



Patient Engagement in Benefit-Risk Assessment throughout the Life Cycle of Medical Products*

Conference Short Summary

September 17-18, 2015
Bethesda North Marriott, Bethesda, MD, USA

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Materials from this meeting, including the agenda and list of speakers, are available at:

<http://www.diaglobal.org/en/resources/topics-of-interest/csp>

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BACKGROUND AND ISSUES

Benefit-risk assessments of medical products, the weighing of benefits against the risks for harm from using the product for treatment, are the foundation for making decisions about the product all through its life cycle.¹⁻³ The researcher and developer use the information to decide whether a product will be developed and submitted for regulatory approval. The regulator uses benefit-risk information to make decisions about approval of the product for release or retention on the market. The patient or caregiver utilizes benefit-risk information to make decisions about using the product for treatment.

For a medical product to truly meet the needs of the patient for whom it is intended, its benefits and risks must be balanced in the context of the patient's perspective, making patient input central to benefit-risk decision-making.⁴⁻¹³ Balancing benefits and risks involves both technical assessments of the evidence base and societal value judgments about relative importance. Because patients are the beneficiaries of more effective treatments and also bear the possible risks associated with those treatments, their perspectives and judgments about value and relative importance are at the heart of this process.

Researchers in medical product development in both academic and industry settings have studied strategic frameworks for benefit-risk decision-making for a number of years and have made great strides in reaching consensus on the core elements that should be included in an effective framework.^{14, 15} Methodologies for benefit-risk assessment have also been developed and are well-documented in the literature.¹⁶ However, in many cases, patients or caregivers are not engaged effectively or at all in the benefit-risk assessment process, especially in the early development stages of medical products.¹⁷ It is still very unclear what kinds of interventions and mechanisms for gathering and incorporating patient perspectives are both valid and effective,¹⁸⁻²⁰ and current evaluation practices do not yet require quantification or even formal consideration of the values of patients in the treatment review and approval process.²¹⁻²⁴ This will only change with widespread awareness of the importance of patient engagement and with collaboration among all research stakeholders, including the patients, to develop and adopt more effective engagement tools and processes.

The conference "*Patient Engagement in Benefit-Risk Assessment throughout the Life Cycle of Medical Products*" was targeted to patient partners (patients, family, caregivers, advocates, and patient organizations), industry and academic medical researchers, and regulators, and addressed the important challenge of how and when to best engage patient partners in benefit-risk assessments. The overall goals of the conference were to 1) raise awareness of patient, academic and industry medical product research/development, and regulatory stakeholders of the importance of patient engagement in benefit-risk assessment throughout the life cycle of the medical product; 2) to involve these stakeholders in sharing of existing approaches, identifying implementation challenges and gaps or needs for new information and practices; and 3) to identify recommended next steps for addressing the identified gaps, to inform stakeholder actions including current legislative and regulatory processes. The long term goal is to improve patient engagement practices among all stakeholders in benefit-risk assessment and decision-making.

Landmark bipartisan legislation, such as the *21st Century Cures*, is currently under consideration by the US Congress. Recommendations for elevating the patient voice have specifically cited the need for including the patient perspective, directly or indirectly, in the drug development enterprise and throughout FDA review.^{25, 26} The conference came at an opportune time to help inform this dialogue.

The objectives of the conference were to:

1. Establish consensus among patient, academic and industry medical product researcher, and regulator participants on the appropriate engagement of stakeholders in benefit-risk assessments throughout the medical-product life cycle, including at the point of drug development decision, during drug development and peri-approval, and during the post-approval period;
2. Evaluate and propose solutions to regulatory, methodological, and operational challenges for all aspects of patient engagement in benefit-risk assessment, including:
 - Collecting and interpreting information on patient perspectives and preferences
 - Incorporating patient input in benefit-risk assessments
 - Incorporating engagement of multiple stakeholders in decision-making throughout the medical product life cycle
 - Defining what information to disseminate among stakeholders and how to communicate information effectively
 - Building organizational capacities in biopharmaceutical companies to facilitate patient engagement
3. To identify gaps in current knowledge and practice of stakeholder collaboration in engaging patients and incorporating patient input in benefit-risk assessment
4. To propose improvements in knowledge and practice that will result in better outcomes for patients and to identify next steps toward their achievement

CONFERENCE FORMAT NOTES

The conference took place over two full days and included plenary sessions as well as small group breakouts where participants worked to refine a visual model²⁷⁻³⁰ of patient engagement in benefit-risk assessment through the medical product life cycle. The model denoted challenges experienced and gaps in knowledge. A graphic facilitator captured discussion and small and large group feedback early in the conference (Session 4) to create the basic model. In a small group breakout in Session 9, conference participants used replicas of the basic model to add challenges, gaps, and needs for improvement in specific areas from their perspective. The larger group reconvened to report out and to seek consensus about priorities and next steps using a focused facilitated discussion technique.³¹ The visual model was used as a tool to facilitate stakeholder interaction and capture thinking during the conference, and is being refined to support dissemination of conference learnings and recommendations for actions to address knowledge and practice gaps.

