KEY CONSIDERATIONS FOR DEVELOPING & INTEGRATING PATIENT PERSPECTIVES IN DRUG DEVELOPMENT:

EXAMINATION OF THE DUCHENNE CASE STUDY

Biotechnology Innovation Organization

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

A LETTER FROM JAMES GREENWOOD, PRESIDENT AND CEO OF BIO & PAT FURLONG, PRESIDENT AND CEO OF PPMD

On behalf of the Biotechnology Innovation Organization (BIO) and Parent Project Muscular Dystrophy (PPMD), we are pleased to share this report outlining key considerations and decision-making processes for obtaining data on patient perspectives, and, more specifically, on patients' stated preferences, that can be integrated into the drug development process.

It is a time of exciting transformation in healthcare, with patients moving to the center of efforts to understand and manage disease. Today's patients play an increasingly proactive role in this process, driving and shaping the development and delivery of management approaches and therapies that will best meet their needs. As patients and caregivers move "from passengers to co-pilots"[1] in the disease journey, healthcare providers, academic researchers, drug developers, regulators, and advocacy organizations are exploring new ways of engaging with them to accelerate medical progress. This transition was described recently in Science Translational Medicine as, "an extension of patient advocacy [that] has evolved into an emerging scientific discipline aimed at understanding and incorporating patient needs into the processes of developing, regulating, and delivering new therapies."[2]

Our PPMD-BIO initiative is designed to assist all stakeholders in advancing this emerging paradigm by providing an overview of Patient-Focused Drug Development (PFDD) and the multiple methods and approaches for generating information on patient perspectives. Our goal is to provide an overview of these multiple efforts to enhance the voice of the patients in the drug-development process, along with information on key decision points, practical tools, and best practice considerations for the use of patient perspectives and patient preference studies.

This report takes a "deep-dive" into specific approaches for generating patient preference information, exploring the pioneering work of the Duchenne muscular dystrophy community in launching a milestone patient preference study and a community-led draft guidance for integrating patient and caregiver perspectives into drug development and regulatory decision-making. The Duchenne experience continues to play out in real-time, offering a landmark case study from which we draw general principles about the collection of information on patient perspectives, including assessing the option of using patient preference studies to advance PFDD in different disease and drug development settings.

When we launched this project, we received enthusiastic responses across the stakeholder community, including the leadership of the FDA. We are especially grateful to Dr. Janet Woodcock of the Center for Drug Evaluation and Research (CDER) for her statement of support of this effort: "FDA supports the efforts of BIO and Parent Project Muscular Dystrophy (PPMD) as they work to bring insights and contributions from patients and their caregivers to the drug development process. We look forward to reviewing their report on patient preferences studies and gaining a deeper understanding of patients' needs as we seek new treatment options."

We salute the work of the many leaders from across the stakeholder community – including academia, health authorities, industry, patient groups, policy-makers, and multi-sector entities – who together have built a framework upon which the next chapters of PFDD are now being written.

We are especially grateful to the visionary leaders who serve on our Expert Review Committee. Individually and as a group, they have provided invaluable guidance and feedback for the design, content, and execution of this report. We appreciate their time, enthusiasm, and passionate commitment to the science of patient input.

As the field of patient engagement continues to evolve and mature, we encourage you to view this document as one component of a growing body of resources and tools that will shape the future of our collective work in delivering better options for patients and their families.

Jim Greenwood & Pat Furlong
June 2016

[1] Anderson, Margaret, McCleary, K. Kimberly McCleary, From Passengers to Co-Pilots: Patient Roles Expand, *Sience Translational Medicine* 10 Jun 2015: Vol. 7, Issue 291, pp. 291fs25, DOI: 10.1126/scitranslmed.aac6023
[2] Anderson, Margaret , McCleary, K. Kimberly,, "*From Passengers to Co-Pilots: Patient Roles Expand*", Science Translational Medicine 10 Jun 2015: Vol. 7, Issue 291, pp. 291fs25, DOI: 10.1126/scitranslmed.aac6023

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In developing this report, the project team reviewed key sources from the literature, published articles, reports, regulatory document, and news articles. A compilation of these references is provided in tan appendix to this report. In addition, detailed individual interviews were conducted with each member of the Expert Review Committee, as well as other experts in the field. The project team met frequently to review plans and drafts, and met via teleconference several times with the ERC members. Drafts were shared for review with the ERC at multiple points in the process.

EXECUTIVE SUMMARY

The goal of this collaboration and resulting report was to provide information about key considerations for developing and integrating patient perspectives into the drug development and regulatory review processes. The pioneering initiative undertaken by Parent Project Muscular Dystrophy (PPMD), working with the Duchenne muscular dystrophy community, to conduct a patient preference study that resulted in a community-led U.S. Food and Drug Administration (FDA) Draft Guidance, provides unique and valuable lessons to everyone working to advance Patient-Focused Drug Development (PFDD).

The central goal of medicine is to provide benefits to patients, while protecting them from unnecessary or unjustified risks. Technological and scientific advancements, along with increasingly sophisticated patient advocacy organizations, are fueling new opportunities for medical progress, contributing to a new paradigm where patients and caregivers can provide direct input to key stakeholders throughout the process of drug development.

This report discusses how understanding what matters most to patients and applying that information to drug development can serve to inform clinical development and impact regulatory decision-making. Specifically, the report focuses on how the collection and analysis of patient perspectives can be used to characterize the burden of the disease, design clinical trials, develop endpoints that matter to patients, impact regulatory decisions, and provide patients with information important to their medical decision making process.

This report also provides a “deep-dive” examination of considerations for conducting patient preference studies using the work done by PPMD as a case study to help provide real-world insights on what went into the development of the landmark study. Specifically, the report provides information on why and whether to conduct a patient preference study, when a study should be conducted, who should conduct the study, and how to develop and implement a patient preference study. Key themes highlighted include: the importance of developing collaborations with a shared understanding of the purpose and use of information generated; the significance of using sound science; the usefulness of having a clear understanding of objectives and choosing the appropriate methodologies to achieve those objectives; and the value in engaging regulators throughout the process.

This document is just one component of a growing body of resources and tools designed to help advance the collection and integration of the patients’ voices in drug development and regulatory processes. Advancing this field of work will ultimately help deliver better options for patients and their families. While much work remains to be done, the Biotechnology Innovation Organization (BIO) and PPMD are committed to working with all stakeholders in advancing this exciting new paradigm.

CHAPTER 1: EVOLUTION OF PATIENT-FOCUSED DRUG DEVELOPMENT & PATIENT PERSPECTIVE INFORMATION

The central goal of medicine is to provide benefits to patients, while protecting them from unnecessary or unjustified risks. Cutting edge science and technology have delivered tremendous results in eradicating certain serious diseases, extending life expectancies, and improving quality of life for many.

The Internet, social media, health authorities, and, increasingly, sophisticated patient advocacy organizations are fueling new opportunities for medical progress, contributing to a new paradigm where patients and their caregivers are empowered and encouraged to provide direct input to key stakeholders throughout the process of drug development.[3]

This phenomenon makes true patient centricity in medicine ever more desirable and attainable, with new models and methods emerging to enhance patient engagement and enable the collection of robust patient perspective information that can inform and improve basic and translational research, drug development, regulatory review, and delivery of care. There are now opportunities to follow the example of many other "high-value" product-development fields, which tap directly into consumer input to drive effective development and efficient delivery of new products and services.[4]

As patient engagement has grown in recent years, there have been multiple terms used to describe the input that patients and their caregivers can bring to the continuum of drug development.

PAUL HASTINGS – ONCOMED PHARMACEUTICALS

"The interest around this issue is broadening across stakeholders, especially among the patient advocacy groups, biopharmaceutical companies, and the FDA. However, this is a classic "chicken and egg" situation – there are no guidelines or universal consensus on what type of data is best suited for which purpose, how to best collect that data, and how to ensure all of this is done in a way that can be utilized to inform/influence drug development and regulatory decision making. Raising awareness is key to doing the right thing by all stakeholders. As we socialize this, there will be differing opinions based on different patient populations and diseases.

"We should work together to understand where these differences need to be addressed in the form of data collection and analysis and continue to advance the integration of patient perspectives into drug development and regulatory review. The simplest, most straightforward way to move this forward is to use the case study of PPMD and learn from the thought processes this organization utilized to make decisions on what information they collected, how they collected it, and for what intended purposes. This will serve to pave the way for the next wave of sophisticated and impactful collection and utilization of patient perspectives to ensure that what matters most to patients is a core part of the entire drug development and review process."

Experts recognize that the language of Patient-Focused Drug Development (PFDD) is evolving. For the purpose of this report, we use the overarching term "Patient Perspective Information" to encompass a broad range of input from patients relating to their experience with their disease. This term was recently defined by FasterCures as:

> ***Information gathered from the perspective of the patient or caregiver about their experience of the disease or condition that includes, but is not limited to: symptoms experienced, chief complaints (description of the most significant or serious symptoms or signs of illness or dysfunction that cause the patient to seek health care), the burden of living with a disease, the burden of managing a disease, impacts on activities of daily living and functioning, effect of current therapeutic options, unmet medical need, disease severity and chronicity, natural history, minimum expectations of benefits, maximum tolerable harms or risks that a patient might be willing to accept in pursuit of desired benefits, attitudes toward uncertainty, other types of patient preferences, and preference-sensitive decisions that patients might encounter.***[5]

[3] Hoos, Anton, MD, et al. *Partnering With Patients in the Development and Lifecycle of Medicines A Call for Action*; *Therapeutic Innovation & Regulatory Science* November 2015 vol. 49 no. 6929-939

[4] BIOCentury Week of September 7, 2015: *"Changing the Subject"* http://www.biocentury.com/biotech-pharma-news/coverstory/2015-09-07/23rd-biocentury-back-to-school-issue-let-patients-show-the-way-in-drug-development-a01

[5] "*From Anecdotal to Actionable,"* FasterCures, November 2015, http://www.fastercures.org/reports/view/49

RECENT PATIENT-FOCUSED DRUG DEVELOPMENT ACTIVITIES

- The FDA Patient-Focused Drug Development (PFDD) Initiative mandated as part of the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2012. To date, FDA's Center for Drugs Evaluation and Review (CDER) and Center for Biologics Evaluation and Review (CBER) have developed and convened more than 20 public meetings to hear directly from patients and caregivers about their experiences with specific diseases and conditions.[6] This commitment and the efforts it launched came, in large measure, in response to "growing agreement that regulatory benefit-risk evaluations should be informed by the perspectives of patients and caregivers who will ultimately make treatment decisions and bear the associated risks."[7] FDA's CDER expressly encouraged external entities to lead additional PFDD meetings to supplement those it is convening under PDUFA V.[8]
- The Patient Preference Initiative launched by the FDA's Center for Devices and Radiologic Health (CDRH) following its 2012 Guidance "Factors to Consider When Making Benefit Risk Determinations in Medical Device Premarket Approval and De Novo Classifications." FDA-CDRH conducted a proof-of-principle study on the preferences of people with obesity regarding use of medical devices to achieve weight loss. Information from this study was subsequently used by FDA-CDRH in the approval of the EnteroMedics Maestro Rechargeable System for weight loss.[9, 10]
- An initiative led by the National Health Council (NHC) and the Genetic Alliance to convene a multi-stakeholder group of key thought leaders to produce a report that to guide transformation of the existing drug development paradigm and make the patient voice an integral part of the process. This initiative is identifying key PFDD regulatory issues for clarification and development of future FDA Guidance.[11]
- The Medical Device Innovation Consortium (MDIC) "Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology" released in 2015.[12]
- The House-passed 21st Century Cures Act (HR 6), which included a provision that would require FDA to develop a structured framework to incorporate patient perspectives into the assessment of a drug's benefits and risks, including information about the impact of a disease or a therapy on patients' lives.[13] A complementary Senate Biomedical Innovation package is in development.
- PDUFA VI negotiations, where PFDD is a leading priority for industry and patient advocacy groups, including proposing future FDA Guidance to advance the science of patient input in the regulatory process and integration of patient perspectives in the Structured Benefit-Risk Framework (sB/R).[14,15]
- The bipartisan Patient-Focused Impact Assessment Act (S 1597), legislation calling on FDA to develop a public report on use of PFDD tools in regulatory decision-making.[16]

In the U.S., this has been an active arena for legislative and governmental policy activities, with a significant focus on advancing efforts to collect and integrate patient perspective data into drug development, regulatory review processes, and care delivery channels. There are also several non-profit, patient advocacy organizations, academic researchers, and biopharmaceutical industry experts working individually and in collaboration to advance the science of PFDD. A common denominator for recent and ongoing activities is the goal of directly tapping into the perspectives of patients and their caregivers. These efforts will further enable all stakeholders in the medicines development ecosystem to better understand and respond to patients' needs and priorities in living with their medical conditions.

