Co-design materials whenever possible.

Collective Opportunities

- Present case studies at conferences and through publications to document successes (and shortfalls) and help advance the practice of patient involvement for the benefit all stakeholders. Highlight the unique contributions and takeaways each stakeholder can offer. Aim for venues with active participation by regulators and payers.
- Hold training programs for your organization to inform colleagues about the benefits of and best practices for patient-focused therapy development.
- Develop a strong competency for plain language writing, especially when summarizing scientific or medical information. Ensure study information posted to clinicaltrials.gov is clear and accessible to all the patients and families you hope to attract to participate. *[#69, #74, #97]*
- Develop culturally-competent patient-facing materials, in languages in addition to English as may be warranted by community demographics.
- Expand outreach to include non-traditional outlets so resources reach individuals who may not be connected through existing channels. *[#69]*
- Work to create new regulatory meeting types to convey PED- and patient-engagement-related information to regulators to gain the benefit of their input and improve chances that the resulting information will be used in decision-making. *[#6]* Open more avenues to patient advocacy organizations and other stakeholders with valuable PED reports to contribute.
- Innovate the PFDD meeting and "voice of the patient" report format to increase the likelihood it will inform regulatory decision-making more often than has been reported. *[#6]*

Resources

84. Best Practices for Communicating Benefit, Risk, and Uncertainty for Medical Devices (Medical Device Innovation Consortium)
85. Storytelling Resources (TED)
86. Health Literacy for Science Communication (National Health Council)
87. Health Literacy in Clinical Research (Multi-Regional Clinical Trials Center)
88. Plain Language Resources (Multi-Regional Clinical Trials Center)
89. Sample: Report on Industry Collaboration (Cure SMA)
90. Sample: Patient Registry Report (Cystic Fibrosis Foundation)
91. Sample: Patient Registry Infographic (PFIC Advocacy & Resource Network)
92. Sample: Podcast (Wake Up Narcolepsy)
93. Sample: Storytelling (Emily's Entourage)
94. Sample: Storytelling Program (EveryLife Foundation for Rare Diseases)
95. Sample: Storytelling Program (Sick Cells)
96. Advertising and Promotion Guidances (FDA)
97. Drug Trials Snapshots (FDA-CDER)

DEMONSTRATING VALUE

A series of recent studies supported by the EveryLife Foundation, the Government Accountability Office (GAO) and the National Institutes of Health (NIH) have found that people with rare diseases face significantly higher health care costs that stem from lengthy diagnostic delays and heavy reliance on healthcare services, including recurrent hospitalizations, to sustain life and relieve pain and suffering. *[#49, #98-99]*

Drugs, biologics, cell- and gene-therapies and medical devices approved to treat rare diseases account for just a portion of the total costs that a family and the overall system bears. The National Economic Burden of Rare Disease Study assessed that 60% of the costs were attributed to indirect and non-medical expenses – costs incurred directly by families. *[#49]* Yet, high costs of developing novel therapies for small populations often result in high per-product prices. Determining the value of a rare disease medical product – and how it will be paid for at launch and over time – can create challenges for patients attempting to access the therapy.

Patient-relevant outcomes can be a unifying element for defining value, especially if alignment occurs early in development and PED is part of the regulatory evidence base available for coverage and formulary decisions. Products approved under expedited pathways *[#100-101]* and one-time therapies *[#102]* face additional evidence requirements following approval and this data may factor into initial and ongoing value and coverage decisions. *[#103-104]*

Over time, the accruing knowledge base must support all stakeholders' needs – including individual patients – to make informed decisions.

Actions for Patient Advocacy Leaders to Consider

GET SMART

- Recognize that patient perspectives on value often are not adequately considered, due to limited capacity to engage and limited expertise in these areas. *[#105]* Make it a priority to build that expertise and develop capabilities to engage.
- Learn about the market access ecosystem and how rare disease products are valued, covered and reimbursed by different payers. *[#106]* For example, Medicare uses "reasonable and necessary" criteria to determine coverage *[#107]* and the Institute of Clinical and Economic Review (ICER) uses clinical comparative effectiveness in its assessments. *[#108]*
- Include questions about coverage types in your registry or community profile surveys to better understand which payers might be especially important for you to engage.
- Help educate community members about navigating health insurance benefits and patient support programs. *[#109]*

REACH OUT

- Partner with rare disease organizations within a broader set of conditions (i.e., neuromuscular diseases, rare epilepsies) to do outreach to payers, health economists and value assessors. Few companies are staffed to allow time for disease-by-disease interactions; they may be receptive to opportunities to learn about a set of rare conditions.
- Connect with leaders of other patient advocacy organizations who have participated in ICER reviews as soon as ICER announces a review of one or more products being developed for or used to treat the rare disease you represent. First-hand perspectives will help identify the resources that will be required to participate effectively.
- Work with medical advisors and clinical networks to identify and reduce use of low value care elements, especially as a new therapy is adopted. Products and services that contribute to total costs with negligible improvement in patient outcomes should be eliminated, whenever possible.

Understanding the value a rare disease therapy delivers is important to every stakeholder in the system, from an individual patient to the caregiver, prescribers, payers, policymakers and the sponsor.

Actions for Sponsors to Consider

PRIORITIZE EVIDENCE-GENERATION TO INFORM VALUE AND ACCESS

- Communicate with payers about products in advance of approval to help them budget and plan for future coverage and reimbursement, as described in FDA guidance. *[#110]* Such discussions may illuminate additional health care economic information that would be helpful to guide coverage and reimbursement decision-making when the product is approved.
- Prepare for the possibility that products being developed through expedited pathways may face added scrutiny by payers. Some have special processes to determine medication use and formulary placement for drugs that come through the Accelerated Approval Pathway. Plan how you will support patient access if coverage policies are more limited than the label allows.
- Expedite required post-market and confirmatory trials to generate the evidence required to refine value assessments, coverage policies and shared decision-making by patients and their care teams.

PREPARE AND EQUIP PATIENT ADVOCACY PARTNERS

- Help educate patient advocacy partners about the current access environment and processes used by different entities in the U.S. (and other countries) to assess value and establish coverage policies, especially if the product your company is developing (or has approval to market) is a first-of-its-kind (e.g., disease-modifying therapy, one-time therapy) for this patient community.
- Recognize that patient advocacy leaders must represent community needs and perspectives. Avoid expectations that they will defend product pricing or payer contracting terms that place undue burdens on patients and families.
- Provide appropriate financial remuneration for data collection efforts conducted by patient advocacy partners that can be used in value assessments both at the time of approval and over the longer term as more experience with a therapy accrues.

Collective Opportunities

- Collaborate to collect and report data based on total costs of care to inform timely and appropriate access to specific medical products. The understanding of who is most likely to benefit from what care and treatments may evolve over time, which ultimately may affect how a particular product is prescribed and used.
- Aggregate the disparate sources and types of information about costs of care delivered in different settings by different providers, including family caregivers. Identify means to calculate savings achieved through improved care as new therapies become available. Incorporate savings generated by the avoidance of harms that lack of treatment or inappropriate treatment might have caused.
- Enlist appropriate stakeholders to support the early and ongoing assessment of value, drawing on evidence collected in the kind of comprehensive system described on page 11. Consider whether patient preference studies can help to support this assessment. *[#111]*
- Participate in and advance forums that lead to better appreciation for the merits and integration of patient perspectives in value assessment, benefit design and coverage and utilization policies. *[#112]*

Resources

98. The IDeaS Initiative: Pilot Study to Assess the Impact of Rare Diseases on Patients and Healthcare Systems (Office of Rare Diseases Research, NIH-NCATS)
99. Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial (Government Accountability Office)
100. Expedited Programs for Serious Conditions (FDA-CBER and FDA-CDER)
101. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (FDA-CBER)
102. Long Term Follow-up After Administration of Human Gene Therapy Products (FDA-CBER)
103. Cures for Life: Long-Term Follow-Up Data Collection for Cell and Gene Therapies (FasterCures)
104. Emerging Market Solutions for Financing and Reimbursement of Durable Cell and Gene Therapies (MIT New Drug Development Paradigms Initiative)
105. A Dialogue on Value Assessment that Meets the Needs of Patients and Employers (National Health Council)
106. Meeting the Affordability Challenges Posed by Orphan Drugs: A survey of payers, providers, and employers (Academy of Managed Care Pharmacy)
107. Medicare Coverage Determination Process (Centers for Medicare & Medicaid Services (CMS))
108. Methods Update: Treatments for Ultra-Rare Diseases (ICER)
109. Sample: Patient Education About Access & Coverage (Sick Cells)
110. Drug and Device Manufacturer Communications with Payors, Formulary Committees and Similar Entities: Questions and Answers (FDA)
111. Sample: Preference Study to Demonstrate Value – PAVING Study of Gene Therapy in Hemophilia (IMI PREFER)
112. Principles for Value Assessment in the U.S. (Innovation and Value Initiative)

ACKNOWLEDGEMENTS

With sincere appreciation to the following individuals who made extensive contributions to the design and convening of the workshop series and development of this Guide:

Project Leadership

- Annie Kennedy, EveryLife Foundation for Rare Diseases
- Eric Gascho, National Health Council
- Danielle Friend, BIO (through Aug. 7, 2021)
- Victoria Dohnal, BIO (from Aug. 10, 2021-Nov. 17, 2021)
- Katherine Donigan, BIO (from Nov. 22, 2021)
- Maria Apostolaros, PhRMA
- Christine Harhaj, PhRMA
- Kim McCleary, Kith Collective
- Samantha Mayberry, Kith Collective

Project Steering Committee

- Jennifer Bright, The Innovation & Value Initiative
- Nimi Chhina, BioMarin
- Ryan Fischer, Parent Project Muscular Dystrophy (PPMD)
- Emily Freeman (formerly of Lundbeck)
- Danielle Friend, Johnson & Johnson
- Lauren Hetrick, AbbVie
- Paul Howard, Amicus Therapeutics
- Jill Jarecki (Cure SMA)
- Alexis Miller, Merck
- Steve Morin, Merck
- Amy Nicole Nayar, Novartis Gene Therapies
- Cara O'Neill, Cure Sanfilippo Foundation
- Samantha Roberts, Genentech
- Sean Tunis, Rubix Health
- Pujita Vaidya, Amgen
- Kristin VanGoor, Vertex

Sponsors

- Biotechnology Innovation Organization (BIO)
- EveryLife Foundation for Rare Diseases
- National Health Council
- Pharmaceutical Researchers and Manufacturers of America (PhRMA)

Primary authorship of this Guide and workshop planning and support was provided by Kim McCleary and Samantha Mayberry of the Kith Collective.

Graphic design and layout services were provided by Julie Rathjens of Hello Brand | Design Creative.

INITIATIVE SPONSORS

About the EveryLife Foundation for Rare Diseases

The EveryLife Foundation for Rare Diseases is a 501(c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments and cures. We do not speak for patients. We provide the training, education, resources and opportunities to make their voices heard. By activating the patient advocate, we can change public policy and save lives. Learn more at everylifefoundation.org.

About the National Health Council

Created by and for patient organizations 100 years ago, the National Health Council (NHC) brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, sustainable health care. Made up of more than 140 national health- related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses representing biopharmaceutical, device, diagnostic, generic drug, and payer organizations. Learn more at nationalhealthcouncil.org.

About the Biotechnology Innovation Organization

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products. BIO also produces the BIO International Convention, the world's largest gathering of the biotechnology industry, along with industry-leading investor and partnering meetings held around the world. BIOtechNOW is BIO's blog chronicling "innovations transforming our world" and the Good Day BIO Newsletter is the organization's daily email newsletter.

About the Pharmaceutical Research and Manufacturers of America

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier and more productive lives. Since 2000, PhRMA member companies have invested more than $1 trillion in the search for new treatments and cures, including $91.1 billion in 2020 alone. Learn more at phrma.org.

APPENDIX:

THE RARE DISEASE PFDD GUIDANCE COMPENDIUM WORKSHOP SERIES

HOSTED BY: EveryLife Foundation for Rare Diseases · Bio Biotechnology Innovation Organization · Putting Patients First National Health Council · PhRMA Research · Progress · Hope

OVERVIEW OF THE PFDD COMPENDIUM INITIATIVE

To inform the understanding of how patient-focused medical product development and related FDA guidances can be applied to development of therapeutics for rare diseases, the EveryLife Foundation for Rare Diseases joined with the National Health Council, BIO and PhRMA in a multi-stakeholder, collaborative effort to assess these guidances through the lens of rare disease medical product development.

A series of four virtual "PFDD Guidance Compendium" workshops, held between June and October 2021, convened nearly 100 leaders to consider the application of guidances across four lifecycle stages of medical product development for rare diseases. These discussions informed creation of the "Guide to Patient Involvement in Rare Disease Therapy Development."

A summary of each of the four workshops follows, to help build an understanding of stage-specific opportunities to involve rare disease patients in therapy development.

WORKSHOP 1 // June 23, 2021

RESEARCH AND EARLY DEVELOPMENT

Workshop 1 was held June 23, 2021. It was planned and facilitated by the following members of the Compendium Initiative Steering Committee:

- **Jill Jarecki, PhD,** Chief Scientific Officer, CureSMA
- **Pujita Vaidya, MPH,** Global Regulatory and R&D Policy Director, Amgen
- **Kristin Van Goor, PhD,** Senior Director, North America Regulatory Policy and Intelligence, Vertex

Annie Kennedy, chief of policy and advocacy for the EveryLife Foundation, provided an overview of the Compendium meeting series. Case studies were presented by **Jill Jarecki, PhD,** CSO of CureSMA, and **Jessica Riviere**, Vice President for Global Patient Engagement and Advocacy at Ultragenyx, to stimulate dialogue. **Kim McCleary** of the Kith Collective summarized the session.

35 individuals representing academia/research institutes, life science companies, patient advocacy organizations and consulting firms participated in the session. An interactive whiteboard, Miro, was used during the meeting to capture participants' ideas and comments in response to questions posed for each of four discussion topics. Support for development and management of this workshop and the Compendium series was provided by **Samantha Mayberry** and Kim McCleary of the Kith Collective.

> "There was general agreement that engagement at this early stage has tremendous benefits to all stakeholders.

SUMMARY OF WORKSHOP 1: RESEARCH AND EARLY DEVELOPMENT

Workshop organizers led with the often-stated mantra of patient engagement, "early and often," yet recognized it rarely begins as early as it should for a variety of reasons that were explored during this three-hour participatory discussion. In the early stage of product development, researchers have myriad opportunities to be inspired by curiosity, rather than directed by regulatory guidance, as they engage with patients and caregivers. Exploratory interactions and qualitative data gathering can serve to identify signals and form the basis of more structured and targeted activities that may follow.

Fostering Early Engagement

There was general agreement that engagement at this stage has tremendous benefits to all stakeholders. Importantly, it is an opportunity to set a foundational understanding of the rare disease and the lived experience of that disease to guide later stages of development. Yet, there are some barriers to engaging this early in a program that must be overcome by all stakeholders in order to realize these benefits. Challenges are amplified in rare disease settings, with many conditions being "ultra-rare" and having to overcome a lack of commercial incentive. Participants identified the following:

Key advantages of early engagement:

- An open-minded, "de novo" approach is possible, before too many program details are solidified, and patients can lead the way in terms of informing what matters most to patient community
- Serves as a "reality check" to fill gaps in the knowledge base and complement traditional information sources that may derive from a specific viewpoint on the disease of interest, including treating physicians and key opinion leaders (KOLs) whose observations and data-gathering are often rooted in the clinical setting and not lived experience

- Even small-scale, discussion-based interactions can provide durable and useful information, providing the chance for all parties to gain more comfort and experience with one another
- Pre-competitive, multi-stakeholder collaborations can reduce burdens on the patient community that may be called upon to provide similar input about the disease experience to different entities while conserving limited resources (a common, shared challenge across stakeholder groups in early development)
- Some within industry may view patient engagement as useful only for helping recruit or retain patients in clinical trials and therefore have limited awareness of the benefits of engagement at earlier stages
- Ability and willingness to share information with advocates may be hampered by the timeline for disclosure to investors, lack of trust in them maintaining confidential information and the inability to guarantee that a program will progress to the next stage

In rare diseases, early input from patients and their advocates can be especially helpful because there are often fewer publications and less clinical expertise to draw from to guide development of new therapies, compared to what might exist for more prevalent conditions.

- Patients and caregivers can actively participate and contribute with little or no training or much advance preparation since their lived experience is the primary focus at this stage
- Can illuminate blind spots in a medical product development team's thinking about the focus, scope or intent of their research
- Can identify a patient community's readiness for other types of engagements in medical product development, as well as the opportunity to enhance capacity
- Establishes early bi-directional expectations and learning which can set a positive direction for building relationships that support meaningful interactions as a development program advances

Challenges of early engagement:

- Stakeholders from all perspectives may see early engagement as risky, due to perceived conflicts of interest, possibility of raising expectations, or there being less well-established processes for interactions at this early stage
- Advocacy organizations and companies may not have sufficient staff/bandwidth to conduct early interaction, especially organizations that serve ultra-rare disease communities
- Patient advocacy organizations' hesitancy may stem from prior experience with industry where mutual benefit was not achieved, concerns about what may be expected later in development, or lack of capacity to repeat activities previously conducted with/for another stakeholder
- Gaps in communication from industry about a program may be filled by speculation, which can arouse mistrust and complicate future interactions
- Programs may not advance at the same rate across all geographies, which can be difficult to explain to well-connected global patient advocacy communities
- Using off-the-shelf legal contracts designed for interactions with other types of KOLs can chill budding relationships between industry and patient advocates

Concepts of Greatest Interest in Early Development

In contrast to many PFDD frameworks that are rather vague in defining what can be learned from patients in the early stage of development, meeting participants identified numerous aspects of patients' experiences relevant to this phase. One comment posted to the interactive board summed it up well: "Begin with the end in mind – a more precise definition of 'unmet need' that would be a true benefit in patients' lives." This is the optimal time for patients' direct views to inform the target product profile as it is being developed, before endpoints and outcome measures are set. It is also timely to explore existing "legacy" outcome measures – especially patient reported outcome measures (PROs) – to determine whether they are appropriate for use, how well they reflect domains that truly matter to patients and the nature of improvements that would constitute meaningful change to a person living with the disease. Finally, rare disease patient communities can begin discussions with FDA early – through formal and informal channels – to educate them about the burdens of the disease and unmet needs.