Pre-conference Workshop

Stated Preference Methods and the Science of Patient Engagement

John F. P. Bridges, PhD, Associate Professor in the Department of Health Policy & Management at Johns Hopkins Bloomberg School of Public Health presented an optional half-day, pre-conference workshop to explore stated-preferences research methods and their application to particular research questions. Invigorated by the FDA's patient-focused drug development initiative and patient preference initiative for medical devices, there has been growing interest in the study of the preferences and priorities of patients and other stakeholders throughout the product life cycle. While preferences can be identified both qualitatively and quantitatively, emphasis has been placed on using scientifically valid ways of measuring preferences. Grounded in theories of choice from the disciplines of economics and psychology, stated-preference methods are a class of methods that can be used to identify what patients and stakeholders value most and what tradeoffs they are willing to make. This workshop provided a basic overview of the variety of stated-preferences methods that can be used to measure the preferences of patients and other stakeholders in medicine. Lectures, case studies, and hands-on exercises were used to facilitate a practical understanding of stated-preference methods such as conjoint analysis, discrete-choice experiments, contingent valuation, and best-worst scaling.

The objectives of the pre-conference workshop were to:

- Describe the variety of stated-preferences methods that can be used to measure patient preferences
- Discuss the advantages of stated-preferences methods over alternative approaches to measuring values
- Determine when a particular stated-preference method is appropriate for a particular research question and where to find appropriate guidance to apply the methods successfully

Conference Opening Remarks

Conference participants were welcomed and heard that benefit-risk assessments are used in every stage of the drug development process, starting at the product candidate level, moving through clinical trials, impacting regulatory approval and retention, and continuing through the patient and caregiver decision making processes. The benefit-risk balance changes over time as diseases progress, treatments evolve, and patients themselves change. Incorporating the patient perspective is an important part of the process because it is the patients who ultimately receive the benefits but shoulder the risks associated with use of medical products.

Session 1: Medical Product Development, Benefit-Risk Assessment, and Patient Engagement – Concepts and Context

Session 1 provided foundational concepts, establishing the context of benefit-risk and patient engagement in medical product development, and creating agreement on common terminology to be used throughout the conference. The importance of benefit-risk assessment, the key times it takes place in the product cycle, its meaning in the context of patient need, which stakeholders should be involved, and the importance of patient partner engagement were discussed. The foundations and meaning of many types of patient engagement were an important focus of this session.

Session 1 Key Learnings

- Patient engagement is evolving from a practice of looking at patients as study subjects and assuming that a few patients can represent all to a more collaborative relationship in treatment and research that views patients' complex lives holistically.
- Structured methods and instruments, and the audiences for them, need agreed approaches for choosing and using endpoints that allow clearer decision making.
- Patient-group-led efforts to define the usual course and experience(s) of diseases and demonstrate the importance of endpoints can best inform the decision making in a more robust way that considers a broader range of patient experiences rather than token patient participation.

Session 2: Approaches to Patient Engagement in Benefit-Risk Assessment throughout the Product Life Cycle

Drug development takes place in a highly regulated, timeline-driven environment. Presenters discussed how and when patient engagement occurs as benefits, risks, and balances are assessed, and at what points during the product cycle this takes place. For each key point in the product life cycle, the session addressed what decisions must be made, which stakeholders are most involved, effective and cutting-edge methods for expressing patient preferences and perspectives, approaches for patient engagement, objectives of communication among key stakeholders, uncertainties around information used for assessment, and the impact of uncertainty on decision-making processes, including the need to understand patient tolerance for uncertainty.

