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.

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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

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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.

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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.

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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.

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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.

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> **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**

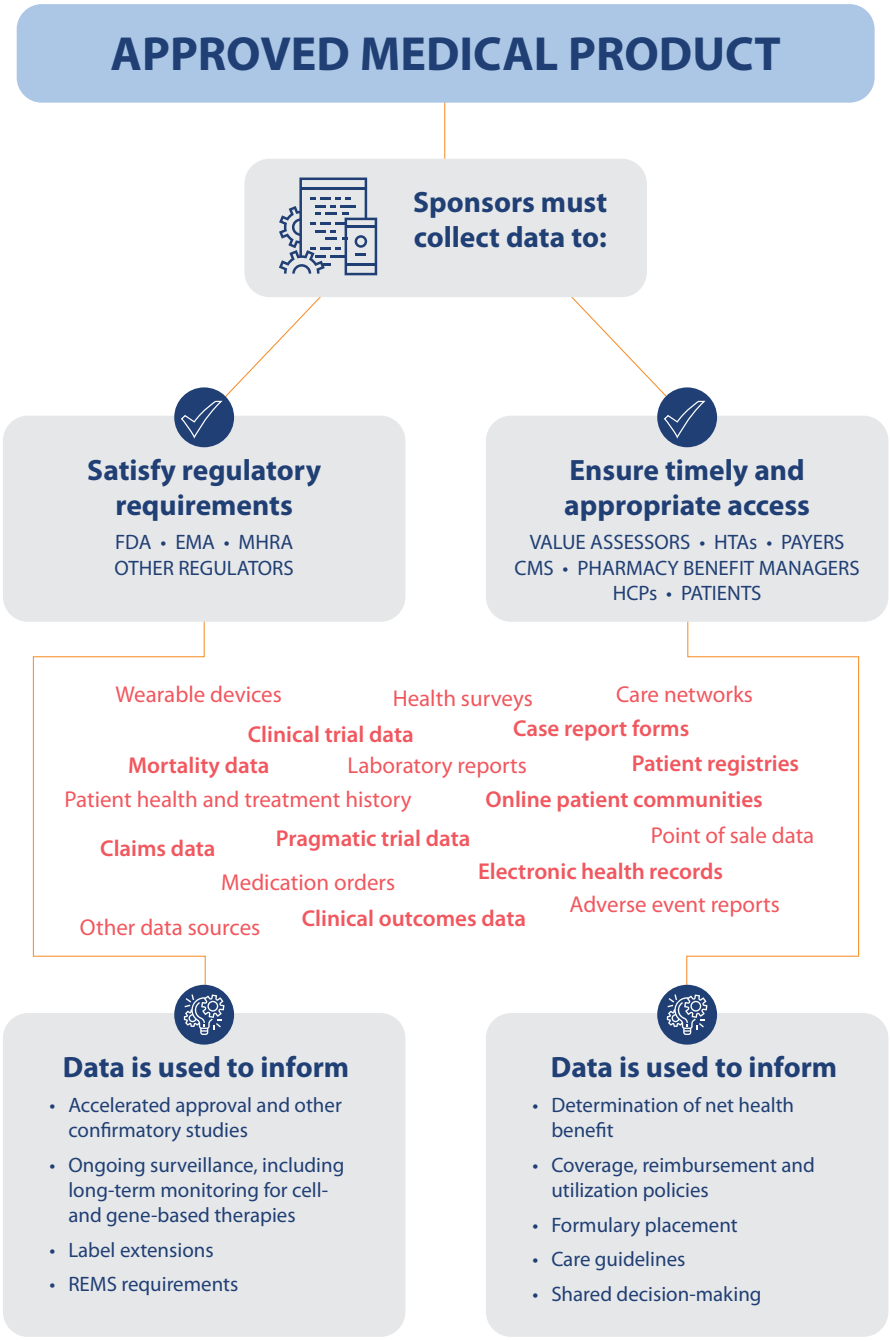
Workshop participants were provided a written backgrounder, summarizing FDA guidance and other key resources and a set of discussion questions specific to each of these three topics. Two case studies, spinal muscular atrophy (SMA) and hemophilia, were identified and advocacy organization leaders prepped 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

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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.

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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.

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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.