Concepts of interest highlighted by participants:

- Patient journey, including the path to diagnosis, common misdiagnoses, comorbidities and complications experienced
- Burdens arising from symptoms and current therapies/standard of care
- Greatest unmet medical needs
- Clarity about treatment benefits and outcomes for heath and function that are most meaningful to patients and what magnitude would make a difference to their lives
- Treatment approaches patients commonly use to relieve symptoms and achieve the best health and function possible (including off-label, over-the-counter, complementary/alternative and supportive therapies)
- Patient insights on natural history, heterogeneity and subtypes within the rare disease (including different patterns of symptom expression, subpopulation nuances, changes across the lifespan, treatment responses, etc.), prevalence and incidence of the disease
- Tolerance for risk (various side effects, adverse events, etc.), uncertainty (of benefit, durability, etc.) and different types of treatment modalities and modes of administration

"Begin with the end in mind – a more precise definition of 'unmet need' that would be a true benefit in patients' lives."

WORKSHOP 1 // June 23, 2021

RESEARCH AND EARLY DEVELOPMENT

A key theme repeated throughout the session was the huge opportunity in the early stage of development for multistakeholder, pre-competitive interactions to facilitate dialogue and understanding, conserve resources and avoid burning out patient communities. Such engagements might focus on a single disease, a group of related conditions, or across rare diseases. This is especially important to advance therapies in ultra-rare diseases where there may be less commercial incentive to drive investment by industry alone.

Constructive approaches to obtain information at this stage:

Participants identified a number of productive ways to learn more from patients and their experiences as they relate to medical product development, ranging from low-risk/low-resource observational activities to more engaged and resource-intensive activities, listed here in that general order:

- Close review of patient advocacy organization websites and community-generated materials
- Social media listening
- Individual patient interviews
- Patient panels (to share experiences)
- Patient advisory boards/focus groups (to provide input) conducted in-person, virtually and through privacy-protected online bulletin boards
- Patient surveys (circulated widely to people living with the disease)
- Natural history studies and tissue banking (supported by patient advocacy organizations, academic institutions, industry and other funders)
- Preference studies (especially to prioritize outcomes of greatest interest)
- Patient journey maps developed by (or with) patients and advocates
- Industry roundtable meetings (convened by patient advocacy organization)
- Patient-focused drug development meetings and/or listening sessions in collaboration with FDA
- Ethnography studies

Emerging Best Practices

While the era of patient-focused therapy development is still young, especially as it relates to engagement very early in the development cycle, participants shared the following practices that can help achieve success and build momentum:

- To build trust, approach engagement as a long-term relationship with mutual benefits, not a one-off transaction and be as transparent as possible about goals and project status
- Begin early enough that patient involvement can inform thinking, planning and decisions, not just "check a box"
- Meet patients where they are and help build their knowledge base and confidence in participating in therapy development
- Build in feedback loops to share information with participants about how their input was utilized
- Designate single points of contact to cultivate relationships, share updates and direct requests
- Proactively provide timely updates to foster understanding and trust, especially about study results (favorable and disappointing, alike), new program launches and changes to existing programs
- Avoid using contracts or memoranda that were written with a different stakeholder in mind; make sure they are written in plain language and appropriate to the type of engagement
- Recognize opportunities to provide (and accept) "in-kind" technical support based on the different types of expertise each party may have to offer
- Patient advocacy organizations can adopt proactive guidelines to clarify the types of activities they will and will not engage in with life science companies
- Break down barriers between stakeholder "audiences" to expand opportunities for co-learning and interaction, for instance by hosting scientific and community meetings at the same time and location with overlapping sessions
- Publish learnings so they benefit all stakeholders, document successes (and failures) and help advance the practice of early patient involvement

Opportunities to Expand Patient Involvement Early in Development

Much of the discussion during this final segment of the meeting focused on creating and leveraging precompetitive avenues for information exchange (see sidebar at left). Participants from industry and advocacy organizations articulated a growing need for channels to engage with regulators about patient-related information early in a therapy program to propose novel patient-centered outcome measures, exploratory endpoints and trial designs. These early-stage discussions could also address specific expectations for collecting patient experience data that would be useful to support novel measures, endpoints and designs. While there was not a call for specific regulatory guidance to address patient involvement at this early stage of involvement, participants felt it would be beneficial for regulators to reinforce the value to all stakeholders of early engagement with patients and the merits of investigative, pragmatic efforts as a foundation for more rigorous activities later in development.

Two side-by-side posts to the virtual whiteboard served as fitting closing aspirations for incorporating much of what was discussed during the session:

"Leadership within the company to make early patient engagement a required pre-IND milestone" *(industry perspective)*

"Courage to err on the side of sharing 'too much' information with patient organizations" *(patient advocacy perspective)*

WORKSHOP 2 // July 29, 2021

CLINICAL DEVELOPMENT

Workshop 2 was held July 29, 2021. It was planned and facilitated by the following members of the Compendium Initiative Steering Committee:

- **Emily Freeman, PhD**, Senior Director, Patient Insights, Global R&D, Lundbeck
- **Lauren Hetrick**, Senior Director, Regulatory Policy, AbbVie
- **Cara O'Neill, MD**, Chief Science Officer, Cure Sanfilippo Foundation
- **Samantha Roberts, PhD**, Group Director, US Regulatory Policy, Genentech

Annie Kennedy, chief of policy and advocacy for the EveryLife Foundation, provided an overview of the Compendium meeting series and **Kristin Van Goor, PhD**, Senior Director, North America Regulatory Policy and Intelligence, Vertex, described highlights from the first workshop exploring patient involvement in research and early development phases. **Kim McCleary** of the Kith Collective summarized the session at its conclusion.

39 individuals representing academia/research institutes, life science companies, patient advocacy organizations and consulting firms participated in the session. Support for development and management of this workshop and the Compendium series was provided by **Samantha Mayberry** and Kim McCleary of the Kith Collective.

> "Although FDA guidance speaks to these topics, the content is generally high level and not always specific to rare disease drug development.

SUMMARY OF WORKSHOP 2: CLINICAL DEVELOPMENT

Advance Preparation

Meeting planners conducted an in-depth review of numerous FDA guidances relevant to the clinical development phase, which was defined for this meeting as, "the conduct of trials intended to demonstrate safety and efficacy in those with the disease/condition under study." Given the breadth of potential topics to address, two areas each with two sub-topics were selected as focal points for discussion during the three-hour workshop:

1. **Patient Input into Clinical Outcomes**
   a. **Selecting endpoints**
   b. **Defining meaningful change**
2. **Patient Input into Trial Designs**
   a. **Reducing burden and improving access**
   b. **Practical trial design considerations**

Meeting planners provided participants with a summary of FDA guidance specific to these topic areas in advance of the Roundtable. The background document begins, "Generally speaking, although FDA guidance speaks to these topics, the content is generally high level and not always specific to rare disease drug development, nor does it include details that go beyond a basic acknowledgement." The backgrounder and online meeting platform provided links to source documents used in planning the session.

Pairs of key discussants were identified and prepped to help lead-off meeting segments dedicated to each of the four subtopics; one individual represented a patient advocacy perspective and the other represented a sponsor perspective. These introductory comments followed a short recap of relevant FDA guidance by a member of the workshop planning team who also facilitated the broader conversation during that meeting segment.

Involving Patients in Defining, Selecting and Measuring Clinical Outcomes

Building on discussion that began in the series' first workshop, participants identified the opportunity to come into this phase of development with a solid understanding of the outcomes that matter most to patients. More often, however, rare disease outcomes are selected on the basis of published research, the consensus of treating professionals and/or outcomes that have been used to gain approval for other therapies in the same disease or clinically "adjacent" diseases. Several participants underscored the need to understand the nuances of the patient journey across the lifespan as a foundational aspect of defining and measuring meaningful outcomes and making clinical trials less burdensome for patient, caregivers and family member participants.

Endpoint Selection

Attendees spoke to the tension between developing novel outcome measures that might better align with patient experience and sticking with those that have achieved some degree of regulatory endorsement. With so many sources of uncertainty in the development of rare disease therapies, sponsor representatives admitted the tendency to avoid introducing more uncertainty, including by using novel outcome measures. Others cited a tendency to overcorrect, by including multiple exploratory outcome measures to reflect domains they believe are important to patients. The downside of that approach is the potential added study burden for sites and participants – if the domains of interest are not relevant to their experience.