Session 2 Key Learnings

- Patient perspective on benefit-risk changes based on a variety of factors, including stage of disease. We need to quantify patient input all along the spectrum, and the evolving science of patient engagement/input will help with this.
- Obtaining patient preference is useful in assessing the importance of benefits and risks associated with a new technology; in understanding the relative importance to patients of attributes of benefit and risk (how do patients think about trade-offs); and understanding how patient preferences vary across patient populations.
- Qualitative and quantitative measures are both useful; qualitative may be especially useful early in the product life cycle.
- CDRH believes that the Patient Preference Initiative (PPI) can be a part of the data/evidence for regulatory decision-making.
- There are several frameworks for benefit-risk assessment; patient preference input can fit into all of them at several stages.
- In the post-marketing period of the life cycle, uncontrolled information is coming in from multiple individuals. Diversity of feedback is desirable, but the challenge is determining what is representative of the patient population in which you are interested.
- A very useful resource is the Medical Device Innovation Consortium (MDIC) work released this year: the catalog of methods and the framework, which indicates when various methods may be useful.
- Patients and physicians think differently, so we must engage patients at the time of medical decision-making.
- For effective engagement to occur at this time, the buy-in of all stakeholders (health care practitioner and patient partners) is needed. Other musts for true shared decision-making: Patients must recognize that there is a choice, patients must be effectively informed, and patients must be supported to construct their preferences.
- Overall patient preference input thoughts: we are pioneering in this area, from collecting perspective data to using it, so it's important to share the information. Implementation will happen over the next couple of years.
- Regarding uncertainty, we need to have the conversation with patients, and for this we need a common language, transparency, and honest communication.

Session 3: Learnings from Patient Engagement in Clinical Trials and Other Types of Health Research

Awareness of the importance of patient engagement in benefit-risk assessment and decision-making is growing, but there is still limited evidence about effective engagement practices. This session focused on what can be learned from patient engagement in other aspects of the clinical trial, such as the qualification of patient-reported outcome measures (PROs), and in other types of health research, such as PCORI-funded research.

Session co-Chairs moderated this frank panel discussion about successes and failures, as well as barriers and antecedents, in related areas, and how to motivate patients to be engaged and to stay engaged. The panel looked at engagement across the continuum of patient experience: community

engagement – finding patients, motivating and sustaining their participation; use of patient reported outcomes (PROs) in clinical research; and in the postmarket setting, incorporating patient perceptions on safety and effectiveness of medicines that are in the marketplace.

The session discussion addressed the following topics:

- Patients must be well-equipped in conversations about benefit risk with an understanding of key terms including “safety,” “effectiveness,” “benefit,” “risk,” and “tradeoff.”
- “Activated patients,” those who are educated in these concepts, share their voices more readily, but it is critical to get input from all patients. How do we do that?
- When patients are marginalized, their motivation to engage is lost. They need to see value in the engagement.
- Patient-centered PRO development is a way to build true patient engagement. It requires finding out what matters to patients and what treatment benefits will be meaningful to them.
- Discussions about PROs must begin early in the medical product life cycle (Phase I). It’s difficult to change direction later in studies.
- European companies seem to be more proactive in the engagement of patients. This may be cultural: Europeans take a holistic approach and consider daily living activities and health related quality of life in their treatment plans. The US approach is more focused on well-defined benefits.

Session 3 Key Learnings

- Respect for patients is demonstrated by meaningful, long lasting relationships.
- It is not only about efficacy and safety; it is about finding treatments that have meaningful benefits with acceptable risks.
- Europeans are currently better at broad definitions of benefits; the US is stuck on symptoms and functioning.

Session 4: Creating a Visual Model for Patient Engagement in Benefit-Risk Assessment

Elaine H. Morrato, DrPH, MPH, CPH, an Associate Professor (with Tenure) in the Department of Health Systems, Policy, & Management at the Colorado School of Public Health’s University of Colorado Anschutz Medical Campus and Meredith Y. Smith, PhD, MPA, the Global Risk Management Officer in Global Patient Safety at Amgen moderated this session in which participants interacted with the graphic facilitator to modify a “straw man” **visual model** of patient engagement in benefit-risk assessment and decision making at key points in the medical product life cycle. The engagement and input gathering processes at each point were described within the context of patient needs and experience by exploring such questions as, “Who are the stakeholders? What decisions must be made? How do factors like patient diversity, methodology limitations, availability of existing therapies, and others affect perspectives on benefit and risk?” The group began thinking about effective approaches,

barriers, and the needs for research and change to better incorporate the patient voice in benefit-risk assessment and decision making.

Session 5: Patient Engagement In Benefit-Risk Assessment: Regulatory, Methodological, and Operational Challenges And Gaps

This session examined real-world implementation of patient engagement in benefit-risk assessment and began a deeper exploration of methodological and operational challenges and how these may be addressed to assure the capture and incorporation of patient perspective. Special focus was placed on the impact and accommodation of crosscutting factors: what types of medical treatment/benefit-risk situations lend themselves to patient preference assessment? When in development should patient preferences be assessed? Whose input should be elicited (e.g. group vs. individual input, experienced patients vs. the community at large)? How can heterogeneity in patient populations and their views be handled? Practical challenges for researchers, including managing diverse views within companies and across disciplines, were also discussed.

