

**Medical Device Innovation Consortium (MDIC) Patient Centered
Benefit-Risk Project Report:**

**A Framework for Incorporating Information on Patient Preferences
Regarding Benefit and Risk into Regulatory Assessments of New
Medical Technology**

Medical Device Innovation Consortium

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A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of Medical Technology: Executive Summary

The Medical Device Innovation Consortium (MDIC) is the first-ever public-private partnership created with the sole objective of advancing the regulatory science around the development and assessment of medical devices. Members of MDIC share a vision of providing U.S. citizens with timely access to high-quality, safe, and effective medical devices without unnecessary delay.

Background on the MDIC Patient Centered Benefit-Risk Project

The MDIC Patient Centered Benefit-Risk (PCBR) Project grew out of Food and Drug Administration (FDA) Centers for Devices and Radiological Health (CDRH) emphasis on benefit-risk assessment as a central component of the medical device approval process. CDRH's 2012 "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" discusses the importance of bringing the patient's perspective into CDRH benefit-risk assessments, and recommends that sponsors interact with FDA staff regarding the development of patient centered benefit-risk information. However, the document does not discuss in what situations or how sponsors should collect and present that information.

Given that there are no widely accepted approaches for assessing patient preferences that have been used in the regulatory process to date, MDIC saw an opportunity to help industry and the FDA think about when and how patient preference information might be incorporated into regulatory decision making. To oversee this project, the MDIC set up a PCBR Steering Committee consisting of interested participants among MDIC's member organizations supplemented with experts in decision science and preference assessment methods from academia and other organizations. The members of the PCBR Steering Committee are listed in Exhibit 1-2 of the report. The Steering Committee divided the PCBR Project down into two complementary efforts: 1) the development of a "framework" for incorporating patient preference information into benefit-risk assessment, which became this "Framework Report;" and 2) the development of a "catalog of methods" that can be used to collect and analyze patient preference information, which is the "Catalog of Methods" included as Appendix A. The MDIC PCBR Steering Committee contracted the development of the Catalog of Methods to RTI Health Solutions with the assistance of a "Catalog Working Group" that included experts in a variety of methods related to assessing patient preferences, as listed in Exhibit 1-4. Financial support from a FDA BAA contract (HHSF223201400011C) made this Framework Report possible, and was primarily used to fund the work of RTI and outside experts on the Catalog.

Purpose of the PCBR Framework Report

This Framework Report is intended to improve the understanding of industry, FDA staff, and others of how the patient's perspective might be incorporated into the regulatory approval process. The Framework Report provides background on the concepts of benefit-risk and patient preference, discusses the potential value of including benefit-risk in a regulatory submission, discusses when in the product lifecycle such information might be collected, outlines factors to consider when selecting a patient preference method, and discusses considerations regarding the use of patient preference information in the

regulatory process as well as potential uses in the reimbursement, marketing, and shared medical decision making. Appendix A of this report is a “Catalog of Methods of Assessing Patient Preferences,” which is the first compendium of the range of research methods available to collect and analyze patient preference information. The report concludes with a discussion of areas in which additional work would be useful to improve the ability to collect and use patient preference information in the regulatory approval process.

The Framework Report should be considered an initial thought piece that outlines a range of considerations for how industry and FDA might incorporate patient preference information into the regulatory approval process. The Report is not intended to be a prescriptive, “how-to” guide, nor does it purport to be a definitive document about incorporating patient preference information into the regulatory process. Rather, it is intended to be an initial version of what MDIC hopes will be a working document about this emerging field that is updated over time as industry, FDA, and others gain more experience with collecting and using patient preference information in the regulatory process.

Overview of this Framework Report

Section I: Introduction to the MDIC Patient Centered Benefit-Risk Project Framework Report provides background information on MDIC; the origins of the PCBR Project and the vision and process for developing this Framework Report; and the limitations of the report.

Section II: Patient Centered Benefit-Risk Assessment: Definitions and Background Concepts defines several important terms used throughout the report, including “benefit,” “harm,” “risk”, “preferences,” and product “attributes.” The section also introduces several important concepts regarding patient preferences used through the rest of the report, including “maximum acceptable risk,” “minimum acceptable benefit,” “uncertainty attitude,” and the important concept of “preference sensitive decisions,” which are illustrated in several hypothetical examples.