Another facet of rare disease that complicates selection of patient-centered outcomes is the multiple sources of heterogeneity within even small populations of diagnosed individuals. Participants identified factors that may contribute to heterogeneity within a given disease:

- Patient age (at diagnosis and/or at the time of evaluation)
- Stage of disease
- Frequency, severity and impact of particular symptoms
- Rate of change of functional status
- Access and response to standard of care
- Racial, social, cultural, economic and other influences on lived experience
- Personal preferences and priorities

The lack of documented natural history and agreed-upon subtypes of a disease can add to the challenge of understanding different presentations. While FDA guidance suggests that sponsors define endpoints that are most important to a broad range of patients, meeting participants agreed that broad quality of life measures may not show sufficient change within the study period to support efficacy and they may not be included in the label due to a lack of specificity. Individual signs or symptoms can be hard to define in ways that are relevant to all study participants and/or at all stages of progression or points across the lifespan. Decisions about endpoints and exploratory outcomes often require balancing specificity and sensitivity with inclusivity.

Measuring Meaningful Change

With the emphasis in guidance on anchor-based methods of measuring within-patient change, participants explored several limitations of applying these methods in the setting of rare diseases. There was strong consensus that working with patients and caregivers to understand the dynamics of the concept of interest based on lived experience is crucial to understanding variability, identifying suitable anchors, determining meaningful-change thresholds and interpreting measurement data. Disease-monitoring studies and "run-in" studies can also be helpful to establish baseline understanding and guide interpretation. Determining the minimal increment of change that is meaningful to

> "Composite quality of life measures that apply to a broad group of patients within a rare disease may not show enough change in response to a given therapy within the study timeframe.

patients might also depend on the type of intervention being studied and the potential risks associated with it.

Although not all rare diseases are progressive, there were several diseases cited in which stopping or slowing progression is a widely endorsed treatment outcome by patients and caregivers, but this too can be hard to adequately define and document across study subjects. With disease progression, there is a constant need to accommodate functional losses, and this can be hard to capture in clinical trial measures. There may also be potential ethical concerns related to posing questions about functions that haven't yet been lost, especially in pediatric trials. It is very difficult for respondents to know how something feels that they haven't yet experienced, such as loss of the ability to stand and the effect of that loss on other functions like independent toileting.

Discussion illuminated how vital it is to develop instruments that measure a concept of importance to patients in terms that resonate with their experience, getting to the heart of establishing "meaningfulness." One participant spoke about the mental asterisk she often wishes she could add to clarify responses to symptom questionnaires – a "yes, but" answer that would identify particular circumstances or limitations. Compound questions that ask about two or more constructs at a time are particularly

The "holy grail" of rare disease endpoints is an outcome measure that is meaningful to patients and measurable in a manner and timeframe that will be convincing to regulators of the safety and efficacy of the therapy being tested.

problematic to answer. The resulting lack of clarity about what an answer might truly mean undermines the utility of information collected, both from individual respondents over time and across a group of individuals with the same disease.

Similarly, involving patients and caregivers in the interpretation of data from outcome measures can be very helpful. For instance, while increments of change along a scale might be mathematically equivalent, they could be quite different in terms of the change represented in the life of the individual. For example, losing that last increment of function might be more devastating than same-point decrements along the way. Terms like "moderate" can mean different things to different people and to the same person over time as the impacts of the disease evolve. Patients and caregivers can also help elucidate challenges with recall and assessment frames and generally help provide context for the analysis.

Opportunities to Advance Patient-Focused Outcome Selection and Measurement

At an overarching level, participants highlighted the opportunity to build the understanding of a disease from the different perspectives of the patient, the family/caregiver, the clinician, the academic researcher, the sponsor and the regulator. Bringing stakeholders together to learn and benefit from deeper, multi-dimensional awareness of one another's viewpoints has the potential to enhance outcome selection, tool design, anchoring, and assessment and interpretation of change.

There was great interest in involving more social scientists, including ethnographers, in drug development and regulatory reviews. In particular, there was a stated desire to develop a mixed methods approach that blends qualitative and quantitative data to document and contextualize the patient experience. For instance, scores on pre- and post-study outcome measures could be paired with qualitative in-depth interviews that provide participants with the opportunity to describe their baseline status and changes they noticed in the way they feel and function day-to-day and over the course of the study. Use of video-based outcome measures to document improvements and/or slowed progression might be useful in some situations. In general, storytelling techniques could help contextualize and provide a narrative explanation for data-driven elements to reviewers and other stakeholders.

Participants recognized the opportunity to utilize patient preference studies to help identify and prioritize endpoints; however, the lack of guidance from CDER for this approach adds to the challenge of securing resources to conduct such studies. Similarly, while novel endpoints such as personalized endpoints or comparisons with untreated patients might offer means to overcome some of the challenges for rare diseases, the regulatory expectations for acceptability of these approaches remains unknown.

Participants agreed that the qualification process for outcome measures has become onerous to the point of there being a widespread sense of futility. Patient advocacy representatives were frustrated by the lack of a clear pathway for their involvement, including ways for relevant data and/or expertise to be considered as part of the outcome review process. In general, there was a desire for the qualification process (at both the disease level and specific product level) to facilitate better understanding by reviewers of the dynamics of the disease itself, rather than being narrowly focused on one or more particular concepts of interest and an instrument's psychometric properties and performance.

"

While increments of change along a scale might be mathematically equivalent, they could be quite different in terms of the change represented in the life of the individual.

Involving Patients in Trial Design and Conduct

Existing FDA guidance recognizes that patient input on trial design and logistics can help to improve and accelerate clinical study recruitment, enrollment and completion with fewer protocol amendments and better overall data quality. However, existing guidance stops short of providing advice on systemic and integrated ways to engage patients and caregivers in trial design and clinical operations. In this session, participants explored these topics.

Trial Design Considerations

FDA guidance across all diseases strongly favors randomized controlled clinical trials as the most efficient and accurate way to determine whether a drug has a clinically meaningful effect on a disease. In rare diseases, especially those that are severely progressive and neurodegenerative, placebo-controlled studies may be challenging to

"

Concerns about enrolling or remaining in placebo-controlled studies are amplified when the burdens to participants are significant, such as frequent long-distance travel, lengthy clinic visits and invasive procedures.

> **Protocol reviews with patients and caregivers should include open-ended opportunities for advisors to bring forward study-related challenges that study teams might not be aware of. This can yield powerful new insights, as well as practical action items.**

recruit, enroll and complete with adequate data given the smaller population to draw from. It was suggested that in rare disease development, there is a need to show a bigger treatment benefit in light of smaller study sizes to be convincing to regulators – and later possibly to payers, if the product is approved. This point led back to the importance stated earlier of selecting sensitive and specific endpoints and outcome measures that will maximize the signal-to-noise ratio within the smaller number of participants characteristic of rare disease trials.

Also drawing on earlier discussion was the potential to innovate clinical trial design in rare diseases. The use of comparators other than a placebo arm, such as historical (external) controls, is recognized in FDA guidance for rare disease drug development, but is reserved for circumstances where there is "unmet medical need; well-documented, highly predictable disease course that can be objectively measured and verified; and where the expected treatment effect is large, self-evident, and temporally closely associated with the intervention." A recent FDA guidance outlines a process for proposing study designs that utilize complex adaptive, Bayesian, master protocol and other novel clinical trial designs and could be applied to rare diseases. While expressing favor for Bayesian approaches, participants indicated a need for more information about the utility in rare diseases that do not have previous treatment outcomes to include in the model.

In rare disease, it is also possible to make use of accelerated pathways for conducting studies and regulatory review; however, some of these pathways have come under recent scrutiny by payers as being less rigorous and equating to less-than-full approval. Such perceptions might discourage appropriate use of these pathways to address unmet needs and could compound challenges for patient access to therapies approved under these pathways.

Minimizing Burdens and Improving Equitable Access

This discussion again began with recognition that a solid foundation of the lived experience is essential to a holistic understanding of the sources of burden and barriers related to clinical trial participation. Making use of this information across a development program was essential to conserve resources of both patient advisors and companies. Learnings about what might make a trial more feasible for participants to agree to and stick with can be pulled through to other functions within a sponsor organization to guide future discussions about clinical adoption, market access and patient support. Up-front planning for stewardship of patient insights can reap long-term benefits, especially as staff and programmatic needs evolve.

Several participants addressed the need to bridge the gap between what occurs in the setting of a clinical trial and the patient's ongoing need to receive care for their disease. If results from laboratory and imaging tests performed as part of a study protocol were able to be shared with the treating clinician, this could reduce patient burdens as well as improve resource utilization overall. Similarly, study protocols should be informed by optimal care standards so that patients are not precluded from or overly taxed by obtaining attentive care from medical disciplines that may not be involved in a particular study.