Session 5 Key Learnings

- Regarding regulators' receptiveness to reviewing and using patient preference data, we are trying to improve upon the current state in which patient preference input comes from a limited number of patients. This is an inclusionary issue, so let's start with "baby steps" if necessary and get one approval in which patient preference data was part of the review.
- We must recognize the real world heterogeneity of patients and address it in the development of medical products.
- To advance the science of patient input, we must work together collaboratively in an engaged way to determine what patients need and want.

Day 2

Session 6: Patient Engagement in Benefit-Risk Assessment: Regulatory Challenges in Integrating Quantitative and Qualitative Data into Benefit-Risk Assessments

Currently, the medical product submission process in the US does not include a way to provide quantitative data on patient preferences and perspectives regarding benefit and risk, creating an imbalance between safety and efficacy considerations and benefit-risk balance considerations at regulatory decision time. There are recent indications that FDA is receptive to including such data in regulatory decision-making, and in this session, FDA staff from CDER (drugs/biologics) and CDRH (devices and diagnostics) discussed progress on this issue. Quantitative versus qualitative approaches that might be used and special considerations for patient input on post-market safety information

were examined. A panel of FDA speakers interacted with conference participants to conclude this session.

Session 6 Key Learnings

- Benefit-risk decisions involve both evidence and value considerations; value judgements are necessary because outcomes are not of equal significance. The patient-centered measure of value considers the patients' perspectives on net benefit of beneficial and harmful outcomes.
- The perception of a lack of scientifically validated methods to quantify patient preferences is one barrier to adoption of patient-centered value measures.
- Patient reported outcomes, such as the existence and severity of symptoms, daily functioning, and health-related quality of life issues, can answer questions on efficacy, safety, and tolerability to complement standard safety data and be incorporated into labeling.
- Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) has been developed by the NIH as a publically available instrument and determined fit for purpose by the FDA for descriptive labeling.
- FDA is charged with population-level decisions based on law and regulation.
- FDA CDER uses a formalized benefit-risk assessment framework with the goal of better external communication of the reasoning behind CDER's decisions.
- It is possible to take another step beyond the qualitative assessment framework and incorporate quantitative assessments in decision making, similar to cost-benefit analyses that sponsors and payors may conduct. Several analyses yield quantitative data about benefit-risk. All include some subjectivity that and require judgements about levels of importance, presenting a clear role for patient preferences in defining categories, rankings, and weights.
- At FDA, there currently appears to be top level and staff level support for increasing patient engagement in the regulatory process.
- A decision aid tool jointly developed by CDRH and RTI Health Solutions quantifies minimum benefit for a given risk, and maximum risk for a given benefit, based on patient preference input. It was used in a January 2015 approval of a medical device and can be adapted for other medical device products.
- A May 2015 CDRH draft guidance states that submission of patient preference data is optional for interested parties; to assist interested parties and reviewers, the MDIC catalog of methods was developed (see Resources and References). Parties who are interested in collecting and submitting patient information should talk to CDRH staff early in the product development process.
- Product researchers should demonstrate the scientific validity and reproducibility of the patient preference study data used.
- The Regulatory Agency could help by issuing standards/pathways for patient preference studies and use of patient preference data to encourage sponsors to allocate resources to develop appropriate measures. All realize that these actions represent a cultural change at the organizational level and will take time to be fully adopted.

Session 7: Equipping Patient Partners to Provide Input

Patient partners have significant contributions to make in benefit-risk assessment and decision-making, and a clear understanding of the medical product life cycle process helps to enable their proactive involvement. Recognizing the unique and varied knowledge and experience of patient partners, this session discussed model initiatives to provide knowledge resources for patient partners.

Session 7 Key Learnings

- Effectively engaging patients in drug development will allow us to get information about their preferences into labeling. Clinical outcomes of treatments can then be presented in the context of the patients' goals, allowing patients and caregivers to make the choices that are right for them. This model also drives down costs, with a positive impact on the entire health ecosystem.
- The FDA Patient Network is an active educational resource for patients, caregivers, independent patient advocates, and patient advocacy organizations.
- iConquerMS is a patient-centric, data driven research initiative with extensive computational capabilities for integration and analysis of complex data. It can catalyze multi-stakeholder collaborations and is a model that can be implemented for patient-centric research in other diseases.
- Conducting patient engagement on a large scale (15,000-20,000) requires significant resources, so the patient community needs to self-organize and “power” itself over time.
- A variety of touch-points (timing, style) are necessary to serve the needs of a diverse community.