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[6] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm
[7] http://www.clinicaltherapeutics.com/article/S0149-2918(14)00209-4/fulltext
[8] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm
[9] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf
[10] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[11] http://www.nationalhealthcouncil.org/sites/default/files/PatientEngagement-WhitePaper.pdf
[12] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[13] https://www.fas.org/sgp/crs/misc/R44071.pdf
[14] https://www.bio.org/sites/default/files/FDA_STBRA_WP.pdf
[15] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM472906.pdf
[16] https://www.congress.gov/114/bills/s1597/BILLS-114s1597is.pdf

KEY MILESTONES IN ADVANCING THE SCIENCE OF PFDD	
1997	Seminal papers by Mandy Ryan, F. Reed Johnson, and others
2000	Daniel McFadden awarded Nobel Prize theory/analysis of choice
2000	Seminal book on stated choice methods by Louviere, Hensher, and Swait
2000	RTI Health Solutions Health Preference Assessment group formed
2001	First stated-preference methods course at iHEA
2005	Stated-preference data on Tysabri help with resubmission to the FDA
2006	ISPOR conjoint analysis working group formed (Until 2011)
2007	First Conjoint Analysis & Health Conference (running until 2012)
2007	Next Steps Working Group formed
2008	The Patient – Patient-Centered Outcomes Research launched
2008	The first ISPOR conjoint analysis taskforce launched (ISPOR Checklist published in 2011)
2008	PhRMA Benefit-Risk Action Team (BRAT) case studies for statins and triptans
2009	Launch of Innovative Medicines Initiative (IMI) in Europe
2010	ISPOR experimental design for discrete-choice experiments formed (published in 2013)
2013	ISPOR Statistical Methods for discrete-choice experiments form (published in 2016)
2013	Medical Device Innovation Consortium (MDIC) patient-center benefit-risk project initiated (published 2015)
2014	The International Academy of Health Preference Research (IAHPR) launched
2014	Society for Medical Decision Making (SMDM) adds preference research as an abstract category and has first plenary session on stated-preference methods
2014	The FasterCures Benefit-Risk Advisory Council formed
2015	The new ISPOR Stated-Preference Methods SIG formed leading the to the ISPOR Patient-focused Benefit-Risk Analysis working group (2015)

CHAPTER 2: GENERATING PATIENT PERSPECTIVES INFORMATION

For a variety of reasons, patient perspectives historically have been obtained by proxy or through individual patient stories and anecdotes, with input primarily coming from clinicians, researchers, regulators, and even payers.[17]

However, as noted by the authors of the 2015 Medical Device Innovation Consortium (MDIC) Framework Report, "Patient perspectives might differ significantly from what would be expected by providers, FDA staff, or others who do not experience the challenges of living with the disease, particularly in the context of rare diseases, end-of-life care, or coping with debilitating chronic diseases." [22]

Patient-Focused Drug Development activities underscore the importance of this point, and the need to place more direct focus on engaging the unique viewpoints of patients and their caregivers. Stakeholders across the continuum of medical research and innovation have been augmenting scientific and clinical data at every phase of drug development by engaging the perspectives and preferences of patients and their caregivers.[23]

The avenues routinely employed to generate patient perspectives include: community engagement and outreach; public comment and individual testimony from patients, caregivers, advocacy organizations, and other stakeholders; qualitative research, such as focus groups and/or interviews; and quantitative approaches, such as surveys.

DUCHENNE CASE STUDY: CHANGING THE COURSE OF DISEASE

Duchenne muscular dystrophy is the most common fatal genetic disorder diagnosed in childhood, with about 20,000 new cases each year, worldwide. Duchenne results in progressive loss of strength, leading to serious medical problems, loss of mobility usually before the age of 13, and death for most patients before they turn 30. There is currently no cure for Duchenne.[18]

Parent Project Muscular Dystrophy (PPMD) was founded in 1994 by a small group of parents whose children were diagnosed with Duchenne and whose mission is to end Duchenne. The group of parents included Pat Furlong, an ICU nurse who lost two sons to Duchenne. In an effort to change the course of this disease under her leadership, PPMD has engaged the community in defining the natural history of Duchenne and catalyzing drug discovery, with the goal of improving the treatment, quality of life, and long-term outlook for all patients. This commitment drives the organization's sophisticated program of work and professional staff in its focus on research, advocacy, education, care, and community support.[19]

When FDA launched its PFDD program, Duchenne muscular dystrophy was not selected as one of the 20 disease states for the agency's initial focus for community engagement. However, PPMD saw an opportunity to leverage the Agency's overall focus on patient engagement. The organization launched its own landmark effort to develop scientific data based on the input of families facing Duchenne – data that could be used to inform FDA's regulatory process and ensure that all stakeholders involved in the development and review of treatments for Duchenne could incorporate patient perspectives into the development and evaluation of new therapies.

The authors of a 2014 Clinical Therapeutics journal article on Duchenne treatment preferences (including meaningful benefit and risk tolerance) describe the opportunity to build upon individual testimonials from patients in impacting the drug development process, writing "Although the individual stories of highly motivated advocates are powerful and influential, it is difficult to know whether these testimonials represent the perspectives of the majority of patients and families."[20] As a result, additional methods and approaches are emerging to enhance the impact of patient perspectives by developing transparent and defensible data.[21]

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[17] Boutin, Marc, CEO, National Health Council, October 20, 2015 Interview
[18] http://www.parentprojectmd.org/site/PageServer?pagename=Understand_about#sthash.CN1AMNvq.dpuf
[19] http://www.parentprojectmd.org/site/PageServer?pagename=About_mission#sthash.KqMkZrJP.dpuf
[20] *Peay, Holly L. et al.,* A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy, *Clinical Therapeutics*, *Volume 36 , Issue 5 , 624 - 637*
[21] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[22] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[23] Perfetto, Eleanor. *Patient-Focused Drug Development: A New Direction for Collaboration*" http://www.ncbi.nlm.nih.gov/pubmed/25494232

These efforts are often implemented through or used to augment the work of:

- Patient advisory boards;
- Regulatory proceedings;
- Patient advocacy organizations;
- Patient registries;
- Patient-powered research networks; and
- Social media communities.

In 2012, as part of its PFDD Initiative, FDA's Center for Drug Evaluation and Review (CDER) launched a series of disease-focused public meetings focused on gathering patient perspectives and developed corresponding "Voice of the Patient" reports.[24] FDA-CDER used these activities as a vehicle to better understand patients' perspectives on the diseases and conditions they are living with, what elements of these diseases and conditions affect their lives the most, and what role treatments may provide in helping patients manage their disease and its symptoms.[25]

Given the number of serious and debilitating illnesses to address, and constraints on FDA-CDER's finite resources, the agency has actively encouraged other stakeholders – specifically patient groups – to initiate meetings and workshops designed to generate additional information on patient perspectives.[26] This is exactly what the Duchenne community, led by PPMD, undertook and implemented.

[24] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm
[25] http://www.raps.org/Regulatory-Focus/News/Databases/2015/07/01/19640/Patient-Focused-Drug-Development-Tracker/
[26] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm

CHAPTER 3: THE ROLE OF PATIENT PERSPECTIVES INFORMATION

In seeking to understand what matters to patients by generating information on patient perspectives, it is important that stakeholders clearly understand their specific objectives. Stakeholders should determine what data is needed, the purpose for gathering that data and, based on that assessment, which methods are most appropriate for generating the more relevant information.

MARC BOUTIN – NATIONAL HEALTH COUNCIL

"Many decisions along the lifecycle of drug development should be informed by patient-provided information and may not always require the same level of scientific rigor as patient preference assessment. A company should look at where it is in the development lifecycle, what information it is trying to gather, who it wants that information from, who will use the information, etc., and then decide which methods will work best.

"Collecting data from patients, caregivers, and advocates -- such as on the natural history of disease or experiences with treatments – will require using a variety of methods. The right information to achieve the best results must come from multiple audiences via multiple means."

Information on patient perspectives can be obtained through a wide variety of robust, valid research approaches that span qualitative and quantitative methods and can be used for a variety of purposes, including:

- ***Characterizing the burden of disease, unmet need, and treatment options,*** including identifying what is most important to patients, recognizing that perspectives may differ based on demographics, geography, and other differentiating factors within a specific disease;
- Applying patient perspective data to inform ***clinical trial design***, including what endpoints to measure in a clinical trial, trial cohorts and stratification, meaningful effect sizes for endpoints, how to promote patient participation and avoid discontinuation in clinical trials, and ways to enhance reach among relevant groups of patients being studied;
- Collecting data relevant to patients' perspectives that could be utilized within the ***regulatory setting*** and could inform benefit/risk assessments; and
- Developing the most appropriate ***clinical outcome assessments*** for use in regulatory decision-making and communications to patients (e.g. labeling).

Characterizing Burden of Disease, Unmet Need, and Treatment Options

Assessment of patient perspectives on the burden of their disease (not just in terms of survival, but also in terms of symptoms and treatment impact) can serve to identify whether their needs are being met by current standard-of-care options. Assessment of unmet needs can also serve to identify targets for interventions, spurring innovation as drug developers identify unique opportunities for therapeutic development. [27]

Industry experts recognize that information about how patients assess available options for treating their disease can be used to inform a company's decision-making about what molecules would be a meaningful addition to the treatment space.[28] [29]

Unmet need is also an important consideration for health authorities assessing benefit-risk, as regulators may be more tolerant of adverse events when there are few or no good existing treatments.[30]

[27] McCleary, K. Kimberly, Managing Director, FasterCures, October 16, 2015 Interview
[28] Holdsworth, Stacy, Senior Advisor, US Regulatory Policy & Strategy, Eli Lilly, October 28, 2015 Interview
[29] Holdsworth, Stacy, Senior Advisor, US Regulatory Policy & Strategy, Eli Lilly, October 28, 2015 Interview
[30] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm;

Though there are many methods for obtaining data from patients, caregivers, and other stakeholders (including clinicians and other health care providers) about the impact of disease, it is important that the methods chosen in a given situation are appropriately robust for the intended use of the information. This is especially true when information is intended for use within the drug development and regulatory processes. For example, it is common within drug development for surveys to be used for commercial and marketing purposes. While important for their intended purposes, these efforts are not generally designed to provide results that can be used to inform clinical study design or the regulatory process.

BRETT HAUBER – RTI

"There are two different, but complementary goals: one is to get patient input on what the world should be like. The other is to get a patient's interpretation of what is. Both goals are necessary to have patient-centered drug development. You need to start from the beginning of understanding what the priorities and needs of the patients and then get an assessment of how well you did. Have you developed a product that meets the needs for the patients? Have you provided benefits that outweigh risks or provided value? How big is that value? In one sense, to be patient-focused you need to start at the beginning and then at the end you can demonstrate how you've done."

For PFDD, methods selected to generate patient perspectives data should support efforts to inform patients, drug developers, and regulators in their decision-making processes. This has been defined by some leaders in the field as "the science of patient input."[31] Whenever a quantitative method is selected, and when such objectives are consistent with the study aims, the researchers should provide confidence to stakeholders that the findings are as representative as possible of the relevant population and take into account the possibility that perspectives may vary among sub-groups of the disease population.

Improving Clinical Trial Design

Understanding impacts of disease and unmet needs from the perspective of patients can help to ensure that clinical trials are designed in a manner that is conducive to meeting patients' needs and their ability to participate fully in the study. For example, depending on the disease state and the demographics of a specific patient population, some patients may face difficulty completing a trial protocol or complying with detailed requirements for participation. Understanding these constraints up front can help those designing the study consider ways to adjust a trial's requirements, where possible.[32]

There are multiple other decisions that must be made in establishing trial protocols, including defining inclusion/exclusion criteria, selection of comparator medicines (when relevant), and consideration of lifestyle and diet factors that may impact treatment adherence. These decisions can be informed with a direct understanding of patients' perspectives.