> **Patient engagement activities can be structured to facilitate co-learning. The sponsor gains a better understanding of patients' perspectives, while patient and caregiver participants learn more about clinical trials.**

> **Sponsors could benefit by shifting their perspective *from* how to fit a patient into their clinical trial *to* how to fit their clinical trial into the life of a patient and his or her family.**

Trial feasibility should also be optimized not just for the type of patient who might typically be part of a clinical trial, but for all patients, including those that have often been overlooked as potential participants. This requires evaluating sources of burden that might stem from practical issues such as access to and support for transportation, child care, weekend and evening clinic hours, time off from work, virtual visits and at-home assessments. It may also require addressing inequities due to racial, ethnic and cultural identities. Depending on the community's experience with clinical trials, there may be an even greater need to educate potential participants about important aspects of a trial such as randomization, blinding, adherence to the protocol and reporting expectations to gain acceptance. Site simulations can uncover pain points that might confound study conduct if unresolved; patients and caregivers can help identify workable solutions that study teams alone might not conceive of.

// continued on page 33

Opportunities to Advance Patient-Focused Trial Design and Conduct

Throughout this session, participants identified catalysts for involving patients in the design and operation of clinical trials. Therapy trials are complex undertakings and identifying the best way to engage them in the process can feel overwhelming. The advice was given just to start, even with a seemingly small activity like asking patients and caregivers to review a draft recruitment flyer or proposed schedule of events. A positive experience can generate important insights as well as momentum for more ambitious engagements.

This discussion prompted an important reminder about the benefit of engaging patients for their thoughts, ideas and problem-solving skills as being distinct from collecting patient experience data. Both have value and warrant purposeful planning and coordination. Asking "why?" and "what do we hope to learn?" at the beginning of any patient-related activity can help focus the effort. Participants underscored the distinction between extractive patient engagement positioned as, "What I think I need to know," versus more descriptive patient engagement that opens with, "What do you think I need to learn?" Patient input can replace assumptions, especially for projecting the lengths to which patients and families may be willing to go for a therapy's potential benefit, traded off against its potential risks and the vast uncertainties of participating in a clinical trial. In the process of engagement, patient/caregiver advisors learn more about the clinical trials process.

Participants were eager to know more about FDA's expectations for involving patients in clinical trial design and suggested that more case studies would be useful so all stakeholders could focus their efforts more effectively. There was uncertainty about how and when to communicate with the FDA about such activities. The limitations of Type B and C meetings and the multitude of topics to be covered make it challenging to add PFDD-related items to an already long list. Getting direction about how and where to cite this work in regulatory submissions would be helpful, as would having a dedicated pathway – open to sponsors and non-sponsors – to introduce and dialogue with FDA on PFDD-specific topics. There was brief discussion about proposals to make patient engagement a regulatory requirement, reflecting some hesitancy in participants' minds. As an interim step, it was felt that having more visibility to the way in which patient engagement and patient experience data are viewed, interpreted and used by the agency would help shape best practices so that any future requirements do not become "check the box" exercises.

Finally, participants expressed hope that in rare disease there can be some progress in evolving the standard for conducting double-blind placebo-controlled trials to reduce the burdens on patients, as well as to make trials more accessible to the largest group of patients possible. The implications for study design to affect payers' coverage decisions was another important patient-centered consideration to keep in mind as well. Getting patient and caregiver input early and throughout the clinical development program can help support the value proposition for all stakeholders in the system as a therapy advances.

"

Having more visibility to the way in which patient engagement and patient experience data are viewed, interpreted and used by the agency would help shape best practices so that any future requirements do not become "check the box" exercises.

WORKSHOP 3 // September 17, 2021

HEALTH AUTHORITY REVIEW & MARKETING AUTHORIZATION

Workshop 3 was held September 17, 2021. It was planned and facilitated by the following members of the Compendium Initiative Leadership and Steering Committees:

- **Nimi Chhina**, JD, PhD, Senior Director, Global R&D and Regulatory Policy, BioMarin
- **Victoria Dohnal**, RAC, Director, Science & Regulatory, BIO
- **Danielle Friend**, PhD, Director, Regulatory Policy and Intelligence, Janssen
- **Ryan Fischer**, Chief Advocacy Officer, Parent Project Muscular Dystrophy
- **Steve Morin**, Director, Global Regulatory Policy, Merck

Annie Kennedy, chief of policy and advocacy for the EveryLife Foundation, provided an overview of the Compendium meeting series and described highlights from the first two workshops exploring patient involvement in research and across early- and late-stage clinical development phases. **Kim McCleary** of the Kith Collective summarized the session at its conclusion.

36 individuals representing academia/ research institutes, life science companies, patient advocacy organizations and consulting firms participated in the session. Support for development and management of this workshop and the Compendium series was provided by **Samantha Mayberry** and Kim McCleary of the Kith Collective.

> “PROs are the form of patient experience data most often cited by FDA reviewers, per a recent report.

SUMMARY OF WORKSHOP 3: HEALTH AUTHORITY REVIEW & MARKETING AUTHORIZATION

Advance Preparation

Meeting planners conducted an in-depth review of numerous FDA guidances and related resources relevant to this phase. Three areas were selected as focal points for discussion during the three-hour workshop:

1. **Patient-Centered Benefit-Risk Assessment**
2. **Patient Preference Information**
3. **Other Opportunities for Patient Involvement to Inform Regulatory Decision-Making**

Workshop participants were provided a written backgrounder, summarizing FDA guidance and discussion questions specific to each of these three topics. Key discussants were identified and prepped to help lead-off each meeting segment and members of the workshop planning team prepared to facilitate a dialogue among meeting participants.

Current Status of FDA Use of Patient Experience Data in Regulatory Decision-Making

The workshop began with a brief review of two public-facing reporting tools used by FDA to communicate its consideration of patient experience data (PED) in regulatory decision-making: the Benefit-Risk Framework (implemented under the 2012 FDA Safety and Innovation Act) and the Patient Experience Data Table (required under the 21st Century Cures Act, signed into law in 2016). A report prepared by Eastern Research Group (ERG) and released by FDA in June 2021 indicates that 68 percent of FDA reviews of new molecular entity New Drug Applications (NDAs) and Biologic License Applications (BLAs) included in the assessment cohort (total of 176 applications) mention PED. Of those 120 applications, FDA reviewers primarily relied on PED from the applicant

> The language patients use to describe symptoms and functional limitations can be quite different from that used by clinical development teams. "Translation" by a physician or another experienced professional may be required to turn patient insights into action steps for the team.

(97%), most often citing patient-reported outcome measures (PROs) (84%). Just three percent of reviews cited patient preference data. Eleven percent cited PED from sources other than the applicant, with only four percent citing patient-focused drug development meetings and three percent citing natural history studies. (See Table 2-3.)

Patient-Centered Benefit-Risk Assessment

This session launched with recognition of the need to develop an understanding of patients' and caregivers' benefit expectations and tolerance for risk and harms much earlier in the clinical development program. Sponsors who wait until they are preparing to file for marketing approval to engage patients and caregivers about these foundational elements of patient-focused therapy development run the risk of appearing to regulators as conducting a "check-the-box" exercise or as a "rescue mission" to fill gaps in safety and/or efficacy data.

Drawing on experience starting much earlier in the development cycle, participants emphasized the need to challenge assumptions that are made about patients' benefit expectations and risk tolerance. They provided examples of dramatic differences between medical key opinion leaders' views of the outcomes of greatest interest and patients' priorities. One participant with clinical experience described the vastly different learning opportunity when patients' experiences and expectations are articulated in a group setting (as in a patient-focused drug development meeting), compared to the exchange between a single patient and his or her physician in the care setting. Other participants described situations in which sponsor assumptions about patients' inability to reliably articulate their needs and expectations impeded studies to garner their perspectives. Others identified that the language patients use to describe symptoms and functional limitations can be quite different from that used by clinical development teams. "Translation" by a physician or another experienced professional to turn patient insights into action steps for the team.

To address these challenges, participants highlighted the merits of taking an exploration-based approach to conducting qualitative research (e.g., interviews, focus groups, etc.) early in the clinical development program, an observation made during Workshop 2, as well. A more open-ended approach provides the opportunity to learn what matters to patients and where their pain points lie. It also establishes a firm foundation from which to build quantitative studies (described below). Qualitative research can also help to identify patient-centered language and terminology, as well as boundaries for what types of questions might be sensitive or problematic for patients and caregivers to answer.

In conducting research to understand benefit-risk tradeoffs, the dynamic nature of an individual's benefit-risk calculus must be acknowledged as a factor of personal demographic characteristics, stage of disease, severity of disease, access to care and other life circumstances. Similarly, the continuum of benefit expectations and risk tolerance across a community must be recognized as well. Even among relatively small numbers of people affected by a given rare disease, the sources of heterogeneity in individuals' experiences at a specific point in time and over time can lead to a range of viewpoints, potentially impacting the benefit each desires and risks they are willing to accept. Patients' views might differ from caregivers' perspectives, and caregivers for the same patient may not agree. This underscored the need to conduct multiple assessments over time and to be as inclusive as possible in recruitment. On the topic of representativeness in these studies, participants stressed the need to reflect the diversity of the community in the sample and to effectively describe the sample population so it's clear how generalizable learnings might be. This description may also highlight gaps in the sample that could be addressed in future studies.