Section III: Evaluating the Potential Value of Patient Preference Information in Regulatory Benefit-Risk Assessments of Medical Technology discusses how to evaluate whether patient preference information would be valuable in the regulatory consideration of a specific technology. Rather than take an algorithmic or “cookbook” approach, this section discusses three categories of factors to consider in assessing whether patient preference information would be useful in a particular regulatory situation: 1) factors related to the perspective of patients as stakeholders, 2) factors related to the benefit-risk tradeoffs inherent in the use of a particular technology, and 3) factors related to regulatory novelty.

Section IV: Potential Use and Value of Patient Preference Information in the Product Development Lifecycle begins with a discussion of the three major uses of patient preference information: 1) framing benefit risk issues, 2) identifying groups of patients that would prefer the use of a particular technology, and 3) providing the information needed to build a quantitative benefit-risk model. The section then introduces the concept of the product development lifecycle, and goes on to discuss how patient

preference information might be useful at each stage of this lifecycle and when in the product lifecycle it might be helpful to collect such information.

Section V: Factors to Consider in Undertaking a Patient Preference Study summarizes the work underlying Appendix A, the Catalog of Methods, including discussing the differences between qualitative and quantitative methods and listing the quantitative methods included in the Catalog. The section then discusses factors that can help someone thinking about undertaking a patient preference study select among the methods available. These factors include: factors related to defining the research question; factors related to the fit of particular methods to the research question; and factors related to the resources available to undertake a patient preference study. The final portion of the section discusses how to use these factors to help select among the methods available.

Section VI: Considerations in Using Patient Preference Information in the Regulatory Process discusses a range of topics, including what roles such information can play in regulatory approval, product labeling, and post-market studies; patient preference information being optional at the election of sponsors; when in the product development cycle to determine if patient preference information should be collected, and how patient preference studies might help identify and understand benefit-risk issues in emerging areas of technology.

Section VII: Potential Value of Patient Preference Information Beyond the Regulatory Process discusses at a high level the potential use of patient preference information in areas outside the regulatory process, namely reimbursement, marketing, and shared medical decision making.

Section VIII: Future Work in the Collection and Use of Patient Preference Information for Regulatory Purposes concludes the report with a discussion of areas for future work that would improve the ability of FDA, industry, and others to collect and use patient preference information in the regulatory process and in the total product lifecycle. The section begins with a summary of the “gap analysis” performed as part of the development of the Catalog of Methods, and then highlights several additional areas for future work identified during the course of the MDIC PCBR Project.

Appendix A: Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies summarizes the methods available for quantitative assessment of patient preferences regarding the benefit, risks, and other attributes of medical technologies. The Catalog includes a discussion of the key considerations in evaluating these methods, and then reviews each method identified. A concluding section identified areas for future research to improve the ability to assess patient preference information for regulatory purposes.

Appendix B: Glossary of Terms offers a handy summary of terms related to patient preference assessment used throughout the Framework Report and Catalog of Methods.

Key Points Emphasized in the Framework Report

Important take-away points from the PCBR Benefit-Risk Project Framework Report include:

- **Collecting and using patient preference information can help sponsors and the FDA ensure that the benefit-risk assessment process is patient-centric.** Patient preference information can help identify those benefits and harms most important to patients, frame the benefit-risk issues and tradeoffs from the patient perspective, identify whether there are subgroups of patients that would choose to use the technology over other alternatives, and support quantitative benefit-risk modeling that may assist in challenging benefit-risk assessments.
- **Patient preference information does not replace or reduce existing information requirements or change the process for FDA approval of medical technology.** Patient preference information can be a supplement to clinical and safety data and provide additional information for consideration by the FDA, but does not change the existing regulatory requirements.
- **Patient preference information is not a requirement for FDA PMA, 510k or *de novo* approval of medical devices, and its inclusion in a regulatory submission is optional at the election of the sponsor.** The collection and submission of patient preference information can be viewed as a means of enhancing regulatory submissions to help assure that benefit-risk determinations are patient-centric. Such information can be collected and included in an approval application at the option of the sponsor.
- **The timing for collection of patient preference information is at the discretion of the sponsor, although sponsors may benefit from early conversations with FDA regarding plans for collecting and submitting such information.** Patient preference information can be assessed when the sponsor believes there is a sufficient understanding of the particular benefits and risks expected with the treatment to identify if patient preference information might be valuable in the development or regulatory process. It would be prudent for sponsors to discuss plans for collecting and submitting patient preference information with FDA staff early in the regulatory process.