Additionally, collecting data to better understand impacts of a disease and what is most important to patients before trials are designed and launched can help inform what could or should be measured in a specific study. For example, it is important to assess the natural history of a specific condition to evaluate symptoms that might change over time or impact different sub-groups of patients within the disease setting.[33]

Integrating Patient Perspectives into Regulatory Decision Making

Regulatory approvals in the US are based on careful review by the FDA of the safety and efficacy of new drugs. Since the 2012 PDUFA V reauthorization, FDA has been implementing a Structured Benefit-Risk Framework[34] designed to "summarize the relevant facts, uncertainties, and key areas of judgment, and clearly explain how these factors influence a regulatory decision."[35]

Industry and patient advocacy stakeholders have been working to proactively incorporate the patient's voice into the FDA's Structured Benefit-Risk framework, as well as other frameworks used by industry such as those developed by the Pharmaceutical Research and Manufacturers of America's (PhRMA) Benefit Risk Action Team (BRAT)[36] and the European PROTECT Benefit-Risk group.[37]

[31] Anderson, Margaret & McCleary, K. Kimberly. *On the Path to a Science of Patient Input,* Science Translational Medicine 27 Apr 2016: Vol. 8, Issue 336, pp. 336ps11, DOI: 10.1126/scitranslmed.aaf6730
[32] http://www.ctti-clinicaltrials.org/files/PatientGroups/PGCTrecs.pdf
[33] Patrick-Lake, Bray, Director Stakeholder Engagement, CTTI, October 13, 2015 Interview
[34] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm
[35] FDA, Structured Approach to Benefit-Risk Assessment in Drug regulatory Decision-Making, February 2013 http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf
[36] http://protectbenefitrisk.eu/BRAT.html
[37] http://protect-wp5.ema.europa.eu/protectwp5/

DUCHENNE CASE STUDY: DEFINING WHAT MATTERS TO PATIETS

As a result of scientific progress, multiple compounds for treating Duchenne have recently entered Phase 2 or Phase 3 clinical trials, with several coming forward for regulatory review.[38] However, the path toward commercial approval in Duchenne is fraught with hurdles, exacerbated by the complexity of the underlying disease, the nature of its patient population, and the difficulty in measuring clinical benefit.[39]

Patients and families within the Duchenne community have experienced disappointing failures in previous efforts to bring new compounds to market. These setbacks have fueled frustration with clinical study endpoints focused on traditional outcome measures (including survival benefit) that are generally defined by clinicians (without direct patient input). PPMD Founding President & CEO Pat Furlong saw an opportunity for PPMD to help define and validate trial endpoints based on what matters most to patients and their families. "In a chronic, debilitating disease, stability is improvement -- and maybe stability can't be measured in the context of a clinical trial."[40]

In its 2012 White Paper, "Putting Patients First," PPMD issued a call to regulators to implement greater flexibility in the review process for new therapies, specifically in exercising discretion for determining the type of evidence needed to approve a new drug for a serious or life-threatening disease with unmet medical need. PPMD has developed a solid foundation of understanding Duchenne, funding multiple Natural History studies to define the progression of the disease and launching a patient registry called DuchenneConnect to gather patient reported data (currently the largest Duchenne registry in the world).[41] Among the recommendations in its White Paper, PPMD encouraged FDA to consider novel endpoints in evaluating improvement in function of Duchenne patients and to give greater weight to demonstrated benefit-risk preferences of patients and caregivers.[42]

In 2015, BIO issued a White Paper identifying considerations for biopharmaceutical companies who choose to use the FDA's Structured Benefit-Risk Assessment Framework throughout a product's lifecycle, describing "an iterative, evolving, and collaborative process among the sponsor, the Agency, and patients, with the aim of achieving a common understanding of benefit-risk in a patient-centric manner."[43]

The goal of these efforts has been to generate patient perspectives information that can be relevant within regulatory decision-making processes[44] and develop a more formal way to ensure that the input from patients is considered in the regulatory setting.[45,46] This goal also underpins the work initiated by PPMD in launching its patient preference initiative.

Informing Development and Utilization of Clinical Outcome Assessments and Endpoints That Matter to Patients

Patient perspectives associated with a specific therapy can be used to inform discussions and decision-making among patients and their healthcare professionals. This becomes a more achievable outcome if patient perspectives information, especially relating to quality of life metrics, is included in the label and accompanying marketing materials for an approved product.[47,48,49] This point was underscored in the 2015 MDIC Framework Report, "[T]he information developed initially for regulatory purposes may be used in the development of shared decision making tools to help a patient understand the potential benefits and risks of a treatment approach to them."[50]

Collection and analysis of patient perspectives can also help determine which efficacy and safety endpoints are most relevant to specific patient populations and/or caregivers. This includes providing information that may help in the development,

[38] http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_patients#sthash.GqxRdl61.dpuf
[39] http://www.parentprojectmd.org/site/DocServer/WhitePaper_2013FINAL.pdf?docID=13883&AddInterest=1821
[40] Pat Furlong, Founding President & CEO, PPMD, September 14, 2015 Interview
[41] https://www.youtube.com/watch?v=1WUOXEDTmAI; www.duchenneconnect.org
[42] "*Putting Patients First*" 2012 White Paper, PPMD
[43] BIO, *A Lifecycle Approach to FDA's Structured Benefit-Risk Assessment Framework*, https://www.bio.org/node/92436
[44] "*Changing the Subject*," BioCentury, September 7, 2015 http://www.biocentury.com/biotech-pharma-news/coverstory/2015-09-07/23rd-biocentury-back-to-school-issue-let-patients-show-the-way-in-drug-development-a01
[45] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[46] Perfetto, Eleanor M., PhD & Oehrlein, Elisabeth M. *Assessing Meaningful Patient Engagement in Drug Development: A Definition, Framework, and Rubric.* http://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/pfdd/mcersi-pfdd-framework-rubric.pdf
[47] Ferris, Andrea, Founder & Chair, LUNGevity Foundation, November 5, 2015 Interview
[48] McLeary, Kimberly, Managing Director, FasterCures, October 16, 2015 Interview
[49] Holdsworth, Stacy, Senior Advisor, US Regulatory Policy & Strategy, Lilly, October 28, 2015 Interview
[50] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)

inclusion, and assessment of Clinical Outcome Assessments (COAs).[51,52,53] FDA defines COAs as those that measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. There are four types of COA measures: Patient-reported outcomes (PROs); Clinician-reported outcome (ClinRO); Observer-reported outcome (ObsRO); and, Performance outcome (PerfO). COAs can be used to determine whether a drug or biologic has demonstrated a treatment benefit, including a safety benefit compared to other treatments. Treatment benefits demonstrated by COAs are described in the labeling in terms of what is measured by the COA and can provide valuable information to patients and caregivers.

BRAY PATRICK-LAKE – CITTI

"It is important to stop 'best-guess medicine,' using observer-reported behavior where we think because we treat patients, this is the risk they are willing to accept. Really only the patients experiencing the condition can make that decision."

Determining what matters most to patients may also help inform the development of novel clinical trial endpoints that can be used for the primary basis of approval. For example, patient perspectives can be helpful in a rare disease setting where this type of information can mitigate lack of experience and uncertainty about the best endpoints to use.

As the collection of this type of information continues to advance and expand, and depending on the patients and diseases being evaluated, it may be important to develop an understanding of when and how to collect information that accounts for potential changes in patients' perspectives about a therapy over time, especially post-approval, as more information about the benefits and risks of its use becomes available.

ANDREA FERRIS – LUNGEVITY

"Too often we go about creating medicines for people without having asked the patients what they actually want. We make assumptions that people want a longer life at all costs. When speaking with people we often hear that they would be willing to trade-off duration of life for a higher quality of life - many will say they choose a certain therapy because it allows them to continue working and feel like themselves.

"We also know that some patients diagnosed with lung cancer are starting to live longer lives by stringing together a series of therapies including those still in clinical trials. This too is changing the dynamic of what people are looking for from each drug individually and often changes the side-effects that patients are willing to tolerate. We are fielding our large patient preference study to move from assumptions - to evidence-based conclusions about patient desires and ensure that patient's preferences are recognized, their voices are valued, and that living well with lung cancer can ultimately become the norm."

[51] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview.
[52] A Patient Reported Outcome (PRO) is defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." https://www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx
[53] Johnson FR, Hauber AB. *Are chemotherapy patients' HRQoL importance weights consistent with linear scoring rules? A stated-choice approach*. Qual Life Res. 2006;15:285-98.

DUCHENNE CASE STUDY: FDA GUIDANCE

In its landmark submission of draft guidance to the FDA in 2014, PPMD proposed steps and processes for drug developers, the patient community, and regulators to generate information on patient and caregiver perspectives that would fill gaps in evidence and assist regulatory decision-making for therapies for Duchenne muscular dystrophy.[54]

In its ongoing dialogue with regulators in the US and Europe, PPMD recognized the need to have regulatory guidance for drug developers focusing on Duchenne that would reflect the input of a broad array of stakeholders, including the patient community. However, citing resource constraints and a multitude of diseases within their purview, the regulators were unlikely to take this effort on by themselves. With encouragement from the FDA, in 2014, PPMD submitted draft guidance that had been carefully developed through a modified deliberative process that included working groups comprised of clinical and research experts, therapy developers, and a Community Advisory Board comprised of members of the patient community and representatives of partner organizations in the Duchenne space. The draft guidance -- "Duchenne Muscular Dystrophy: Developing Drugs for Treatment over the spectrum of Disease" -- was submitted in June 2014, marking the first time a patient group developed and formally submitted to FDA a draft guidance to help facilitate the development and regulatory review of potential therapies for a rare disease.[55]

PPMD's draft guidance was developed with insights from the PPMD patient preference initiative, especially the data demonstrating that most parents of children with Duchenne will accept substantial risk when balanced with non-curative slowing or stopping of the progression of muscle weakness, even with no improvement in life expectancy.

The PPMD document encouraged the FDA and trial sponsors to engage patients and their families at all stages of trial development and to take into account what the community considers acceptable risk in clinical trials.[56]

Each section of the draft guidance included extensive published or in-press peer-reviewed articles, focusing on overcoming the challenges in trial design and implementation, including Benefit/Risk Assessment, Diagnosis, Natural History, Clinical Trial Designs, Outcome Measures and Considerations, Muscle Biopsy-Based Biomarkers, and Non-Muscle Biopsy-Based Biomarkers.[57] The PPMD-led draft guidance also included a cover letter conceptualized as the community's "Imperatives" -- the community's expectations of regulators when engaging in clinical trials.

The draft guidance, while specific to issues in Duchenne, also provided a proposed blueprint for general FDA guidance relating to bringing patient preferences directly into the regulatory review process, including a summary of various methods for eliciting patient preference information using the Duchenne Patient Preference Study as an example. PPMD's draft guidance document states, "Clinical trial sponsors should take patient and/or caregiver preferences and priorities into account when designing clinical trials and when preparing for FDA submission. If relevant preference data does not already exist in the target decision-making population, sponsors should obtain this information. . . The need to include patient/caregiver preferences is especially compelling for serious, progressive disorders with limited treatment options. Thus, sponsors should provide the FDA with robust data on patient/caregiver preferences."[58,59]

[54] http://www.parentprojectmd.org/site/DocServer/Duchenne_Community_Imperatives_and_Cover_Letter_-_Draft_.pdf?docID=15284
[55] PPMD Draft Guidance Submission Cover Letter, June 25, 2015, https://drive.google.com/file/d/0BznHl9zgmlY3WkhGY3VZaGZ3blk/view
[56] http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance
[57] http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance#sthash.gQ9uFfvE.dpuf
[58] http://www.parentprojectmd.org/site/DocServer/Guidance_Document_Submission_-_Duchenne_Muscular_Dystrop.pdf?docID=15283
[59] Furlong, P., Bridges, J., et al. *How a patient advocacy group developed the first proposed draft guidance document for industry for submission to the U.S. Food and Drug Administration,* Orphanet J Rare Dis. 2015; 10: 82. Published online 2015 Jun 24. doi: 10.1186/s13023-015-0281-2

DUCHENNE CASE STUDY: FDA GUIDANCE (cont.)

In mid-2015, just less than a year after submission of PPMD's draft, FDA released its draft guidance, "Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment," to assist drug companies in the clinical development of drugs for the treatment of Duchenne. This marked the first time the FDA issued a guidance preceded by submission of a draft independently prepared by a patient advocacy organization.[60] EMA published its own Duchenne guidance in late 2015.[61]

The FDA's draft guidance included important encouragement to drug developers about the Agency's interest in considering patient preference information as part of the regulatory review process. "FDA recognizes that those affected by life-threatening and severely debilitating illnesses with unmet medical need are generally willing to accept greater risks and greater uncertainty about risks. Nonetheless, it is important that drug developers understand from affected individuals how treatment goals and risk tolerance are related to specific patient circumstances, such as age, disease stage, and phenotype, among others. . . As development proceeds and the potential benefits and risks of a drug become more clearly understood, input from patients and caregivers should be further elicited."[62]

Further, FDA's draft guidance states, "When making regulatory decisions regarding drugs for dystrophinopathies, FDA will consider patient and caregiver tolerance for risk, and the serious and life-threatening nature of these conditions. Patients and caregivers may be willing to tolerate substantial risk of harm if a drug might delay loss of important abilities, such as ambulation.