> On the topic of representativeness, participants stressed the need to reflect the diversity of the community in the sample and to effectively describe the sample population so it's clear how generalizable learnings might be.

Participants referred to sponsors' tendency to submit volumes of patient experience data in unwieldy formats without a clear narrative or strategic storyline about what was learned and how it applies to the filing. Novel presentation formats may be needed to effectively communicate patient experience information in a way that draws reviewers' attention and provides what they need to inform regulatory decision-making. This is essential to achieving the full promise of PFDD.

Opportunities to Advance Patient-Centered Benefit-Risk Assessment

- Stay curious about what matters to patients and why it matters
- Address internal/cultural barriers to conducting and accepting the learnings from patient-centered research
- Don't be overly prescriptive in qualitative research
- Co-develop instruments with patients and caregivers, or **at least pilot test them**
- Don't rely on a single study to understand patients' and caregivers' benefit expectations and tolerance for harms and risks
- Present patient experience data to regulators in a manner that tells a story and strategically links evidence from multiple studies together
- Link entries in the published Benefit-Risk Framework to Patient Experience Data considered in the review of NDAs and BLAs

> "Advocacy participants cited positive engagement with regulators about patient experience data collection but were uncertain how to formally submit these studies and how this information might be used to inform decision-making.

For sponsors that have conducted studies to understand and apply patients' benefit expectations and tolerance for risk, at this stage of development the most important action might be how that information is described and presented in the filing package. Participants referred to sponsors' tendency to submit volumes of patient experience data in unwieldy formats without a clear narrative or strategic storyline about what was learned and how it applies to the filing. Novel presentation formats may be needed to effectively communicate patient experience information in a way that draws reviewers' attention and provides what they need to inform decision-making. This is essential to achieving the full promise of PFDD.

After the review is complete, participants wanted to gain a better understanding of how FDA utilizes patient experience data to arrive at entries made in the Benefit-Risk Framework. In the case of approved products, this would map PED information as reported in the PED Table to the Benefit-Risk Framework. This would be useful to sponsors of applications for which the review outcome is unfavorable, as well, although it would not be made public by FDA. According to the 2021 ERG report, 16 percent of FDA reviews of assessed NDAs and BLAs explicitly cite patient experience data in the Benefit-Risk Framework or in other discussions of factors contributing to a regulatory recommendation or decision (See Table 2-4).

Patient Preference Information

Throughout this session participants recognized the enormous progress made in establishing methods and use cases for patient preference information (PPI) to gain acceptance as an increasingly useful tool for therapy development. Noted were the contributions of FDA's Center for Devices and Radiologic Health (CDRH) and Center for Biologics Evaluation and Research (CBER) through the issue of guidances, sponsoring studies, and citing PPI in regulatory decisions. Also commended was the commitment by the Center for Drug Evaluation and Research (CDER) and CBER to develop draft guidance on the use and submission of patient preference information to support regulatory decision making, as stated in the PDUFA-VII goals letter released publicly in late August. Internationally, the PREFER project funded through the Innovative Medicines Initiative in the EU was recognized as having influenced utilization of PPI in therapy development and value assessment.

At the point of regulatory decision-making, patient preference studies often focus on quantifying patients' tradeoffs of specific treatment benefits in exchange for specific (potential) risks. Alternatively, preference studies might focus on trade-offs of benefits and risks related to one treatment as compared to another. Participants noted that in most rare diseases, there are few treatments to use as comparators and regulators appear less compelled by preference data favoring a novel treatment (and its potential risks) compared to no treatment (and its potential risks). Other uses for PPI to guide earlier decisions in therapy development included: prioritizing unmet needs, prioritizing outcomes to measure in a study, establishing the preferred magnitude of specific outcomes, selecting the mode of administration (or understanding its acceptability) and identifying other preference-sensitive aspects of the trial design or treatment approach.

Participants sought dedicated opportunities to engage with FDA "early and often" in the design of these PED-generating studies to gain the benefit of their input and improve the chances that the resulting information will have regulatory utility. They defined an ideal scenario as a less formal meeting, scheduled on a short timeline and characterized by a substantive exchange of ideas that results in shared understanding of the objectives of a study and acceptable ways to address challenges. It was suggested the new "Type-D" meeting outlined in the PDUFA-VII goals letter could potentially serve this purpose. Another stated desire was for more FDA staff to receive training about PPI and methods to collect it. Now a relatively small number of internal FDA experts consult with review teams but may not have sufficient bandwidth to meet the need, especially as more programs include PPI from sponsors and other stakeholders and reviews require their expertise.

Opportunities to Advance Collection & Use of Patient Preference Information

- Continue to engage in multistakeholder initiatives to advance PPI methods and use cases across the full lifecycle
- Seek opportunities to get FDA feedback on planned PED-generating studies
- Organize professional development sessions on PPI-related topics, including at professional meetings with strong attendance by regulators
- Support pilot programs and other innovative ways for regulators and other stakeholders to benefit from PPI and other types of PED collected by patient advocacy organizations.

At present, the lack of a timely forum to review preference study plans with regulators was viewed as an obstacle to committing resources to conduct them, especially by smaller companies focused on rare disease therapies where resources are tight and internal expertise is potentially more limited. Also, in rare diseases in which patients are challenging to identify and recruit into clinical studies, it can be daunting to introduce additional participant burden by conducting preference studies. Patient advocacy organizations conducting patient preference studies expressed frustration about the lack of a clear pathway to submit PPI to regulators. Advocacy participants cited positive engagement with regulators about such studies but were uncertain how this information might have been used to inform decision-making.

Other Opportunities for Patient Involvement to Inform Regulatory Decision-Making

A recap of FDA programs initiated since the 1990s to engage patients and caregivers acknowledged the deepening value FDA has placed on hearing directly from individuals with lived experience and ways that has translated into more openness to novel types of interactions and evidence generation. What is less certain is the effect this shift has had on specific regulatory decisions.

For patient communities early in building relationships with FDA and therapy developers, participants advised that they start small with a listening session or by collecting patient stories in a format that can inform research and by used by regulators and sponsors to guide therapy development. As more experience is gained, these efforts can take on more structure toward hosting an externally-led PFDD meeting, conducting qualitative and quantitative studies and encouraging sponsors to include patient advisors in their closed-door meetings with regulators. Expanding the frequency of sponsors' willingness to utilize patient advisors in these meetings would create valuable co-learning opportunities for all of the stakeholders involved.

The growth of CDER's PFDD meeting series beyond the initial commitment of 20 meetings under FDASIA to the current total of about 80 meetings was seen as a tangible sign of the value FDA has found in these sessions. It was noted roughly half have focused on rare diseases. Workshop participants shared new insights gleaned through these meetings, some of which were identified as the origins for specific clinical development projects. One participant remarked that the topics for the initial FDA-hosted meetings were selected on the basis of reviewers' needs, which generated strong interest and participation by review staff. The current volume of PFDD meetings may make it harder for review staff to devote attention to them and the timing may not necessarily align with review issues, due to scheduling being determined by the host patient advocacy organization, in consultation with an FDA liaison. The formulaic meeting structure may also make them less interesting to FDA staff now than they were at first. It was also noted that the "voice of the patient" reports are often not structured in a way that the information of key interest to reviewers is immediately accessible, possibly why they are not cited more frequently in the ERG report on the use of PED. Even so, these meetings were seen as valuable not only to regulators, but for the entire community of stakeholders focused on a particular rare disease. Participants underscored that a PFDD meeting can serve as an important venue for identifying and developing solutions to a variety of unmet needs.

Opportunities to Expand Patient Involvement to Inform Regulatory Decision-Making

- Develop mentoring programs to enable community leaders newer to these issues to learn from more experienced organizations
- Reinforce the potential benefits of sponsors inviting patient advisors to participate in closed-door meetings with FDA to represent patient perspectives on review issues
- Explore ways to innovate and make PFDD meetings and the related reports are even more useful to reviewers and sponsors
- Patient advocacy organizations can offer to provide annual or biannual briefings to review division staff, especially if there is a substantial change in care or access environment, or with FDA-related staffing changes or reorganization that might create gaps in familiarity with patient experience
- Present patient experience data in ways that join qualitative and quantitative sources and are relevant to clinical development and regulatory issues

While there has been much progress in advancing the availability and utility of PED at regulatory review, workshop participants agreed it is still early days and even greater opportunities lie ahead for the full benefits of patient-focused drug development to be borne out in the approval of new medical products that align with patients' needs, preferences and expectations.

WORKSHOP 4 // October 7, 2021

POST-MARKETING

Workshop 4 was held October 7, 2021. It was planned and facilitated by the following members of the Compendium Initiative Leadership and Steering Committees:

- **Jennifer Bright**, Executive Director, Innovation & Value Initiative
- **Eric Gascho**, Vice President, Policy & Government Affairs, National Health Council
- **Christine Harhaj**, Director, Advocacy and Strategic Alliances, PhRMA
- **Paul Howard**, Director of Public Policy, Amicus
- **Alexis Miller**, Executive Director, Global Public Policy, Merck
- **Amy Nicole Nayar**, Vice President, US Patient Advocacy & Government Affairs, Novartis
- **Sean Tunis**, Principal, Rubix

Annie Kennedy, chief of policy and advocacy for the EveryLife Foundation, provided an overview of the Compendium meeting series and described highlights from the first three workshops exploring patient involvement in research, across early- and late-stage clinical development phases and at regulatory review. **Kim McCleary** of the Kith Collective summarized the session at its conclusion.