It is also important to note what this Framework Report is not: it does not represent the opinion or policy of FDA and does not include any specific recommendations to the FDA regarding how to collect or use patient preference information in regulatory approval decisions. It is also not a substitute for FDA guidance documents or for direct discussions with CDRH staff regarding the incorporation of patient preference information into the approval process for a particular technology.*

The MDIC PCBR Steering Committee hopes that this Framework Report and the Catalog of Methods will be helpful to those considering undertaking patient preferences studies, and thereby encourage the continued growth and maturation of this field. MDIC and the PCBR Steering Committee welcome constructive feedback on this report and ideas for further work in the field of patient preference assessment.

*As of the date of publication of this report but independent of this MDIC effort, CDRH was developing a draft guidance regarding the collection and use of patient preference information that should be released in 2015.

Section I: Introduction to the MDIC Patient Centered Benefit-Risk Project Framework Report

A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology

The MDIC Patient Centered Benefit-Risk (PCBR) Framework Report offers a framework for incorporating information on patient preferences regarding benefits and risks into Food and Drug Administration (FDA) Centers for Devices and Radiological Health (CDRH) assessments of medical technology. This introductory section of the report provides background on the Medical Device Innovation Consortium (MDIC), the origins of the Patient Centered Benefit-Risk (PCBR) Project, the process by which MDIC undertook the PCBR Project, and the purpose and organization of this MDIC PCBR “Framework” Report.

Background on the Medical Device Innovation Consortium (MDIC)

The Medical Device Innovation Consortium is the first-ever public-private partnership created with the sole objective of advancing the regulatory science around the development and approval of medical devices. Members of MDIC share a vision of providing U.S. citizens with timely access to high-quality, safe, and effective medical devices without unnecessary delay.

MDIC was formed in 2012, building on discussions between the FDA and LifeScience Alley in Minnesota about how the FDA and industry could work together to improve the regulation of medical devices. MDIC membership and participation is open to representatives of organizations that are substantially involved in medical or medical device research, development, treatment, or education; or in the promotion of public health; or that have expertise or interest in regulatory science. MDIC members include public entities such as FDA, Centers for Medicare and Medicaid Services (CMS), National Institutes of Health (NIH), and Patient-Centered Outcomes Research Institute (PCORI); large and small medical device and diagnostics companies; patient advocacy groups and other interested non-profits; and academic experts in the scientific fields of statistics, engineering, health economics, risk evaluation, and communication.

MDIC has been designed to pursue several strategies that support its mission:

- Create a forum for collaboration and dialogue, working within a flexible governance structure to encourage broad participation from the medical device industry stakeholders, including non-profits, industry, and government.
- Make strategic investments in regulatory science, utilizing working groups to identify and prioritize key issues, and to request, evaluate, and implement project proposals that support MDIC’s mission.
- Provide tools from these projects that drive cost effective innovation, emphasizing education and the development of new methods and approaches with well-documented data and details to enable implementation.

The activities and output from MDIC will:

- ensure that innovative technology is readily available to U.S. patients,
- provide industry and government with methods and tools that may be used to expedite medical device development and regulatory process,
- reduce the risk and expense of clinical research, and
- reduce the time and cost of medical device development.

Member organizations help set MDIC priorities and provide experts to work on each of MDIC's projects. Through its projects, MDIC seeks to improve the understanding of important aspects of medical device regulation and to help develop methods, tools, and resources used in managing the total product life cycle of a medical device, thereby improving patient access to cutting-edge medical technology. MDIC has undertaken three initial projects to improve regulatory science:

1. Clinical Trial Innovation and Reform (CTIR): Restoring U.S. leadership in clinical excellence and med tech innovation by innovating in clinical trial design.
2. Computer Simulation and Modeling (CM&S): Removing risk and increasing the certainty in using CM&S in regulatory submissions.
3. Patient Centered Benefit-Risk (PCBR): Developing a framework and identifying methods for incorporating patient perspectives into benefit-risk determinations.

Additional projects are added as recommended by MDIC members and approved by the MDIC Board.