However, tolerance for risk may vary among individuals, and be affected by disease stage and severity; FDA would consider this heterogeneity in regulatory decisions. FDA considers the totality of the available evidence when conducting a benefit-risk assessment. For example, if the effect size on a sensitive measure of muscle function is modest for a drug with substantial risks, evidence of the clinical impact of the effect provided by patient reported outcomes (PRO) is likely to be an important basis of benefit-risk assessments."[63]

While PPMD was encouraged by the specific references to patient and caregiver preferences and priorities within the draft guidance, the organization sees the need for further progress. PPMD's Steering Committee submitted comments in response to the draft guidance noting, "There have been many advances in patient-focused drug development and in patient-centered benefit-risk assessment in recent years, advances that should be reflected in the guidance. The current section provides a historic view that is not consistent with current regulatory approaches in patient-centered benefit-risk assessments and the advanced disease specific evidence that our group has provided."[64]

[60] http://www.fda.gov/Drugs/DrugSafety/ucm448894.htm
[61] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500199239.pdf
[62] http://www.fda.gov/Drugs/DrugSafety/ucm448894.htm
[63] http://www.fda.gov/Drugs/DrugSafety/ucm448894.htm
[64] http://www.parentprojectmd.org/site/DocServer/Steering_Committee_Commentary_in_response_to_FDA_guidanc.pdf?docID=16403

CHAPTER 4: THE PPMD PATIENT PREFERENCE STUDY: A "DEEP DIVE" INTO ONE APPROACH

Individually and taken together, the approaches described above for developing patient perspectives information provide a rich and vital source of information that can support PFDD. However, some of these approaches do not produce the type of data commonly regarded as evidence in health care. Recognizing the challenges of integrating a traditional reliance on qualitative, anecdotal information with scientific methods for collecting patient preference data, stakeholders and leaders in the field have focused on efforts to quantify patient preferences in large-sample studies for integration with existing evidence-driven decision making.

The effort to enhance available preference information and expand its utility was recently described by Allkermes CEO Richard Pops, "Patients, their families, and the advocacy organizations that serve them already tap into a tremendous reservoir of human emotion. Those of us who discover and develop new medicines, the teams at FDA who review them, and the gatekeepers who decide who ultimately will gain access to them all need to understand that emotion. One of the best ways to do that is to translate it into the common language of science. Then, anecdote becomes evidence and gains even more power."[65]

HOLLY PEAY – RTI

"While stated preference approaches can provide compelling data, the vital first step in this process is thinking through whether this type of study is best suited to achieve your goals, and asking, 'should another type of study, for example, a quantitative interview study, be done instead?' It is important that people first think through what data they need, for what purpose, and then determine what method is required to do that."

The remainder of this report discusses considerations for conducting patient preference studies, an approach used by the Duchenne community to generate data on patient perspectives that could be used as evidence in the drug development and review processes.

What is a Patient Preference Study?

For the purpose of this report, "patient preference studies" are instruments that provide the opportunity to evaluate how patients and their caregivers would evaluate and accept tradeoffs, typically among therapeutic benefits and risks.

A patient preference study has been defined by the MDIC PCBR as, "qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions."[66] Further, experts note the distinction between "stated preferences," defined as what someone says they would do, and "revealed preferences," defined as what someone actually does.[67] In this report, we use the term "patient preference study" to mean that which provides people with a trade-off or choice decision, asks them what they would do in a given situation,[68] and uses quantitative methods. .

Why Conduct a Patient Preference Study?

Given that there are multiple ways to generate information on patient perspectives (many of which have been used successfully for years), it is appropriate, when considering the specific, more resource-intensive quantitative approach of studying stated patient preferences, to ask, "why select this approach?"

Patient preference studies yield many of the benefits of the array of approaches described previously in this report for engaging input from patients. They also offer the added benefit of delivering quantitative data about how patients view their choices. Experts note there are multiple applications for utilization of preference data, including understanding the maximum

[65] Pops, Richard, CEO, Allkermes; FasterCures, *The Power of Ideas*, November 2015 http://www.fastercures.org/assets/Uploads/Power-of-Ideas.pdf
[66] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[67] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[68] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview

risk and/or burden patients would accept, how they would compare benefits and risks between two treatment options, and whether a certain endpoint being studied is of particular importance to patients.[69]

CASE STUDY: FRAGILE X CAREGIVER PREFERENCES[70]

For the neurodevelopmental genetic disorder known as Fragile X syndrome (FXS), stakeholders working to develop new therapeutic agents recognized a need to gain a better understanding of unmet needs in this community, in order to hone in on outcomes that would be most important in determining effectiveness of new therapies.

Patients with FXS experience cognitive delays, including impairments in executive function (visual memory, visual-motor coordination, auditory short-term memory, visual-motor coordination, and sustained attention). Patients often exhibit anxiety, irritability, aggression, agitation, and disrupted communication/social functioning. Existing treatments focus on controlling some of these behaviors and symptoms, not the underlying disease.

Because of the unique characteristics of Fragile X patients, researchers launched a preference study to survey caregivers of males with FXS in an effort to quantify their preferences among a curated list of 6 cognitive, behavioral and social outcomes from treatment. Ultimately, responses from 614 eligible participants were evaluated in the sample group in order to quantify the relative importance to caregivers of various treatment outcomes. Among the conclusions from the study was the finding that caregivers of males with FXS identified the ability for patients to control their own behavior as the most important treatment outcome, more important than addressing problems like inattention or social withdrawal.

These results offer useful insights as drug developers and other stakeholders in the FXS community evaluate future clinical studies and therapy development opportunities. The authors of the study note that, "Advances in drug development and behavioral treatments [for FXS] are likely to be predicated on a consensus of which study endpoints or rating instruments are considered clinically relevant, and what effect sizes are considered clinically meaningful. Tools such as discrete choice experiments may help guide our thinking about future study design and facilitate comprehensive efforts already underway on that front to help improve the conditions and quality of life for individuals with FCX and their families."[71]

In answering the question of "why" a patient preference study approach might be appropriate for a given situation, developers of new medical products should define their data needs by asking questions about: the specific regulatory decision that a patient preference study would inform; the quality of information the decision-maker is looking for; and whether that information can best be obtained using a preference study.[72] Instances where a stakeholder in the drug development ecosystem may choose to pursue a patient preference study include: to assess unmet medical need; to inform strategic drug development decisions; to design clinical trials; to define alternate endpoints for clinical trials; to define sub-groups; and to impact the regulatory review process.

Companies can apply data from patient preference studies to inform "go/no-go" decisions throughout the drug development process, including decisions about which assets to prioritize within a portfolio, as sponsors evaluate the results from their clinical trials with an understanding of how patients might view the significance of the events that are caused or prevented by a study drug.[73]

Patient preference studies yield important insights about how people make medical treatment decisions such as tradeoffs patients say they would make among various outcomes of a therapy, including those relating to quality of life and symptom management.

Additionally, patient preference studies can help identify and define sub-groups within a particular patient population, all of whom are facing the same disease or condition, but who have differing approaches for making trade-off decisions. Individuals often have diverging priorities, with differences of opinions driven by a variety of factors, including stage of illness, severity of symptoms, demographics, and cultural or quality of life preferences. This information can also serve to help design clinical

[69] Levitan, Bennett Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[70] Cross J, Yang JC, Johnson FR, Quiroz J, Dunn J, Raspa M, Bailey DB Jr.,
Caregiver Preferences for the Treatment of Males with Fragile X Syndrome.
J Dev Behav Pediatr. 2016 Jan;37(1):71-9. doi: 10.1097/DBP.0000000000000234.PMID: 26595147
[71] Cross J, Yang JC et. al.,*Caregiver Preferences for the Treatment of Males with Fragile X Syndrome.*
J Dev Behav Pediatr. 2016 Jan 37(1):71-9. doi: 10.1097/DBP.0000000000000234
[72] Holdsworth, Stacy, Senior Advisor, US Regulatory Policy and Strategy, Lilly, October 28, 2015 Interview
[73] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview

trials that take into account the needs of patients and develop endpoints meaningful to patients.[74,75] Understanding these distinctions can provide context for regulators and point to specific treatment opportunities for drug developers.[76,77]

While regulators have a history of working with evidence and have significant experience in how to apply that evidence in their decision-making processes, there is more uncertainty, less experience, and emerging guidance and structure about how regulators can, should, or will consider anecdotal information. This has led stakeholders seeking to use patient input to impact the regulatory process to focus on patient preference studies to generate the type of evidence that can be incorporated into drug development and utilized by regulators.

KIM MCLEARY – FASTERCURES

"The number-one rule for patient preference studies is knowing why you are asking these questions and why you are thinking about doing a patient preference study. What decision do you want to inform? Is it to help a company get interested in a disease state, help patients make decisions about which clinical trial to enter, or help the regulators understand benefit-risk tradeoffs of a particular therapy?"

In its May 2015 Draft Guidance relating to medical devices, FDA-CDRH/CBER discuss what makes patient preference information distinct among the various mechanisms for engaging insights from patients. Specifically, the Draft Guidance points to a definition of patient preference information that includes patients' assessments of the acceptability of attributes that differ among various treatment strategies. The Draft Guidance notes that these assessments, if presented in the form of scientifically generated data, could be relevant to the regulatory process:

> ***Evaluations of patient-centric variations in tolerance to risks and perspectives on benefits may, in the aggregate, reveal a population-level assessment of patient benefit-risk preference for [that device], which may be considered valid scientific evidence (see 21 CFR 860.7) and may inform FDA's benefit-risk assessment for [a device]. If this assessment reveals that a significant number of reasonable and well-informed patients would accept the probable benefits despite the probable risks, this may help support a favorable benefit-risk profile.***[78]

While this approach has been put forth specifically in the context of medical device reviews, there is significant interest within the drug development community to encourage similar consideration by FDA-CDER and CBER as part of its reviews of new drug applications.[79,80]

[74] Hauber, Brett, Senior Economist, RTI Health Solutions, November 19, 2015 Interview
[75] Bridges J**, et al.** (2008) *Things are looking up since we started listening to patients: Recent trends in the application of conjoint analysis in health 1970-2007*, The Patient, 1(4): 273-282.
[76] Patrick-Lake, Bray, Director Stakeholder Engagement, CTTI, October 13, 2015 Interview
[77] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[78] http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf
[79] McLeary, K. Kimberly, Managing Director, FasterCures, October 16, 2015 Interview
[80] Boutin, Marc, CEO National Health Council, October 20, 2015 Interview

DUCHENNE CASE STUDY: "QUANTIFYING THE TEARS"

PPMD recognized a need to enhance the clinical considerations in regulatory review of new drug applications. The goal as described by PPMD Founding President & CEO Pat Furlong was to bring forward a first-hand discussion about "living with a progressive debilitating disease and all of the complications around it. These are things that the FDA couldn't relate to and that [are] critically important for us to talk about. The clinician isn't going to know because the clinician isn't living in [a patient's] house."[81]

This was the Duchenne community's answer to the question of "why" pursue a patient preference study and it is what led PPMD, in 2013, to launch a regulatory science initiative to produce actionable data reflecting the real-life perspectives of those living with Duchenne -- data that could, in the words of PPMD's founder, "quantify the tears."[82]

The initiative provided an important opportunity for PPMD to engage meaningfully with FDA. As described by Holly Peay, PPMD's lead researcher for the preference study, "[G]roups struggle with ways to have constructive interaction with FDA other than providing testimony. This is a way to come to FDA with data and a scientific level of engagement that is professional and constructive. That level opens doors to have other interactions that are mutually beneficial and include high levels of respect."[83]

Encouraged by the FDA's increased engagement with patient communities, PPMD engaged health economist John Bridges, PhD, of Johns Hopkins University, to collaborate in conducting several landmark studies that became a centerpiece of the Duchenne patient preference initiative. In support of these efforts, PPMD convened Stakeholder Community Advisory Groups, which were multi-sector advocacy oversight committees (including caregivers, researchers, clinicians and industry), to guide the projects and, as described by PPMD's head of community engagement, to incorporate "an array of opinions from the stakeholder community."[84]

Duchenne Patient Preference Pilot Study

In order to conduct its Pilot Study, PPMD led recruitment through PPMD's DuchenneConnect patient registry, PPMD outreach channels, including social media and other engagement tools, and through other advocacy organizations, identifying families willing to participate. The resulting study surveyed 119 parents of boys with Duchenne.[85] The initial study used a preference-research approach known as "best-worst scaling"[86] which was then validated by a second approach known as "conjoint analysis."[87]

The survey focused on eliciting preferences and testing the types of trade-offs families would be willing to make in weighing the benefit and risk of potential therapies for Duchenne.

Parents -- the primary caregivers of Duchenne patients -- were asked to rank a hypothetical set of six different potential treatment attributes, chosen by the study team and advocacy oversight committee to be reflective of the current therapy development landscape. Each of the six attributes had three levels associated with them to allow respondents to scale their preference decisions from a total of 18 potential treatment profiles.[88]

A key priority for PPMD in developing its pilot study was to ensure that the data, while scientifically valid, could also be easily understood by both clinicians and families[89] and could also provide an important complement to the PPFD approach undertaken by the FDA.