Session 8: Maximizing Patient Impact on Benefit-Risk Assessment--Patient-Initiated Models for Collecting Patient Perspectives

This session featured patient partner initiatives that collect perspectives from their patient communities on benefit and risk considerations. The initiatives presented highlight the impact of characteristics of the patient community and of the treatment life cycle stage on objectives and approaches. The conference participants engaged in a full group discussion of the presented projects and ideas or awareness of other novel approaches.

Session 8 Key Learnings

- Evolving stakeholder influences include patient organized initiatives that aim to inform FDA's benefit-risk assessments and to systematically obtain patient and caregiver perspectives on disease impact and treatment benefits, thus sharing their patients' voices with FDA and the research community.

- Parent Project Muscular Dystrophy (PPMD) has successfully studied how individuals would appreciate benefit and how much risk they might tolerate for given levels of benefit. The organization has published resources, including a draft guidance for industry, that are of value to other patient organizations through their content and by their example as well.
- JDRF, representing the Type 1 Diabetes (T1D) community, is building a culture of patient engagement in the diabetes community to inform regulatory decision making. Their strategies for interacting with the FDA as well as device and pharmaceutical companies and others to share their patients' voices, fund research, and accelerate treatment and prevention breakthroughs are models that can be of help to other patient organizations.
- It's possible to amplify the patient voice, even for a disease as diverse as diabetes.
- Data cannot substitute for real patient stories; this qualitative input is needed together with quantitative data to express the patient voice.
- Absence of a clear pathway for engagement between patient communities and other stakeholders, e.g. regulatory agencies, creates the potential for mutual misunderstanding.

Session 9: Revisiting the “Visual Model” for Patient Engagement in Benefit-Risk Assessment

In this session, the revisions to the visual model of patient engagement in benefit-risk assessment that resulted from the Session 4 group interaction were presented and reviewed by the conference participants. Small groups were then formed to further examine the revised model and to share their perspectives on the process, challenges, barriers, and areas needing improvement. They captured their ideas for further revision on small replicas of the model at their tables. The larger group then reconvened for a facilitated discussion on how the well-functioning system of gathering and considering patient input should work. Input on significant challenges, gaps in knowledge, and areas that must be improved was shared and recorded for incorporation by the graphic facilitator in the weeks following the conference.

The draft “visual model of patient engagement in benefit-risk assessment throughout the life cycle of medical products” will be shared with conference participants prior to its finalization. The “final” version will be a living document that will be posted on the DIA website and distributed widely to all stakeholders as a tool for discussion, learning, and identification of gaps and needs to be addressed. Collection of input for revision will be ongoing as the model evolves along with the improving practices of engaging patients in the benefit-risk assessment process.

Session 10: Summation and Call to Action

A panel of stakeholders from the program committee (**Elaine Morrato, Marilyn Metcalf, Bennett Levitan, Meredith Smith, and Pat Furlong**) shared their thoughts about the key concepts coming from the two-days of discussion and interaction among the conference participants.

Summary of Conference Key Learnings

Context

- Patient engagement is evolving from looking at patients as subjects to a collaborative process in which the patient is viewed holistically, and treatment and research are viewed within the context of patients' complex lives.
- Structured methods and instruments, and the audiences for them, need some agreed upon approaches for choosing and using endpoints that allow clearer decision making.
- Patient-group-led efforts to define the usual course and experience(s) of diseases and to demonstrate the importance of endpoints can best inform the decision making in a more robust way that considers a broader range of patient experiences rather than token patient participation.

Patient Engagement in Health Research and Healthcare Delivery

- Awareness of the importance of patient engagement is increasing, but there is much room for growth and support – “let’s get on with it!”
- There is a need for consistent terminology. For example, the consistent use of terms in the context of benefit-risk decision making --“engagement”, “patient-reported outcomes”, “patient preference”, “shared decision making”, to facilitate understanding and advancement.

Patient-Preference Methods, Challenges, and Interfacing with the FDA

- Established methods of gathering patient preference information and their application for benefit-risk assessments in drug development is an emerging science.
- Variability in application exists. Devices are ahead of drugs. Europe is ahead of the United States.

The Practice of Patient Engagement

- Interactions with FDA should be multi-directional to foster communication.
- Many ways to facilitate engagement – surveys, policy forums with FDA, and testimony (written and oral)
- Patient/caregiver preferences studies enable communities to engage the broadest (greatest?) number of individuals across the spectrum of the disease of interest.

Conference Agreements

Future State

- There is value in visualizing a unifying framework ('narrative') to advocate for systematic incorporation of patient voice in benefit-risk assessment throughout a medical product's life cycle.
- As stakeholders in this process, we must ask ourselves, where do we go next? What are the commitments we want to make for ourselves?