48 individuals representing academia/research institutes, life science companies, patient advocacy organizations and consulting firms participated in the session. Support for development and management of this workshop and the Compendium series was provided by **Samantha Mayberry** and Kim McCleary of the Kith Collective.

> “
>
> **Once a new therapy is approved by regulators, a new stage of concerted effort is required to ensure it reaches intended patients.**

SUMMARY OF WORKSHOP 4: OPPORTUNITIES FOR PATIENT INPUT IN THE POST-MARKET SETTING

Advance Preparation

Meeting planners conducted an in-depth review of numerous FDA guidances and other resources relevant to this phase. Three areas were selected as focal points for discussion during the three-hour workshop:

1. **Regulatory Data Needs**
2. **Considerations to Ensure Appropriate and Timely Access to Approved Therapeutics**
3. **Data Requirements and Collection**

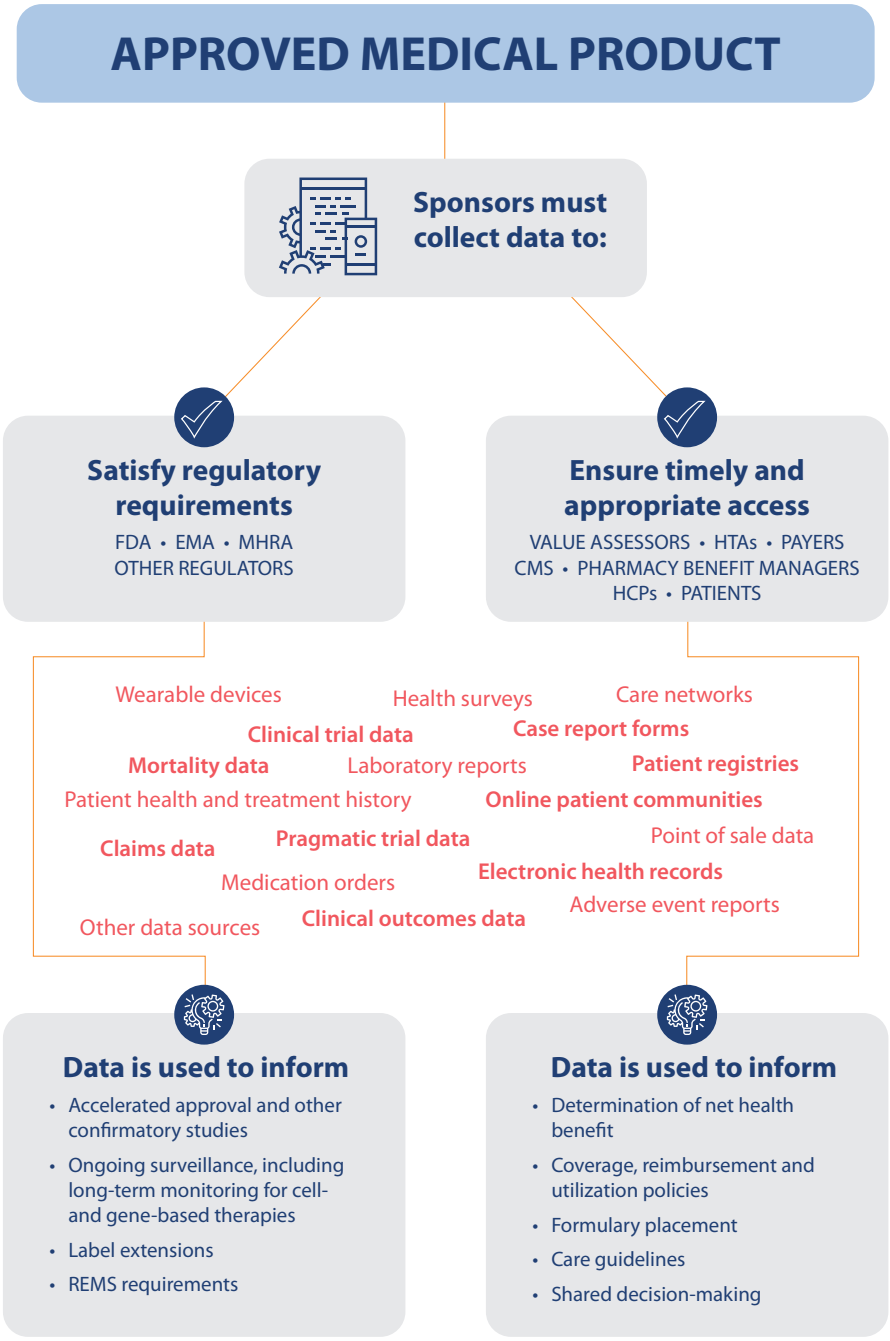
Workshop participants were provided a written backgrounder, summarizing FDA guidance and other key resources and a set of discussion questions specific to each of these three topics. Two case studies, spinal muscular atrophy (SMA) and hemophilia, were identified and advocacy organization leaders prepped to provide context for the discussion which was facilitated by members of the workshop planning team.

Setting the Stage

In light of the fact that the vast majority of the known 7,000 rare diseases have no primary therapy, many rare disease communities are rightfully focused on attracting scientists to study their condition and companies to utilize scientific evidence to develop new therapeutics. The first approval of a new therapy brings celebration but also the realization that a new stage of concerted effort is required to ensure a promising therapy reaches intended patients. Unlike the focus on regulatory approval that can unite various stakeholders, the multiplicity of needs in the post-market setting can come as a surprise – and a shock – to those who find themselves trying to meet an entirely new array of demands and expectations from a variety of stakeholders.

As shown in Figure 1 *(see page 39)*, this workshop focused on two broad sets of needs for patient input and patient experience

FIGURE 1



Enhanced communication from the regulatory agency with more detailed information about what data is to be collected, the purpose and potential applications for the required data would be especially helpful to stakeholders who are not party to discussions between the agency and the sponsor but who may be relied upon to participate and invest in the collection of this data.

data – satisfying post-market regulatory requirements and ensuring appropriate and timely access to therapies. Case studies of the spinal muscular atrophy and hemophilia communities provided examples of two comprehensive, collaborative and evolving approaches to data collection that are aimed at addressing both sets of needs. These models were referenced frequently throughout the workshop, and presenters contributed throughout the session. Each case considered various data needs related to conventional and one-time therapies. Across the discussion, there were also distinctions drawn between products approved via traditional regulatory pathways and those approved via expedited pathways, including under accelerated approval provisions. Another set of opening remarks encouraged an inclusive orientation to data of different types, from a variety of sources, accumulated over time. These remarks also recognized the challenge of building a holistic data collection system disease-by-disease, especially for rare diseases. There was robust engagement among participants in the discussion segments and through the exchange of written comments using the "chat" function.

Meeting Regulatory Data Needs in the Post-Market Setting

A product approval is communicated in writing to the sponsor and made public shortly thereafter by the regulatory agency. The approval letter outlines expectations for any supplemental data that must be collected by the sponsor in addition to standard, ongoing safety monitoring. These may include understanding the product's safety and efficacy in special populations such as children, women of childbearing age or who are treated while pregnant, and/or patients with specific genotypes or phenotypes. Data to fulfill these requirements may come from a variety of sources, ranging from the more structured – specific post-market clinical studies, observational studies and patient registries – to passive data collection activities.

Among the first points of discussion was the need for enhanced communication from the regulatory agency with more detailed information about not only what data is to be collected, but the specific purpose and potential applications for the required data. This was an especially emphatic point made by stakeholders (especially patient advocacy organizations) who are not party

“
The SMA and hemophilia case studies each emphasized the benefits of taking a multi-stakeholder approach – enlisting sponsors, patients, physicians and academics to collaboratively design data collection efforts and to actively attempt to incorporate as many data and evidence needs as is practical.

to discussions between the agency and the sponsor but who may be relied upon to participate (and invest) in the collection of this data. Sponsor requests to leverage existing patient registries hosted by patient advocacy organizations to fulfill post-market requirements often require substantial additional investment by the community, including through direct participation. Clearly understanding regulators' rationale and specific expectations may help patient advocacy organizations overcome challenges associated with adapting their registry to this purpose, especially when there are multiple products in development that could ultimately make use of a restructured registry.

Along these lines, there was general agreement that in rare diseases there are too few resources – including patient participants – to support individual registries dedicated to collecting data for a single product. This discussion drew on the case studies, each of which emphasized the benefits of taking a multi-stakeholder approach – enlisting sponsors, patients, physicians and academics to collaboratively design data collection efforts and to actively attempt to incorporate as many data and evidence needs as is practical. Advocacy organizations were encouraged to proactively establish governance and data access policies so that requests can be evaluated more objectively.