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[81] Pat Furlong, Founding President & CEO, PPMD, September 14, 2015 interview
[82] Pat Furlong, Founding President & CEO, PPMD, September 14, 2015 interview
[83] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview
[84] Fischer, Ryan, Senior Vice President, Community Engagement, PPMD, September 18, 2015 interview
[85] Due to the unique nature of Duchenne, whose patients are virtually all young boys, the decision was made to survey Duchenne parents for this first pilot study to minimize concerns surrounding whether respondents understood the survey and could provide reliable responses.
[86] In the pilot study Best-Worst Scaling (BWS) emphasizes the importance of an item, asking respondents to rank the attributes of a treatment profile. This is one of several validated statistical methodologies used in this type of preference study. See appendix and MDIC Catalogue for a full listing.
[87] In the pilot study Conjoint Analysis emphasizes trade-offs, asking respondents if they would select the treatment options presented. This is one of several validated statistical methodologies used in this type of preference study. See MDIC Catalogue for a full listing.
[88] http://www.clinicaltherapeutics.com/article/S0149-2918(14)00209-4/fulltext
[89] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 interview

DUCHENNE CASE STUDY: "QUANTIFYING THE TEARS" (cont.)

The results of the pilot study validated previous anecdotal reports about the risk-tolerance of many in the Duchenne community and found that most parents of children with Duchenne value quality of life more than length of life. Most respondents said they would be willing to accept the potential of serious risk from a treatment even if it did not offer the possibility of cure, if that treatment could be expected to stop or slow progression of the debilitating effects of the disease.

The survey generated quantitative data to demonstrate how highly parents of Duchenne patients would value moderate improvements in the ability of their sons to function in their daily lives. It also provided important data about parents' willingness to tolerate considerable risk and uncertainty in exchange for the potential of benefit to their children's ability to function.[90]

From the beginning, PPMD and John Bridges agreed that the results of the pilot study would be broadly shared with the Duchenne community, the FDA, industry, and the public. Two key publications (May of 2014 summarizing the results of the pilot study[91] and December of 2014 evaluating the two preference methods used in the study[92]) offered the community important tools for ongoing communication with regulators and drug developers about the needs and preferences of Duchenne families.

The pilot study data also contributed significantly to the evolution of the emerging patient-focused drug development field, establishing an important milestone in the use of statistical methods to quantify patients' disease experiences. "These combined experiments produced results that inform sponsors, regulators, and the broader rare disorder community. They are especially important in the case of progressive, life-threatening conditions with limited treatment options, where regulators may be less able to imagine how a 'typical' patient or caregiver might weigh benefits and risks."[93]

Enhancing Understanding of Preferences in the Duchenne Community: A Second Phase

The Duchenne patient preference initiative has continued to evolve, building on the results of the Pilot study and a collaboration with industry partner Santhera (discussed later in this report).[94] PPMD launched a second phase to expand its original pilot study, with plans to survey a broader set of respondents, including the patients themselves, and to address how preferences among families facing Duchenne might evolve over time as the patient's disease progresses. This second study is designed to address several key questions, including "expanding our understanding of what patients and caregivers consider to be meaningful benefit, how people weigh benefit-risk differently as the disease progresses, how uncertainty impacts decision making, and how caregivers and young adults view benefit-risk differently when looking at the same issue."[95]

PPMD has solicited the support of multiple companies in the Duchenne drug development arena for this second study, and plans to publish the results to inform decision-making across all stakeholders within the community, including industry, the patient community, and regulators.

[90] http://www.clinicaltherapeutics.com/article/S0149-2918(14)00209-4/fulltext
[91] http://www.clinicaltherapeutics.com/article/S0149-2918(14)00209-4/fulltext
[92] http://www.parentprojectmd.org/site/DocServer/Hollin_Patient_2014.pdf?docID=15744
[93] Hollin, I., Peay, H, Bridges J., *Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of Best-Worst Scaling and Conjoint Analysis* Patient DOI 10.1007/s40271-014-0104-x
[94] In late 2014, PPMD and Santhera Pharmaceuticals (a Swiss specialty pharmaceutical company developing a product aimed at improving respiratory function among patients with Duchenne) came together to understand certain tradeoffs facing the Duchenne community. The goal of this pioneering collaboration was to evaluate patient views in context of an actual therapy to address a non-skeletal muscle target in Duchenne.
[95] Kennedy, Annie, Senior Vice President, Legislation & Public Policy, PPMD, September 18, 2015 Interview

Whether to Conduct a Patient Preference Study?

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

The MDIC Framework Report includes a "core set" of factors to evaluate in considering whether a patient preference study might be useful in different situations.[96] Though this project focused on the device arena, many experts see these considerations, listed below, as potentially relevant more broadly to drugs and biologics.[97]

- ***Preference sensitive situations***, defined as "those in which there are multiple [treatment] options and the decision of which option to pursue depends upon the particular preferences of the decision maker."[98] These situations occur when there are multiple options available to the patient and either no option is clearly superior over a plausible range of preferences and/or the evidence supporting one option over others is considerably uncertain.

- ***Situations in which patients, because of their direct, personal experience with the disease, might have differing perspectives*** from those of other stakeholders (including providers, regulators, drug developers, and even other patients within their disease community). For example, the MDIC Framework Report cites situations in which patients' experiences with a therapy are "highly subjective (e.g. pain, fatigue, nausea, paresthesia, itch, depression), or when the impact on quality of life is an important outcome measure."[99]

- ***Situations in which assessing benefit-risk is especially challenging***, including those involving time lags between when patients experience benefits and harms, harms or side effects that are very different from those experienced previously, and harms or side effects that patients would not accept no matter what the potential benefit.[100]

THE VALUE OF PATIENT PREFERENCE INFORMATION AS A FUCTION OF BENEFIT AND RISK[101]

[96] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015Pages 32-36, http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[97] Hauber, Brett, Senior Economist, RTI Health Solutions, November 19, 2015 Interview
[98] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[99] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[100] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[101] Medical Device Innovation Consortium. A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology (http://mdic.org/pcbr/framework-pdf/). 2015.

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

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

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

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

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

DUCHENNE CASE STUDY: LAYING THE FOUNDATION FOR LAUNCHING THE PATIENT PREFERENCE INITIATIVE

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

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

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

When to Conduct a Patient Preference Study?

There are important considerations in determining the optimal time to launch a patient preference study -- the "when" within a specific drug development lifecycle. While it is important to engage input from the patient community throughout the drug development continuum,[106] from the point of view of a patient group, the decision about timing for a preference study relates to the readiness of the community and the ability to adequately engage the appropriate patients and/or caregivers in a substantive effort that can yield the type of data being pursued.

[102] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[103] Fischer, Ryan, Senior VP, Community Engagement, PPMD, September 18, 2015 Interview
[104] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[105] Boutin, Marc, CEO National Health Council, October 20, 2015 Interview
[106] Fischer, Ryan , Senior Vice President, Community Engagement, PPMD, September 18, 2015 interview

From the point of view of a company, there are decision points at every phase of portfolio development that could benefit from quantitative patient input and might specifically justify generating information on trade-off decisions through a patient preference study. For example, as discussed previously in this report, if a company is making internal portfolio decisions among multiple disease settings, having preference information from patients about non-product-specific choices and priorities might be important in choosing where to focus finite resources.[107]

Additionally, there are opportunities for engaging in a patient preference study at various points during the clinical testing of a new drug. If the goal of the preference study is to help shape the clinical trial, then it makes sense to have patient preference information early enough in the process to influence the protocol design. If the goal is to inform the regulatory review of a product it generally makes sense to engage a patient preference study in phase 2 or phase 3 of the development path, although it may not be clear what specific potential harms might be associated with the product or how much tolerance patients have for risk (and for which patient preferences are sought) until larger studies are underway.[108] However, it is important to account for timing as it is often the case that there is insufficient time to design and conduct a preference study in the period between pivotal trial topline results and a regulatory submission.

CASE STUDY: COMPANY-LED INITIATIVE #1

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

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

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

Who Should Conduct a Patient Preference Study?

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

Organizational Approach: Developing Collaborations and Selecting Partners

The initiative for conducting a patient preference study can originate from within the patient community itself, inside a company, from academia, or even within a regulatory agency, and the project can be executed individually or via collaborations. In determining whether and what type of collaborations and partnerships might be needed, it is especially important to evaluate the resources needed for the successful execution of the project, including funding, staff time, expertise, and access to relevant patients or caregivers.[109] If the purpose of the effort is to help inform internal company strategic decisions, it may be appropriate for the company to conduct the study on its own (though ideally with significant input from impacted communities).

[107] Meier, Thomas, CEO, Santhera Pharmaceuticals, November 11, 2015 Interview
[108] Levitan, Bennett Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, 2015 Interview
[109] Ferris, Andrea, Founder & Chair, LUNGevity Foundation, November 5, 2015 Interview

CASE STUDY: COMPANY-LED INITIATIVE #2

A sponsor company sought to understand and quantify patient and provider judgments about treatment-related benefits and harms for antipsychotic treatments for schizophrenia. A sample of 271 U.S. patients with schizophrenia was asked to judge between competing hypothetical treatment scenarios with differing degrees of improvements in symptoms, treatment-related side effects, and different formulation, as well as how prior history of patient adherence to treatment affects these results. A similar survey, using more clinical language, was administered to 394 U.S. and UK psychiatrists.

Both studies demonstrated that relieving positive symptoms of schizophrenia was more important than any other benefit or harm studied, and even minimal improvement in positive symptoms was important enough to be worth experiencing side effects, such as 15 percent weight gain. One major finding of the study was that, for individuals with a poor history of adherence to their treatments, both physicians and patients would accept considerable reductions (~25 percentage points) in efficacy in exchange for getting that individual to switch from an oral formulation to a monthly injectable depot formulation.

These studies provide a basis for sponsor and regulator benefit-risk assessments in schizophrenia treatment, particularly when dealing with considerations of formulation and patient adherence, as well as insight into how patients and their caregivers might evaluate tradeoffs they face when making medical decisions in response to new therapies.

However, increasingly, companies seeking to inform regulatory review processes are concluding that it is necessary to enter into collaborations to conduct patient preference studies, and are engaging with patient groups to leverage collective assets.[110] Selecting one or more patient group partners is a key decision. Patient groups are diverse and have a variety of resources and areas of expertise that could be helpful in advancing a patient preference study, including registries and broad grassroots reach.[111]

Key questions to ask in evaluating potential partners include, does the patient group have the right experience to collaborate on the project, lead the project, or just provide advice? Additionally, it is crucial to assess whether the patient group staff has the time to devote to a project of this magnitude.[112]

Statistical and Methodological Expertise

As the application of the early work in the stated preferences field becomes more specific to the development and regulatory evaluation of medical products, stakeholders note the importance of identifying and engaging the appropriate methodological expertise to ensure adequate scientific rigor when designing and executing a patient preference study. Recent examples in the field point to ongoing collaborative relationships among patient groups, methods experts in academic settings, and preference study experts within industry.[113]

In many cases, the lead entity advancing a patient preference project may not have the technical capabilities in-house and will need to identify external partners with the right knowledge and skills,[114] including community engagement experience, a deep knowledge of the disease and the drug development landscape, and statistical methods expertise.[115] Often, that external expertise is sought from academic partners who can bring experience and credentials to patient preference studies, as well as a knowledge within a specific disease area.[116]

Since the patient preference research paradigm began to emerge in published literature approximately 15 years ago, the field has been defined by a small group of experts from academic institutions developing and publishing on various statistical methodologies and survey approaches for measuring how people make choices.[117] There are ongoing discussions among the stakeholder community about the need to expand the expert "workforce" that can respond to the growing interest in conducting preference studies within drug-development.

How to Conduct a Patient Preference Study?

There is no "right way" for how a patient preference study project should be pursued. The field is still evolving; sponsors have multiple potential objectives for this type of work; disease states and patient populations are diverse; and therapeutic

[110] Holdsworth, Stacy, Senior Advisor, US Regulatory Policy & Strategy, Lilly, October 28, 2015 Interview
[111] Boutin, Marc ,CEO, NHC, October 20, 2015 Interview
[112] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview
[113] Anderson, Margaret & McCleary, K. Kimberly. "*On the Path to a Science of Patient Input"* Science Translational Medicine, April 27, 2016, Vol 8, Issue 336
[114] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview
[115] Boutin, Marc, CEO, NHC, October 20, 2015 Interview
[116] Ferris, Andrea, Founder & Chair, LUNGevity Foundation, November 5, 2015 Interview
[117] Hauber AB, Fairchild AO, Johnson FR. *Quantifying benefit-risk preferences for medical interventions: an overview of a growing empirical literature*. Appl Health Econ Health Policy. 2013; Aug;11(4):319-29.

development landscapes vary. As a result, there will be multiple types of patient preference initiatives undertaken in the coming months and years, offering all stakeholders the opportunity to expand and build upon the significant body of research[118,119] that has already been developed.