Closing Keynote Speaker

Robert M. Califf, FDA's Deputy Commissioner of the Office of Medical Products and Tobacco, discussed his experience seeing how patients are affected by the choices made at FDA, and emphasized how important it is to listen to patient needs. Translating complex information into understandable concepts is also important. Dr. Califf's early clinical trial work involved asking patients for clarity on the tradeoffs that they were willing to make, which instilled his strong sense of belief in the value of patient preference data. The math of decision science can be improved by accessing the right populations. Such data are important, because FDA is entrusted with making regulatory decisions in the best interest of public health. Patient diversity must be taken into consideration.

Closing Remarks

Barbara Lopez Kunz, DIA's Global Chief Executive thanked the audience for attending and participating fully in this important work. Bringing the consumer into the conversation has been done in every other industry, and the beautiful and reasonably accurate picture we are creating will continue to drive its momentum. Ms. Kunz asked the group to provide ongoing feedback and to share the visual model and the final meeting report with the stakeholders who can use it. She thanked PCORI for providing funding for the conference and its output and for driving the patient-centeredness that we are working toward.

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References and Resources (Cited references; resources shared by speakers and attendees.)

References:

1. FDA. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan, Fiscal Years 2013-2017. FDA, 2013. FDA.gov. Web.
<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>
2. Franson, Timothy, and Holly Peay. *Benefit-Risk Assessments in Rare Disorders. The Case for Therapeutic Development in Duchenne Muscular Dystrophy as the Prototype for New Approaches*. Parent Project Muscular Dystrophy, 2014. PPMD. Web.
3. Institute of Medicine of the National Academies. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Washington, DC: National Academies Press, 2007.
4. Garattini, S. "Evaluation of Benefit-risk." *Pharmacoeconomics* 28.11 (2010): 981-986.
5. Caveney, E, and J R. Turner. "Regulatory Landscapes for Future Antidiabetic Drug Development (Part I): FDA Guidance on Assessment of Cardiovascular Risks." *J Clin Stud* 2.1 (2010): 34-36.
6. Califf, R M. How Should We Determine Benefit-Risk and How Much Risk is Acceptable? DIA April 2011 Conference "Cardiovascular Safety in Drug Development: State of the Art Assessments." (Presentation)
7. Morrato, E H., and D B. Allison. "FDA Approval of Obesity Drugs-- a Difference in Risk-Benefit Perceptions." *JAMA* 308.11 (2012): 1097
8. Ferguson, John, and Marilyn Metcalf. "Key Questions, Issues, and Challenges in Benefit-Risk Assessment in Full Clinical Development." *Benefit-Risk Assessment in Pharmaceutical Research and Development*. Boca Raton, FL: CRC Press, 2014. 21-27.
9. Levitan, Bennett, Lawrence D. Phillips, and Stuart Walker. "Structured Approaches to Benefit-Risk Assessment: A Case Study and the Patient Perspective." *Therapeutic Innovation & Regulatory Science* 48.5 (2014): 564-573.
10. EMA. *The Patient's Voice in the Evaluation of Medicines. How Patients Can Contribute to Assessment of Benefit and Risk*. London, UK: European Medicines Agency, 2013.
11. Peay, Holly L., Ilene Hollin, Ryan Fischer, and John F. P. Bridges. "A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy." *Clinical Therapeutics* 36.5 (2014): 624-637.
12. Franson, Tim. "Leadership in Regulatory Transformation: Policy, Promotion and Push for Patients." *Webinar*. Parent Project Muscular Dystrophy, 13 June 2013.
<<https://www.youtube.com/watch?v=uCw9r3hZ2v8>>.