The Origins of the MDIC Patient Centered Benefit-Risk Project

The MDIC Patient Centered Benefit-Risk (PCBR) Project grew out of CDRH's shift to benefit-risk assessment as a central component of pre-market approval (PMA) and *de novo* approvals. The importance of benefit-risk assessment in such approvals is discussed in the 2012 CDRH guidance document, "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."¹

In outlining the key factors that CDRH considers in benefit-risk assessment of PMA applications and *de novo* requests, this CDRH Benefit-Risk Guidance emphasizes the potential value of the patient perspective in regulatory approval decisions and the importance of a patient-centric approach to benefit-risk determinations. Indeed, this guidance goes so far as to state that a product could be approved if a minority of the target patient population would accept the risks of the technology given the perceived benefits. In Section 4.3 of the "Benefit-Risk Guidance," shown more completely in Exhibit 1-1, the FDA acknowledges that:

“When making a benefit-risk determination at the time of approval or *de novo* classification, FDA recognizes that patient tolerance for risk and a patient-centric assessment of risk may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life. When assessing such data [on patient risk tolerance and other patient-centered metrics] in a PMA application or *de novo* petition, FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse. Therefore, FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others.”^{1(p12)}

The document goes on to say that:

“Moreover, it may be appropriate to approve a device where only a minority of the intended patient population would accept the risks as weighed against the benefits if the information necessary for patients and health care practitioners to make well-informed decisions is available and can be presented in a manner that can be understood by the practitioners and patients.”^{1(p12)}

This discussion of the potential value of information on patient views of benefits and risks – which this report will refer to as “patient preference information”^{*} -- is a significant and innovative step by CDRH towards a patient-centered approach towards benefit and risk determinations in FDA approval decisions. The CDRH Benefit-Risk Guidance identifies “the severity of a disease or condition,” “disease chronicity,” and “the availability of alternative treatment/diagnostic options” as important factors that can influence patient risk tolerance. However, it provides limited detail on when and how to collect information on patient views of benefits and risks, or how to incorporate such patient preference information into the CDRH benefit-risk assessments. More clarity on the details of assessing patient views of risks and benefits is needed to increase the utility of this guidance for all stakeholders, including FDA reviewers, members of the medical device industry, and patient groups. The CDRH Benefit-Risk Guidance does recommend that sponsors interact with FDA staff regarding developing such patient preference information, but the document does not discuss in any detail in what situations such information would be helpful, how to determine the level of evidence required for a regulatory decision, what are validated methods and tools

^{*} “Patient preferences” and “patient preference information” can be used in a narrow sense to refer to just the expression of preference about a choice that patients face regarding which treatment option to use, e.g., the preference of a patient to undergo a procedure using device A versus therapy with drug B. However, these terms can also be used more broadly to describe how patients consider the important benefits and risks of a technology, how they think about the tradeoffs of these benefits versus risks, and how they then make a decision to use one treatment over another given these views of benefits and risks. Unless otherwise noted in this report, the terms “patient preferences” and “patient preference information” are used in this broader sense to describe patient views of benefits and risks, and how patients think about benefit-risk tradeoffs.

for collecting such patient preference information, or how sponsors should collect and present that information to CDRH.

The lack of specificity in the CDRH Benefit-Risk Guidance is understandable as the science around assessing patient preferences regarding benefits and risks of a technology is relatively nascent. In order to properly take patient preferences into account, investigators must have reliable and accurate methods, tools, and approaches to capture and analyze the information. There are no widely accepted approaches for assessing patient preferences that have been used in the regulatory process to date, nor are there many experienced people in the medical technology field with knowledge about the collection and use of such patient preference information. From a regulatory science perspective, there is a clear need to improve the understanding of how to collect and present such information about patient preferences and how to incorporate patient preferences into CDRH benefit-risk assessment.

The MDIC Patient Centered Benefit-Risk Project: Vision and Process

The vision of the MDIC PCBR project is "to establish a credible framework for assessing patient preferences regarding the probable benefits and risks of a proposed medical device and for incorporating patient preference information into pre-market and post-market regulatory submissions and decisions." Important issues to be addressed by the PCBR Project are:

- Why is a patient's perspective valuable in benefit-risk determination?
- How do we identify, define, and measure "patient preferences"?
- In what situations should information on patient preferences be captured and incorporated into regulatory decisions?
- When in the product development lifecycle can patient preference information be captured?
- What methods are available to assess a patient's perspectives on benefit and risk and patient preferences regarding the benefits and harms of a particular technology relative to its alternatives (if any)?
- What are the considerations in using patient preference information in regulatory decision making?
- How do we incorporate a patient's perspective regarding benefits and risks to enable regulators to make decisions most congruent with patient preferences?
- What are other potential uses of patient preference information collected for regulatory purposes?
- What are the gaps in methods available to assess patient preferences and where might additional research be focused?