As this field continues to mature, there are ongoing discussions about the level of rigor that should be required for patient preference study data to be evaluated as "evidence" during the regulatory review and approval process. Some have argued that meaningful change in the evidence-based regulatory decision-making process will require that patient preference data satisfy rigorous quality standards similar to those applied to clinical evidence. Others assert that qualitative research maintains a strong, unique role in understanding the patient experience, and there is merit in including qualitative data or data stemming from small samples, especially in rare disease contexts, into the regulatory process, as well as quantitative data.[120] Either way, it is important to continue efforts to develop the field even as stakeholders continue to evaluate its impact with regulators. [121]

DUCHENNE CASE STUDY: CROSS SECTOR PARTNERSHIP[122]

Following the landmark pilot patient preference study, PPMD's next project was to quantify patient and caregiver preferences relating to specific treatment targets and outcomes.

In late 2014, PPMD and Santhera Pharmaceuticals (a Swiss specialty pharmaceutical company developing a product aimed at improving respiratory function among patients with Duchenne) came together to better understand patient and caregiver priorities and preferences for non-skeletal muscle treatment targets in Duchenne.

While the search for effective Duchenne treatments is often aimed at slowing or halting the musculoskeletal decline of patients, Santhera's focus is on delaying a serious complication from the disease: the progressive compromise of lung function. The loss of pulmonary function is often associated with the cause of death in individuals with Duchenne. The company and PPMD recognized shared interest in developing tangible scientific data to understand how Duchenne families would weigh potential benefit and risk in evaluating a therapy that could prevent or delay the decline in pulmonary function.

The resulting collaboration, led by PPMD and supported by Santhera, developed a quantitative study to generate patient preference data that included attributes associated with lung function. The attributes were developed through stakeholder engagement to reflect personally and clinically meaningful outcomes that were based on outcomes used in Santhera's ongoing phase 3 trials. The sponsor's key objective for the patient preference study was to determine the importance of improved pulmonary function, even absent benefit to skeletal muscle. PPMD also addressed a secondary objective, which was to have participants prioritize a group of potential non-muscle therapeutic targets, to inform subsequent drug development activities.

Working together, PPMD and John Bridges successfully designed the protocol, launched the study, and completed data gathering within a span of approximately nine months, including an efficient six-week recruitment period during which PPMD engaged its constituency to secure the participation of Duchenne families. The sponsor, Santhera Pharmaceuticals, was an active participant in the project development and a member of the Stakeholder Committee.

As described by Thomas Meier, CEO of Santhera, "We could not have done this on our own. The methods that are used in this type of study are completely different from a typical clinical trial. From the statistical side and how you set it up, this is a special know-how which we would not have. Second, we would not have had the access to the patients, because you need to be able to expose patients to this survey and we would not have had the means to do this."

From the outset of the collaboration, PPMD and Santhera agreed PPMD would own the data from the study, with Santhera retaining the right to incorporate it or reference it in its regulatory filings. Santhera agreed that PPMD could submit the full results to FDA and publish the findings. The two organizations released the results in late 2015. As of this writing, the regulatory process for Santhera's investigational drug continues.

[118] Johnson F.R., et al. (2013) *Constructing experimental designs for discrete-choice experiments: Report of the ISPOR conjoint analysis experimental design good research practices task force*. Value in Health, 16:3-13.
[119] Bridges, J. et al. *Conjoint analysis application in health – a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force.* Value in Health. 2011; 403-13.
[120] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview
[121] Meier, Thomas, CEO, Santhera Pharmaceuticals, November 11, 2015 Interview
[122] Hollin I, Young C, Hanson C, Bridges J, Peay H. *Developing a patient-centered benefit-risk survey: A community-engaged approach*. Value in Health. (Accepted, To be published).

The following sections of this report discuss best practice considerations that have emerged from early experience, to assist stakeholders in developing and conducting quality patient preference information in drug development.

Planning the Study

As discussed previously in this report, identifying the purpose of the study, framing the questions the study is meant to answer, and engaging the necessary expertise are all key early steps in launching a patient preference study.

Additional planning factors for the study include estimating the resources needed, including budget, staffing, and time. Depending on the size and scope of the planned sample population, and the challenges associated with engaging the necessary patient or caregiver participation, quantitative patient preference surveys can range in cost from the low end of $100,000 to the higher end of $400,000 and up, depending on the methods used. An average "placeholder budget" might be $250,000-300,000, with the bulk of costs associated with recruitment of study participants.[125]

While timeframes for patient preference studies are also variable depending on specific circumstances, a minimum of six to nine months is generally needed to design and conduct a relatively straightforward patient preference study, with some more complex projects taking up to two years to complete.[126]

From the point of view of a patient group's involvement, it is important to realistically assess the organization's capacity to successfully engage in conducting a patient preference study and to plan for the impact of this type of project on its staff and budget.[127]

For a company, it is helpful to have up-front understanding from internal colleagues and senior leadership about the value of undertaking the effort.[128] Successfully making the case internally to develop patient preference information is an important early step.[129]

CASE STUDY: CLINICAL TRIALS TRANSFORMATION INITIATIVE PROJECT

A recent set of recommendations from the Clinical Trials Transformation Initiative (CTTI) stemming from its Patient Group Engagement in Clinical Trials Project (PGCT)[123,124] included a set of considerations for all stakeholders to consider in evaluating potential clinical-trial related partnerships among industry, academia, and patient groups. While the CTTI project was specifically focused on engagement around clinical trials, many of the elements it highlights are relevant to partnerships for patient preference studies.

Putting Agreements in Place from the Outset

In engaging with experts and partners on a patient preference study, it is critical to establish a productive collaborative relationship that is based on trust. As in any partnership, this can be reinforced by putting in place necessary agreements at the outset to ensure clear understanding of key issues, including:[130]

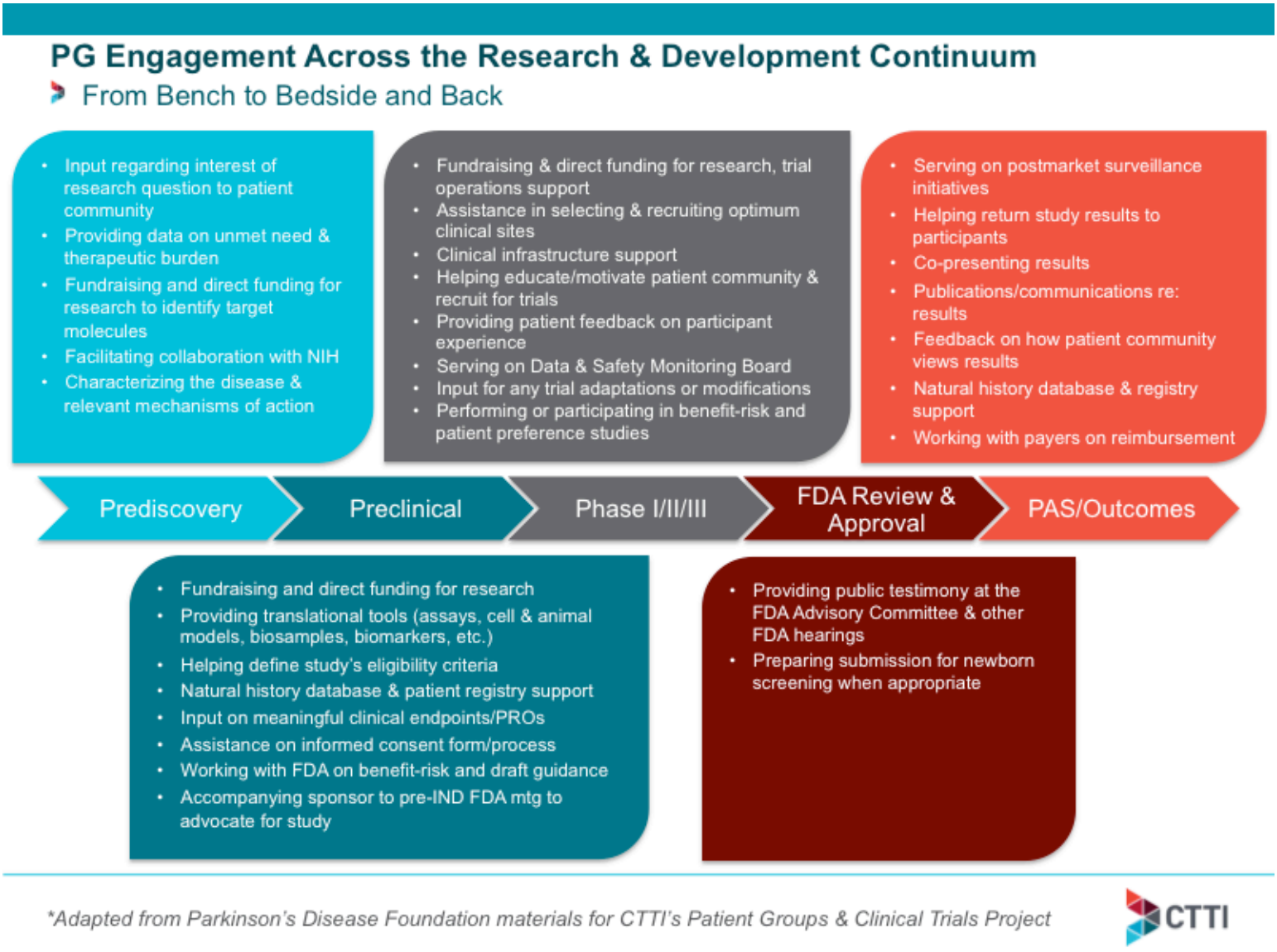
- Scope, leadership, funding, and control of the project;
- Roles and responsibilities;
- Ownership of the survey instrument and the resulting data;
- The timing of and approach for dissemination of results, in lay and professional forums;
- Publication guidelines and limitations; and
- General "rules of the road" for any collaborations relating to the project.

Discussions about eventual use of the data are especially significant, given the inherent uncertainty regarding what the data will ultimately show, determining how or if it will be published, and understanding how it may be used by companies or regulators. Additionally, there are nuances to be discussed regarding the timing of analyses, release of information to interested parties, and the distinction between ownership of the data and decision-making authority regarding making it public.[131]

[123] http://www.ctti-clinicaltrials.org/briefing-room/ctti-blog/finally-evidence-based-recommendations-tools-maximize-effective-engagement#.VytnUfkrKM8
[124] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140232
[125] Hauber, Brett, Senior Economist, RTI Health Solutions, November 19, 2015 Interview
[126] Bridges, John, JHU; Hauber, Brett, RTI; Johnson, Reed, Duke & Levitan, Bennett, J&J 2015 Interviews
[127] Patrick-Lake, Bray, Director Stakeholder Engagement, CTTI, October 13, 2015 Interview
[128] Johnson, Reed, Senior Research Scholar, Duke University, October 30, 2015 Interview
[129] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[130] Hauber, Brett, Senior Economist, RTI Health Solutions, November 19, 2015 Interview
[131] Fischer, Ryan, Senior VP, Community Engagement, PPMD, September 18, 2015 Interview

As in any scientific endeavor, a patient preference study may yield unexpected results and all stakeholders involved in the initiative should be prepared for surprising or even disappointing outcomes. For example, it may turn out that, when faced with a tradeoff among current therapy and a possible new therapy with the potential of more significant side-effects, some groups of patients may not want to accept the described risk. Patients may also express concern about burdens associated with the administration of a potential new therapy or may be more interested in addressing certain symptoms that impact on quality of life, rather than focusing on short-term survival advantage. Regardless of the outcome of a patient preference study, field leaders agree it is important to ultimately provide feedback to the relevant patient community about what was learned and how the learnings will impact future decisions.[132] In addition, the results should eventually be made publicly available in order to advance the field.[133]

To address all of these issues, it is necessary to develop written agreements among partners to ensure clarity and transparency relating to publicizing the study itself, confidentiality requirements, intellectual property issues, and other operational considerations associated with the patient preference study. In general, collaborators sign non-disclosure agreements and spell out plans for future publication of results from the study, as they would for clinical and other research collaborations.[134] Executing these types of agreements also mitigates against the kinds of real and perceived conflicts of interest that generally may arise from lack of clarity between partners.



[132] Fischer, Ryan, Senior VP, Community Engagement, PPMD, September 18, 2015 Interview
[133] Holdsworth, Stacy, Senior Advisor, US Regulatory Policy & Strategy, Lilly, October 28, 2015 Interview
[134] Hauber, Brett, Senior Economist, RTI Health Solutions, November 19, 2015 Interview

Designing and Conducting the Survey

Good Science. Patient preference studies should be undertaken with the same level of commitment to the principles of "good science" applied to any clinical research effort. As in all research, the outcome of the study is not a foregone conclusion, and all participants in the process must appreciate that the study outcome may not advance their own priorities.