13. Karlin, Sarah. "Diabetes Endpoints, CV Requirements Get Special Handling at FDA-Patient Meeting." *The Pink Sheet*. N.p., 17 Nov. 2014. Web.
<<https://www.pharmamedtechbi.com/publications/the-pink-sheet/76/46/diabetes-endpoints-cv-requirements-get-special-handling-at-fdapatient-meeting?elsca1=pink&elsca2=newsltr>>.
14. Noel, Rebecca, Richard Hermann, Bennett Levitan, Douglas J. Watson, and Kristin Van Goor. "Application of the Benefit-Risk Action Team (BRAT) Framework in Pharmaceutical R&D: Results from a Pilot Program." *Drug Information Journal* 46.6 (2012): 736-743.
15. Walker, Stuart, Neil McAuslane, Lawrence Liberti, James Leong, and Sam Salek. "A Universal Framework for the Benefit-Risk Assessment of Medicines: Is This the Way Forward?" *Therapeutic Innovation & Regulatory Science* (2014): 1-9. Web.
16. Hauber, A B., A O. Fairchild, and F R. Johnson. "Quantifying Benefit-risk Preferences for Medical Interventions: an Overview of a Growing Empirical Literature." *Appl Health Econ Health Policy* 11.4 (2013): 319-329.
17. CTTI/DIA Joint Survey: CTTI/DIA Joint Survey: Patient and Researcher Perspectives on the Current State of Engagement. 2014. (Unpublished data)
18. Yuan, Z, B Levitan, and J A. Berlin. "Benefit-risk Assessment: to Quantify or Not to Quantify, That Is the Question." *Pharmacoepidemiol Drug Saf.* 20.6 (2011): 653-656.
19. Hammad, Tarek A., George A. Neyarapally, Solomon Iyasu, Judy A. Staffa, and Gerald Dal Pan. "The Future of Population-Based Postmarket Drug Risk Assessment: a Regulator's Perspective." *Clinical Pharmacology & Therapeutics* 94.3 (2013): 349-358.
20. Johnson, F R., A B. Hauber, and J Zhang. "Quantifying Patient Preferences to Inform Benefit-Risk Evaluations." *Benefit-Risk Assessment in Pharmaceutical Research and Development*. Boca Raton, FL: CRC Press, 2013.
21. *Enhancing Benefit-Risk Assessment in Regulatory Decision-Making*. FDA, n.d. Web.
<<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>>.
22. FDA. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan, Fiscal Years 2013-2017. FDA, 2013. FDA.gov. Web.
<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>
23. "Guidance for Industry and Food and Drug Administration Staff. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications." FDA, Mar. 2012. Web.
<<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm296379.pdf>>.
24. Franson, Timothy R., and Holly Peay. Benefit-Risk Assessments in Rare Disorders. The Case for Therapeutic Development in Duchenne Muscular Dystrophy as the Prototype for New Approaches. Parent. Parent Project Muscular Dystrophy. 2014. Page 5.

25. "Energy and Commerce Cures." *Energy & Commerce Committee*. N.p., n.d. Web. <http://energycommerce.house.gov/cures>.
26. "Food and Drug Administration Activities for Patient Participation in Medical Product Discussions; Establishment of a Public Docket." *Federal Register*. N.p., 4 Nov. 2014. Web. <https://www.federalregister.gov/articles/2014/11/04/2014-26145/food-and-drug-administration-activities-for-patient-participation-in-medical-product-discussions>.
27. Anderson, Meghan K. "What Makes a Presentation Great? Deconstructing an Awe-Inspiring TED Talk." Hubspot, 30 Oct. 2013. Web. <<http://blog.hubspot.com/marketing/great-ted-talk-deconstructed-ht>>.
28. "Formats for Group Presentations." University Of Mary Washington, n.d. Web. <<http://academics.umw.edu/speaking/resources/handouts/formats-for-group-presentations/>>.
29. Roam, Dan. *Blah, Blah, Blah: What to Do When Words Don't Work*. New York, NY: The Penguin Group, 2011.
30. Sibbett, David. *Visual Meetings: How Graphics, Sticky Notes, and Idea Mapping Can Transform Group Productivity*. Hoboken, NJ: John Wiley & Sons, 2010.
31. Stanfield, R. Brian. *The Art of Focused Conversation. 100 Ways to Access Group Wisdom in the Work Place*. Gabriola Island, BC, Canada: New Society Publishers, 2000.

Resources

Pre-Conference Workshop John Bridges

[Patient-Focused Drug Development Initiative](#)

[Patient Preference Initiative for Medical Devices](#)

Session 1 Kimberly McCleary

She is Director of Strategic Initiatives at [Faster Cures](#).

Shared video: "Advancing the Science of Patient Input"
(https://www.youtube.com/watch?v=Zsn_9EplBz8).

Session 1 Andrea Ferris

She is President and Chairman of the [LUNgevity Foundation](#).

Session 1 Richard Forshee

Enhancing Benefit-Risk Assessment in Regulatory Decision-Making
(<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>)

contains several documents describing the Benefit-Risk Assessment Framework and the Patient-Focused Drug Development initiatives.

Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs) (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM451440.pdf>) is draft guidance from CDRH and CBER.

Session 2 Bray Patrick-Lake

She is the Director of Stakeholder Engagement at the [Clinical Trials Transformation Initiative \(CTTI\)](#).

CTTI published [Best Practices for Effective Engagement with Patient Groups around Clinical Trials](#) in October 2015, which proposes five best practices to optimize partnerships between sponsors and advanced patient groups.

Medical Device Innovation Consortium (MDIC) work released this year: the [catalog of methods](#) and the [framework](#), which indicates when various methods may be useful.