These challenges multiply in the setting of one-time therapies with requirements for long-term follow-up studies of treated patients. With the immediate focus on documenting durable benefit and the long-term goal of establishing enduring safety, registry hosts must balance these needs against participant burden and capacity. One participant acknowledged the "messy" picture likely to emerge over the course of studies lasting a decade or more, as individual experience and outcomes are affected by exposure to later generation therapies, different care approaches and any number of life factors. Enlisting as many patients from as many sites as possible was stated to be one way to get the most complete picture possible. Treating physicians were recognized as bearing a dual administrative burden – to collect information for sponsors' post-market reporting requirements, while also providing data to meet insurers' utilization measures required to get patients access to therapy.

Patient Experience Data as a Tool to Inform Access-Related Decisions

Following the approval of a product, payers must make coverage and utilization decisions based on data from clinical trials and any other studies provided by the sponsor in the lead up to marketing authorization. Often, there remains some uncertainty about the product's objective value, especially if a surrogate endpoint is the basis for regulatory approval or if it is a novel therapy. If patient experience data is part of the data set used for regulatory decision-making, then it may also be available as a basis for coverage and formulary decisions. Patient experience data may also be introduced in the public record through the process of assessments conducted by third parties, such as the Institute for Clinical and Economic Review (ICER) or health technology assessors. Once a product is being prescribed for and used by patients, data collects in various places across the healthcare ecosystem (see Figure 1 on page 39) and evidence related to its value builds over time. Collaborative efforts, including expert clinical networks and learning healthcare systems, that seek to optimize care and patient outcomes can be a robust source of such evidence, but it may take many years to fully manifest.

As was pointed out by several participants, the somewhat different evidentiary needs of regulators and payers and timing of their decisions can result in a situation where an approved therapy is not covered by some or all payers or is covered only for a tightly defined subgroup of patients – sometimes in contrast to the product's label. Coverage restrictions may be placed on the product at commercial launch or may emerge over time. This means patients with the potential to benefit from a newly approved therapy may either have to wait for accrual of another evidence base following approval, or alternatively, find that ongoing access to a therapy is jeopardized if coverage restrictions are imposed later. To avoid delays or interruptions in access, participants encouraged sponsors to "consistently collect and report relevant, well-specified, patient-centered outcomes" from the earliest stage of development possible. They also strongly recommended that patient engagement activities conducted during development be substantive and aimed not only at securing regulatory approval but also supporting timely patient access to the therapy.

Taking the concept a step further, discussion raised the possibility to define early, through precompetitive efforts, a core outcome set that reflects factors that make the greatest differences in patients' lives. Evidence collected during the development program on this set of outcomes would be intended to inform both regulators' and payers' decisions.

“
The somewhat different evidentiary needs of regulators and payers and timing of their decisions can result in a situation where an approved therapy is not covered by some or all payers or is covered only for a tightly defined subgroup of patients – sometimes in contrast to the product's label.

To avoid delays or interruptions in access, participants encouraged sponsors to "consistently collect and report relevant, well-specified, patient-centered outcomes" from the earliest stage of development possible. They also strongly recommended that patient engagement activities conducted during development be substantive and aimed not only at securing regulatory approval but also supporting timely patient access to the therapy.

It was also suggested that some outcomes are important across an array of rare diseases, which presents the prospect of working collaboratively across diseases to define cross-cutting outcome sets and develop tools to measure them.

Returning to the issue of timing, participants offered other potential ways to recalibrate access, value and price as evidence accrues in late-stage development and in post-approval clinical experience. Piloting programs for parallel review (by regulators and payers), "dynamic" pricing that incentivizes and rewards outcomes that matter to patients and increased utilization of real-world data sources to bridge data gaps are three possibilities that were raised, although time constraints did not permit detailed exploration.

A final issue raised during this segment of the workshop was the need to address some payers' and HTA bodies' tendency to discount or disallow data and/or evidence developed by patient advocacy organizations that report industry funding among their revenue sources. There are many best practices to guide companies and non-profits in establishing appropriate relationships, protecting against conflicts of interest and reporting funding. However, the expanding practice of patient-focused therapy development may warrant more dialogue and education about the merits of – and guardrails for – close collaboration between sponsors and patient advocacy organizations.

Enhancing Post-Market Data Collection Efforts

Reiterated again at the beginning of this discussion was the need for all stakeholders working on a specific rare disease to align on what is meant by high-value, patient-centered data. Several participants shared examples of post-market data collection efforts to compensate for missing patient experience data from the clinical development program or to rectify a flawed understanding of what matters most to patients, especially in demonstrating a product's value over time. Considering the wide variety of sources of data in the post-market setting, a recurring theme was the opportunity to layer different types of data from different sources together. For instance, qualitative information can be used to identify what is important to measure, as well as to make sense of quantitative information. Others highlighted the opportunity to aggregate data from clinical studies and care settings and to combine patient-entered data with clinician-entered data to get a better understanding of a broader population and range of experiences. One individual stated that this mosaic of data sources and types was vital to improving care and outcomes, recognizing that "a new therapy alone won't fix all the problems patients encounter in the health care system."

Participants identified a number of reasons to move some post-market data collection efforts from private/proprietary control into public settings, including under patient advocacy stewardship or through efforts funded by the National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ) or the Patient-Centered Outcomes Research Institute (PCORI). Primary among the reasons were the potential for enhanced access to data and evidence, greater transparency and increased sustainability (especially if a product is acquired or later becomes generic). Yet not all agreed that that post-market data stewardship should become a shared responsibility. Questions were raised about how likely and appropriate it would be for federal agencies to support data collection for specific medical products. One participant expressed a view that the private sector should produce the data since companies are asking society to pay for [their products]. Although there was not full agreement about the optimal arrangement for supporting post-market data collection, participants concurred that more communication and greater transparency about what is learned through post-marketing studies can help to support the value proposition for the data collection effort itself.

Participants offered other potential ways to recalibrate access, value and price as evidence accrues in late-stage development and in post-approval clinical experience. Piloting programs for parallel review (by regulators and payers), "dynamic" pricing that incentivizes and rewards outcomes that matter to patients and increased utilization of real-world data sources to bridge data gaps are three possibilities that were raised.

"

Some outcomes are important across an array of rare diseases, which presents the prospect of working collaboratively across diseases to define cross-cutting outcome sets and develop tools to measure them.

"

Participants concurred that more communication and greater transparency about what is learned through post-marketing studies can help to support the value proposition for the data collection effort itself.

“

Ultimately, the evolution of this data to become evidence and then knowledge must support all stakeholders’ needs – including the individual patient – to make informed decisions.

Clear objectives, systematic collection, widely adopted data standards and sound governance can help foster a data collection system that serves a variety of needs, from safety and efficacy, to value, to clinical and cost effectiveness, to personal meaningfulness. Ultimately, the evolution of this data to become evidence and then knowledge must support all stakeholders’ needs – including the individual patient – to make informed decisions. It must also be available to inform the next generation of therapies that will address a disease state that is newly defined by what aspects are treatable and the unmet medical needs that remain to be addressed. As Annie Kennedy noted in her closing remarks, “Collection and stewardship of patient experience data may be among the most important topics we have addressed in this workshop series, for we will never stop needing to do this work.”

Opportunities to Improve Collection and Application of Patient Experience Data for Post-Market Decision-Making

Several recommendations relate to the need to begin in early stages of development to consider the post-market needs for patient experience data:

- Align stakeholders early (through pre-competitive collaboration, if possible) on a set of patient-centered core outcomes and measurement tools that will support timely access, as well as regulatory approval
- Collect patient experience data throughout clinical development so this evidence is available for use by value assessors and payers at the time of marketing approval
- Establish patient registry data governance policies and data standards that anticipate post-marketing applications from sponsors
- Work proactively to inform payers about the lived experience, burdens of the disease and what outcomes matter most to patients and families
- Develop and communicate a clear value proposition to the patient community about the ongoing, continuous need for participation in data gathering activities that will ultimately support their decision-making needs as well as those of other stakeholders

In the post-marketing period:

- Foster multi-stakeholder dialogue and understanding of the specific post-marketing data needs, including their purpose and how such data will be used
- Be inclusive in data sources and types in an effort to reflect as great a breadth of experience as possible
- Curate data using mixed methods approaches to enhance understanding of evolving patient experience as new therapies and care models are introduced and adopted
- Balance data collection needs and participant burden to avoid burnout and ensure long-term sustainability
- Consider emerging models for data stewardship that support increased data access and transparency
- Promote learnings from data collection efforts to continually reinforce the value of such efforts and their benefit to all stakeholders

“Collection and stewardship of patient experience data may be among the most important topics we have addressed in this workshop series, for we will never stop needing to do this work.”

– Annie Kennedy, in remarks to conclude the fourth and final workshop

Rare disease patient advocates celebrate a newly approved therapy, then must begin a new stage of concerted effort to ensure that a promising therapy reaches the intended patients.