In its May 2015 Draft Guidance relating to quantitative patient preference information in regulatory review of device applications, FDA-CDRH/CBER outlined 11 "recommended qualities of patient preference studies" that it would consider when determining whether patient preference information constitutes valid scientific evidence.[135]

In undertaking a patient preference study, stakeholders should consider this list of recommended qualities:

- Representativeness of the sample and generalizability of results;
- Capturing heterogeneity of patients' preferences;
- Established good research practices by recognized professional organizations;
- Patient centeredness;
- Effective communication of benefit, harm, uncertainty, and risk;
- Minimal cognitive bias;
- Logical soundness;
- Relevance;
- Robustness of analysis of results;
- Study conduct; and
- Comprehension by study participants.

REED JOHNSON – DUKE UNIVERSITY

"Patient-preference studies will not have an impact on decision making if they are simply dismissed by regulators as public-opinion surveys.

"Stated-preference researchers have targets on our backs. If we can't satisfy widely acceptable standards of evidence--then it will be too easy for defenders of the status quo to dismiss our efforts as just another shouting match."

Once the collaboration agreements are in place, important milestones in the process include finalizing the aims of the study, determining experimental design and developing the actual survey instrument that will be used, and ensuring the target patient or caregiver population can provide the information that is sought.[136]

Considerations of Methods for Assessing Patient Preferences. It is beyond the scope of this effort to delve into a detailed analysis of the various methods available for assessing patient preferences. However, the MDIC Framework Report included an extensive Catalog of Methods for Assessing Patient Preferences for benefits and Harms of Medical Technologies. While the MDIC Catalog is focused on the device arena, it is viewed as an important compilation and discussion of available approaches that have applicability beyond the limited context of devices.[137] Generally, when choosing a method to use, it is important to consider an approach that can be both scientifically robust and understandable to participants and the larger community being surveyed.[138] It is also sometimes recommended that more than one study be conducted, where possible and appropriate, to validate findings and, potentially, pose similar questions using more than one methodology.[139]

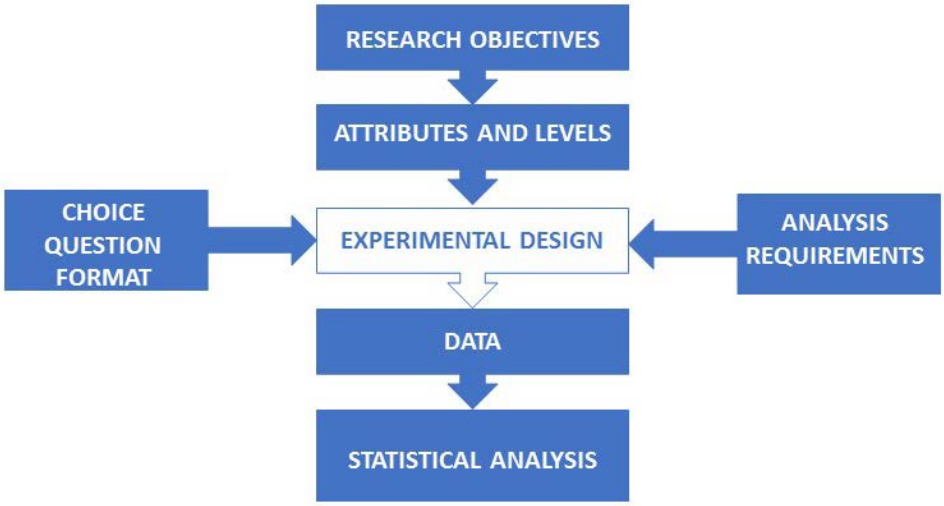
Available approaches and methods for conducting for patient preference studies have different profiles, depending on the specific context of the project, including:[140]

- Current clinical information on benefits and harms;
- Stage of development of a therapeutic agent;
- Time and budget available for the study;
- Organizational culture;
- Audience for the data and analysis; and
- Prior use of the methods in similar circumstances or indication.

[135] http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf
[136] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[137] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[138] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview
[139] Bridges, John, Johns Hopkins University, October 16, 2015 Interview
[140] Johnson, Reed, Senior Research Scholar, Duke University, October 30, 2015 Interview

The International Society For Pharmacoeconomics and Outcomes Research (ISPOR) published in-depth discussions of best practice considerations for stated preference study experimental design, which provides valuable insights for stakeholders seeking to embark on patient preference studies.

"Researchers use an experimental design to map attributes and levels into sets of alternatives to which respondents indicate their choices. The experimental design comes after researchers have determined whose preferences (patients, caregivers, or providers) are being assessed, what health care features are of interest, and what types of models will be used. Experimental designs thus first require the researcher to determine the objectives of the study and to select the component attributes that are believed to characterize the health care object of interest."[141,142]



Patient Preference Survey Instrument. A critical component of the patient preference study is the survey instrument itself – the tool that will be used in generating responses from the target audience. Advocates and researchers who are familiar with more traditional social and behavioral research of clinical research surveys may be surprised at the level of participant "set-up" and teaching required for a successful survey.[143]

A well-designed survey instrument will generally include:[144]

- Screening questions to ensure respondents meet the criteria for participating in the study;
- Informed consent provisions to ensure respondents clearly understand the purpose of the study and the implications of their participation;
- Background information describing the context for the study and any other relevant foundational information necessary for someone to fully participate;
- Training and definitions to ensure that respondents are appropriately equipped to understand and answer the questions posed by the study;
- Testing to address any unexpected issues that may arise in conducting the actual study; and
- Survey questions and, if appropriate and needed, follow-up survey questions.

Developing the survey instrument with input from multiple stakeholders and perspectives is important to the success of the project. It is extremely important to pilot test the instrument to allow for adjustments based on that feedback. In the PPMD case, the organization vigorously engaged an array of stakeholders from the Duchenne community, relying on a stakeholder board, a series of multi-stakeholder committees, and extensive pilot testing using in-person and online tools.[145]

Defining and Engaging the Study Population. Determining the sample population for a patient preference study is critical to generating data that is relevant to the objectives of the effort. Within a specific disease community there will likely be a

[141] Johnson, Reed et. al, *Constructing Experimental Designs for Discrete-Choice Experiments: Report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force*, Value In Health(2013) 3 –13,
Published by Elsevier Inc. http://dx.doi.org/10.1016/j.jval.2012.08.2223
[142] Figure courtesy of Johnson, Reed. 2016
[143] Peay, Holly, PhD, Research Analyst, RTI International; Co-PI, DuchenneConnect Registry (a program of PPMD); Former Senior VP Education & Outreach, PPMD, September 23, 2015 Interview
[144] Levitan, Bennett Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, 2015 Interview
[145] Fischer, Ryan Senior VP, Community Engagement, PPMD, September 18, 2015 Interview

range of points of view and differing preferences, reflecting an array of differences among age, disease burden, symptom severity, lifestyles, and values.[146] Additionally, patients may have different preferences and priorities than their caregivers or their doctors. Consideration in determining the most appropriate sample population should also include an evaluation of where patients are within their experience with the disease (for example, whether they are newly diagnosed or farther along in the progression of their condition), as well as the adequacy and availability of existing treatment options in meeting the needs of those patients.[147]

CASE STUDY: PROJECT TRANSFORM FOR LUNG CANCER[148,149]

Lung cancer is the leading cause of cancer mortality in the US, accounting for 27 percent of cancer deaths. Novel treatments have improved outcomes but increased complexity of treatment decision-making. LUNGevity Foundation and Johns Hopkins University launched Project Transform, a collaboration to understanding treatment preferences of lung cancer patients. The goal of Project Transform is to "change the paradigm in lung cancer from assumptions being made about patient wishes to evidence-based conclusions about patient need and desires."

The team formed a Patient Action Committee (PAC) that consists of 27 people living with lung cancer. The PAC was engaged using principles of patient-centered outcomes research (PCOR) to evaluate meaningful questions and outcomes to patients and caregivers. The team's objective is to understand the "lived experience of people with lung cancer" and develop a sustained relationship with PAC members to develop the objectives and scope of Project Transform.

Next steps in the initiative include fielding a national survey to begin collecting data for Phase II of Project Transform.

In designing a preference study, it is important to determine whose preferences are being sought. As is true in clinical trials generally, this can be a complex determination, given the heterogeneity of many patient communities and the possibility of distinct subgroups within a disease population based on disease burden, demographics, or geographic distinctions.

Ideally, a study would focus on a sample from that group of sufficient size to generate acceptably robust results, including an appropriate group of the actual patients who would be making decisions related to use of relevant medical products, or, where applicable, caregivers and others who are involved in making treatment decisions. While it is often technically not feasible or too costly to draw a truly representative patient sample, experts are focused on defining a sample that can yield reliable results.[150]

Consideration of whether the planned target group of patients is actually able to fully participate in the patient preference study is also critical. For example, there are certain populations of patients who may be unable to engage in some surveys, including children and those whose disease symptoms impede a full understanding and evaluation of the trade-off decisions that are proposed.[151] While caregivers' stated preferences may not always be a true proxy for those of the patients themselves,[152] at times, it may be most effective to focus a study on caregivers (parents and other close family members) who are central to the decision-making process for a particular group of patients, or a combination of both patients and caregivers.

In the case of the PPMD initiative, the leaders of the initiative decided to survey parents of boys with Duchenne for the pilot study, given that the drugs in development at the time were focused on children whose parents would be integral to the decision-making. However, the subsequent Santhera-sponsored study and the ongoing follow-up study expanded the sample population to include the Duchenne teenage and adult patients themselves, allowing an opportunity to evaluate similarities and differences between the preferences of patients and their caregivers.[153]

Data from a patient preference study represents a snapshot of views and potential decisions of key patient and caregiver groups at a specific point in time. All parties should understand and account for the evolving nature of preferences and consider whether conducting repeated studies are needed to evaluate preference variability at specific time intervals in the drug-development process where the treatment paradigm for a certain disease evolves.

There are multiple considerations for obtaining sufficient study participation from among the target sample population, depending on the specific characteristics of the disease, the therapeutic development setting, and the patient community. Study investigators can leverage existing resources, such as patient registries, advisory boards, patient registries, ongoing clinical trials, and partnerships with providers and provider networks to invite participation from the appropriate audience.

[146] Patrick-Lake, Bray, Director Stakeholder Engagement, CTTI, October 13, 2015 Interview
[147] Levitan, Bennett, Senior Director, Benefit-Risk Assessment, Department of Epidemiology, Janssen Research & Development, LLC, October 15, 2015 Interview
[148] https://smdm.confex.com/smdm/2015mo/webprogram/Paper9382.html;
[149] www.lungevity.org
[150] Johnson, Reed, Senior Research Scholar, Duke University, October 30, 2015 Interview
[151] Bridges, John Johns Hopkins University, October 16, 2015 Interview
[152] Johnson, Reed, Senior Research Scholar, Duke University, October 30, 2015 Interview
[153] Fischer, Ryan, Senior VP, Community Engagement, PPMD, September 18, 2015 Interview

Additionally, online networks, social media communities and in-person meetings provide important resources. While efforts are often made to conduct face-to-face interviews, it is important to consider using communications tools (including Skype, FaceTime, and other online channels) to expand the reach of the survey.[154]

Stakeholders have focused on the importance of attempting to achieve an appropriately representative sample, including efforts to reach across geographic boundaries, demographics, socioeconomic status, literacy, and disease trajectory.[155] Additionally, there is an understanding that patients who are most likely to engage with a patient group's activities might not fully represent the patient population as a whole.[156] Efforts should be made to ensure adequate reach within the target patient community, including setting up advisory committees.

Engaging with Regulators. Experts generally suggest reaching out to regulators (especially in the U.S., given recent efforts to elevate patient-focused medical product development activities) early in the process of developing and conducting patient preference studies. While FDA has finite resources and in-house technical expertise in the area of preference study methods, early experience suggests opportunities for productive collaboration.

Specifically, in the device arena, the MDIC Framework Report emphasizes the opportunity to work with FDA-CDRH staff from early stages of product development in considering types of patient preference information that could be useful and determining how best to collect it. "[The] early stages of product development can be a good time to initiate interactions with the FDA regarding the product concept to discuss appropriate regulatory pathway and the potential value of patient preference information."[157]

Further into the development process of a product, sponsors may want to discuss patient preference information and studies with regulators, and ultimately may opt to include data from a patient preference study in their regulatory submissions and advisory committee presentations.