Session 2 Kathryn O'Callaghan

Workshop to launch the September 2013 Patient Preference Initiative <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm361864.htm>

FDA's 2013 Patient Preference Initiative <https://www.federalregister.gov/articles/2013/07/29/2013-18080/the-patient-preference-initiative-incorporating-patient-preference-information-into-the-medical>

FDA's 2015 Draft Guidance document on incorporating patient preference data in the regulatory submission process <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf>

Session 2 Juhaeri Juhaeri

CIRS-BRAT Framework <http://www.cirs-brat.org/>

PrOACT-URL Framework <http://protectbenefitrisk.eu/PrOACT-URL.html>

Session 2 Richard Hermann

BIO White Paper: A Lifecycle Approach to FDA's Structured Benefit-Risk Assessment Framework 8/12/2015 <https://www.bio.org/fdawhitepaper>

Innovative Medicines Initiative (IMI) <http://www.imi.europa.eu/>

Session 2 Liana Fraenkel

The Paternalism Preference — Choosing Unshared Decision Making *New England Journal of Medicine* 2015 <http://www.nejm.org/doi/full/10.1056/NEJMp1508418>

Sample Decision Support Tools

- <https://decisionaid.ohri.ca/decaids.html>
- <http://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/>
- <http://effectivehealthcare.ahrq.gov/index.cfm/tools-and-resources/patient-decision-aids/>
- <https://www.dartmouthhitchcock.org/medical-information/emmpatient-education.html>

Session 3 Darius Tandon

Clinical and Translational Science Award (CTSA) consortium, an initiative led by the National Institutes of Health (NIH) <https://ctsacentral.org/>

Session 5 Bennett Levitan

Medical Device Innovation Consortium Patient-centered Benefit-risk Framework
http://mdic.org/wpcontent/uploads/2015/05/MDIC_PCBR_Framework

Session 5 Meredith Smith

EUPATI, the European Patients' Academy on Therapeutic Innovation
<http://www.patientsacademy.eu/index.php/en/>

Session 6 Theresa Mullin

Information for patients who are interested in conducting their own PFDD meetings:
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm>.

Session 6 Lisa LaVange

Yueqin Zhao, Jyoti Zalkikar, Ram C. Tiwari & Lisa M. LaVange. A Bayesian approach for benefit-risk assessment, *Statistics in Biopharmaceutical Research*, 2014; 6:4, 326-337.

Scott Evans, Daniel Rubin, Dean Follmann, et al. Desirability of outcome ranking (DOOR) and response adjusted for days of antibiotic risk (RADAR). *Clinical Infectious Disease*, pub online June 25, 2015.

Session 6 Telba Irony

FDA CDRH 2012 guidance on factors to consider for benefit-risk assessment in devices.
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>

M Ho, JM Gonzalez, H Lerner, C Neuland, J Whang, M. McMurry Heath, A. Hauber, T. Irony. Incorporating patient-preference evidence into regulatory decision making. *Surgical Endoscopy* 2015.

FDA Draft Guidance on Patient Preference Information issued on May 18, 2015
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf>

Session 7 Marc Boutin

NHC Patient Stratification Tool
<http://www.nationalhealthcouncil.org/sites/default/files/NHCPatientInformationToolandInstructions.pdf>

Dialogue/Advancing Meaningful Patient Engagement in Drug Research, Development, & Review of Drugs <http://www.nationalhealthcouncil.org/meaningful-patient-engagement>

Session 7 Sara Loud

iConquerMS™ Patient Website <https://www.iconquerms.org/>

Session 8 Holly Peay

Parent Project Muscular Dystrophy web site :
http://www.parentprojectmd.org/site/PageServer?pagename=nws_index

Parent Project Duchenne Muscular Dystrophy (DMD): Peay HL, et al. A community engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne Muscular Dystrophy. *Clin Therapeutics* 2014; 36(5):624-637.

“Putting Patients First. Recommendations to speed responsible access to new therapies for Duchenne muscular dystrophy and other rare, serious and life-threatening neurologic disorders”
http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_patients

“Benefit Risk Assessments in Rare Disorders.”
http://www.parentprojectmd.org/site/DocServer/br_paper_v11_2_.pdf;jsessionid=2C381495CB3753608053FD8DD624B686.app247d?docID=14503

Guidance for Industry: Duchenne Muscular Dystrophy: Developing Drugs for Treatment over the Spectrum of Disease.

http://www.parentprojectmd.org/site/DocServer/Guidance_Document_Submission_-_Duchenne_Muscular_Dystrop.pdf?docID=15283

Session 8 Cynthia Rice

JDRF web site: <http://jdrf.org/>

Session 8 Kelly Close

Close Concerns web site: www.closeconcerns.com

DiaTribe web site: www.diaTribe.org

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