From the perspective of many patient groups, engagement with regulators is an important component to advancing the interests of their communities. The PPMD example points to an ongoing dialogue between the patient group and the FDA to create opportunities for feedback throughout the evolution of the patient preference initiative. As Annie Kennedy, PPMD's lead regulatory official notes, "It is important to start engaging with the FDA early so it feels like a conversation and a process. We wanted to make sure the questions we were asking our community were of interest to the FDA."[158]

KEY PPMD ACCOMPLISHMENTS IN ADVANCING PFDD FOR THE DUCHENNE PATIENT COMMUNITY

December 2001	Muscular Dystrophy Community Assistance Research and Education (MD CARE) Act enacted
December 2007	Launch of DuchenneConnect
November 2009	First-ever Duchenne Care Considerations published in Lancet Neurology
January 2013	PPMD launches Benefit Risk Initiative to Quantify the Patient Voice
April 2013	Putting Patients First White Paper
December 2013	PPMD-FDA Policy Forum
January 2014	PPMD assembles draft guidance Steering Committee and Community Advisory Board
May 2014	Publication of Pilot Patient Preference Study Results
June 2014	Publication and submission of PPMD draft guidance for FDA
November 2014	PPMD and Santhera launch Preference Study on Pulmonary Outcomes
June 2015	Publication of FDA Draft Guidance
October 2015	Submission of Santhera Preference Study results to FDA
November 2015	Biomarin FDA Advisory Committee Meeting
January 2016	PPMD launches third preference study, BRAVE
April 2016	Sarepta FDA Advisory Committee Meeting

[154] Fischer, Ryan, Senior VP, Community Engagement, PPMD, September 18, 2015 Interview
[155] Furlong, Pat, Founding President & CEO, PPMD, September 14, 2015 Interview
[156] Johnson, Reed, Senior Research Scholar, Duke University, October 30, 2015 Interview
[157] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[158] Kennedy, Annie, Senior VP, Legislation & Public Policy, PPMD, September 18, 2015 Interview

CHAPTER 5: MAKING AN IMPACT

While there is no formally defined roadmap at this time for how the FDA will incorporate patient preference data in its review of drugs, or whether the data will impact regulatory decision-making in specific ways, stakeholders who invest the significant resources necessary to conduct patient preference studies will nonetheless continue to seek ways to evaluate the impact of their efforts.[159]

WEIGHT LOSS CASE STUDY: TANGIBLE REGULATORY IMPACT[160]

In response to the emergence of multiple new technologies to assist obese people with weight loss, the FDA-CDRH conducted a pilot study to generate and understand preferences of people struggling with obesity. The goal of this effort was to develop information that could be used by regulators in their assessment of the benefits and risks posed by new technologies presented for regulatory review. The initiative was designed to enhance the opportunity for a "patient-centric" regulatory review, as outlined in the CDRH Benefit-Risk Guidance,[161] published in 2012. Leaders of this effort recognized the opportunity to evaluate patient preferences in the obesity context, given the elective and preference sensitive nature of the decision to use a medical device for treating obesity. The study was not tied to a specific medical device, but rather was designed to provide information that could be used in regulatory review for a range of submissions.

The resulting Obesity Study (published in 2015) presented a series of trade-off choices involving benefits and risks from the use of multiple hypothetical medical devices to more than 600 obese respondents.

FDA-CDRH has been using the results of the study for a variety of purposes, including informing clinical trial design for new submissions to the Agency. It is also using the study to inform regulatory decisions, expressing willingness to consider approving a device with an indication for use by patients for whom the benefits outweigh the risks.

The approval in 2015 of EnteroMedics Maestro Rechargeable System demonstrates a concrete example of the use of this preference data in a regulatory approval, even though the device did not meet its clinical trial endpoints. "In considering the benefits and risks of the device in its review of the Maestro Rechargeable System, the FDA considered the clinical study and the Panel's recommendations. Additionally, the Agency looked at an FDA-sponsored survey relating to patient preferences of obesity devices that showed a group of patients would accept risks associated with this surgically implanted device for the amounts of weight loss expected to be provided by the device."[162]

To date, the most definitive example of patient preference information impacting a regulatory decision remains the case of the obesity study conducted by FDA-CDRH and then incorporated into the review of a specific medical device.

In the drug development realm, stakeholders remain hopeful that the continued evolution of the field and expansion of PFDD, as well as the pioneering patient preference initiatives led by PPMD and other patient communities, will lead to additional examples of tangible impact.

While the Duchenne story is still being written, all stakeholders agree that the landscape has already shifted to create a new paradigm as a result of the PPMD initiative.

[159] Levitan, B. et al.; *Therapeutic Innovation & Regulatory Science* 2014 48: 564 originally published online 30 May 2014; DOI: 10.1177/2168479014536500
[160] Medical Device Innovation Consortium (MDIC). *MDIC Patient Centered Benefit-Risk Project Report.* 2015; http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf)
[161] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm
[162] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm

DUCHENNE CASE STUDY: A NEW PARADIGM

In late 2015 and the first half of 2016, there were two FDA Advisory Committee meetings[163,164] to review new drug submissions for Duchenne, providing PPMD and the Duchenne community with the opportunity to take important steps in bringing quantitative patient preference data into the regulatory process. It is also noteworthy that, for each of these Advisory Committee meetings, there were two patient representatives who served as full voting members of the Advisory Committee, one adult patient and one parent of a child with Duchenne, reflecting the evolving understanding within the community and at the FDA that perspectives among those two groups may differ.

The late 2015 Advisory Committee process marked the first time that Duchenne families were exposed, in a systematic way, to the briefing materials and regulatory diligence of a review process. And, while there were disappointments as the product in that case did not receive regulatory approval,[165] PPMD's lead regulatory staff notes the experience was a milestone for PPMD and its constituency in the development of a "sophisticated approach to evaluating benefit-risk, responding to safety and uncertainty and establishing a new vernacular in the community for engaging with drug development."[166]

In the second instance (late April 2016), there were further signs that the FDA and industry sponsors recognize patient perspectives as an integral element of the regulatory review process. The FDA expanded the amount of time allotted to the public to provide input during the review meeting, making sure that anyone who wished to testify would have the opportunity to do so, including patients with direct experience with the product under review, caregivers, clinicians and scientists. The comments from the 52 people who testified provided context to the filing and the review, allowing for a full discussion of the specific issues and questions raised by the Agency.

Additionally, and as a significant departure from traditional practice, the sponsoring company also provided a portion of its time to a patient advocate who presented information relating to the development of a PRO.[167]

This closely-watched Advisory Committee meeting (not only by the Duchenne community, but also by stakeholders across the medical research and drug development enterprise) demonstrated the extent to which the regulatory process is still evolving in developing a clear framework for bringing patient preference information into its decision-making. Although a divided Advisory Committee ultimately voted not to recommend approval of the product based on the submission, the comments made by FDA leadership demonstrate that it ultimately recognizes its flexibility to take the views of the patient community into account and to consider the totality of the information presented.[168] The recommendations of Advisory Committees are just that – advice -- and do not bind the agency to any decision. While committee discussions and final votes are very important to the FDA, the final regulatory decision rests with the Agency. [169] At the time of this writing, the FDA has not announced a final decision in its review of this product.

163 http://www.fda.gov/AdvisoryCommittees/Calendar/ucm467180.htm;

164 http://www.fda.gov/AdvisoryCommittees/Calendar/ucm490665.htm

165 http://investors.bmrn.com/releasedetail.cfm?ReleaseID=950309

166 Kennedy, Annie, Senior VP, Legislation & Public Policy, PPMD, May 12, 2016 Interview

167http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm500823.pdf

168 http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm500819.htm

169 http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143538.htm

CHAPTER 6: MOVING FORWARD

This is an exciting time of opportunity and promise in the field of medical research and drug development. Patient Focused Drug Development (PFDD) and recent efforts to enhance patient centricity offer the promise of a near-term future where the needs, priorities, and preferences of patients can be incorporated much more directly into the drug development and regulatory review processes.

As efforts continue to collect and utilize patient perspective information, including patient preference data, it is important to understand what methodologies are most appropriate for generating the different types of data for differing purposes such as analyzing perspectives among various patient populations and sub-groups and impacting decision-making points throughout the life cycle of a drug or biologic. Additionally, there are key questions to be answered about how this information should be submitted to regulators, what the standards will be for the collection and submission of this data, and in what manner this information will be reviewed and utilized by regulatory agencies around the world.

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"The role of stated-preference research in health is to lend scientific methods to enhance the voice of a broader group of people. Patient preference research is important in regulatory science as it is more democratic than patient testimony. It can also promote justice in decision making. For this work, it is very important to have the imperative from the relevant disease community — the desire of a community to get this stuff done. It was this imperative from PPMD that led to such a productive partnership in our collaborations."

This report provides key considerations for determining why/how/when to integrate patient perspectives in drug development. While much work remains to be done in building upon that foundation, BIO and PPMD are committed to working with all stakeholders in advancing this still-evolving field.

APPENDIX: GLOSSARY, ACKNOWLEDGEMENTS, AND REFERENCES

Glossary

- ***Benefit/Risk Framework:*** Includes key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

- ***Clinical Outcome Assessment (COA):*** Clinical outcome assessments (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. COAs can be used to determine whether or not a drug has been demonstrated to provide treatment benefit. Treatment benefit can also be defined in terms of a safety benefit compared to other treatments. A conclusion of treatment benefit is described in labeling in terms of the concept of interest, the thing measured by the COA. There are four types of COA measures: Patient-reported outcome (PRO) measures; Clinician-reported outcome (ClinRO) measures; Observer-reported outcome (ObsRO) measures; and, Performance outcome (PerfO) measures. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

- ***FDA Guidance***: FDA Guidances, when finalized, describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf (page 1-2)

- ***FDA Patient Focused Drug Development Initiative***: In PDUFA V, FDA committed to a new initiative known as Patient-Focused Drug Development (Initiative) with the objective of obtaining the patient perspective on the condition and the currently available therapies for a set of disease areas. For each identified disease area, FDA committed to conduct a public meeting inviting members from FDA review divisions, the relevant patient advocacy community, and other interested stakeholders to be completed by the end of PDUFA V (FY 2017).

- ***Patient Advocacy Organizations/Patient Groups:*** Terms encompassing patient advocacy organizations, disease advocacy organizations, voluntary health organizations, non-profit research foundations, and public health organizations. http://www.ctti-clinicaltrials.org/files/PatientGroups/PGCTrecs.pdf

- ***Patient Perspectives Information:*** Information gathered from the perspective of the patient or caregiver about their experience of the disease or condition that includes, but is not limited to: symptoms experienced, chief complaints (description of the most significant or serious symptoms or signs of illness or dysfunction that cause the patient to seek health care), the burden of living with a disease, the burden of managing a disease, impacts on activities of daily living and functioning, effect of current therapeutic options, unmet medical need, disease severity and chronicity, natural history, minimum expectations of benefits, maximum tolerable harms or risks that a patient might be willing to accept in pursuit of desired benefits, attitudes toward uncertainty, other types of patient preferences, and preference-sensitive decisions that patients might encounter. http://www.fastercures.org/reports/view/49

- ***Patient Preferences***: Preferences expressed by patients with regard to decisions concerning their health care. Preference refers to the tradeoffs that individuals consider or exhibit in making decisions or choices for themselves. http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web.pdf (page 20)

- ***Patient Reported Outcome (PRO):*** Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. https://www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx

- ***Preference Sensitive Situations:*** Those in which there are multiple [treatment] options and the decision which option to pursue depends on the particular preferences of the decision maker. These situations occur when there are multiple options available to the patient, each associated with different benefits and harms, and a degree of uncertainty about which option would be best. http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web.pdf (page 22)

- ***Representativeness***: A study measuring a sample of adequate size to ensure that the study results can be generalized to the population of interest – may be influenced by sample size, the between-subject variability, and how subjects were sampled from the population of interest. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf (page 12)

- ***Stated Preference Techniques:*** These aim to measure both health and non-health outcomes (ie costs and benefits), and include qualitative analysis, conjoint analysis (often referred to as discrete choice analysis/modelling) and willingness to pay (or contingent valuation). http://europepmc.org/abstract/MED/15119540

- ***Subgroup***: A group of patients in a sample with a common observable characteristic or set of observable characteristics. http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web.pdf (page 151)

- ***Unmet Medical Need***: A condition whose treatment or diagnosis is not addressed adequately by available therapy – includes an immediate need for a defined population (i.e. to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf (page 4)

Acknowledgements

The author would like to thank the members of the Expert Review Committee, the individual experts we spoke with, as well as the leadership at the FDA for their invaluable contributions, guidance and support in this effort. We are also grateful to the PPMD and BIO leadership teams for their vision in launching and shepherding this project to its successful completion. We are indebted to the leaders in the field of patient preference research, whose pioneering efforts have launched the opportunity to tap into the science of patient input. Finally, we are most grateful to the patients, caregivers and families within the Duchenne Muscular Dystrophy community and beyond, who have shared their experiences and perspectives in an effort to accelerate medical progress and improve outcomes for all patients today and in the future.

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