As an initial step in the project, the MDIC set up a PCBR Steering Committee to oversee the project. Members of the PCBR Steering Committee were recruited from interested participants among MDIC's member organizations. As the PCBR Steering Committee formed, the committee leadership attempted to

ensure a wide representation from CDRH, large, mid-sized, and small device companies, regulatory agencies, and patient groups. In addition, the committee sought to bring in experts in decision science and preference assessment methods from academia and other organizations. The members of the PCBR Steering Committee are listed in Exhibit 1-2.

The PCBR Steering Committee developed a vision statement for the PCBR Project, which was approved by the MDIC Board of Directors. The Steering Committee then broke the PCBR Project down into two complementary efforts: 1) the development of a “framework” for incorporating patient preference information into benefit-risk assessment, and 2) the development of a “catalog” of methods that can be used to collect and analyze patient preference information.

The “Framework” was developed by the Framework Working Group, a subgroup of the PCBR Steering Committee members supplemented by involvement of additional FDA reviewers, who represent those who would potentially be using the framework in the future, and other invited experts with experience in patient preference work or medical device assessment. The members of the Framework Working Group are listed in Exhibit 1-3. The Framework Working Group focused on developing a guide to help CDRH staff and applicants think about what patient preference information is, when it might be useful in the regulatory process, how such information might be collected, other potential uses of patient preference information, and what additional research might be valuable to improve the use of patient preference information in the regulatory process. This “Framework Report” represents the output of that Framework Working Group effort.

In parallel, a Catalog Working Group was formed from PCBR Steering Committee members and outside experts in preference assessment methodologies to develop a “Catalog” of the methods that are available to assess patient preferences. Given the technical nature of the development of this Catalog of Methods, the MDIC PCBR Steering Committee sought external expertise for the development of the patient preference methods catalog. RTI Health Solutions (RTI), a health research organization with experience in health preference studies, was contracted to develop the Catalog and to identify areas where future research might be useful in improving the methods available for patient preference assessment. RTI then contracted with academic experts with specific expertise in the methods to be examined in the catalog, who also joined the Catalog Working Group. The members of the Catalog Working Group are show in Exhibit 1-4. RTI also facilitated the identification of unanswered questions related to the use of patient-preference methods and developed suggestions for future research in patient preference assessment methods that are included in the Catalog and in the last section of this Framework Report. Financial support from a FDA BAA contract (HHSF223201400011C) made the Catalog and this Framework Report possible, and was primarily used to fund the work of RTI and outside experts on the Catalog.

The PCBR Framework Report

This Framework Report is intended to improve the understanding of CDRH staff and of applicants on how to identify the potential value of patient preference information in CDRH benefit-risk determinations, how to collect such preference information from patients, and how that information can be used in regulatory decision making. This Framework Report, including the Catalog of Methods as Appendix A to this report, is intended to further the thinking about how patient preference information might be used, not only in the regulatory process, but also more generally in the medical device product development lifecycle. Given the CDRH Benefit-Risk Guidance, the primary focus of this framework is on PMA applications and *de novo* requests, but the concepts explored here will likely apply to 510k submissions as well.*

In order to make the report as easy-to-use as possible, this Framework Report is organized as follows:

- Executive Summary
- Section I: Introduction to the MDIC Patient Centered Benefit-Risk Project Framework Report
- Section II: Patient Centered Benefit-Risk Assessment: Definitions and Background Concepts
- Section III: Evaluating the Potential Value of Patient Preference Information in Regulatory Benefit-Risk Assessments of Medical Technology
- Section IV: Potential Use and Value of Patient Preference Information in the Product Development Lifecycle
- Section V: Factors to Consider in Undertaking a Patient Preference Study
- Section VI: Considerations in Using Patient Preference Information in the Regulatory Process
- Section VII: Potential Value of Patient Preference Information Beyond the Regulatory Process
- Section VIII: Future Work in the Collection and Use of Patient Preference Information for Regulatory Purposes
- References
- Appendix A: Catalog of Methods of Assessing Patient Preferences
- Appendix B: Glossary of Terms

* While the CDRH Benefit-Risk Guidance, published in 2012 and discussed in this section, focuses on PMA approvals and *de novo* classifications, CDRH has also released a draft guidance regarding the application of benefit-risk concepts to 510(k) applications. See: "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics, Draft Guidance for Industry and Food and Drug Administration Staff," July 15, 2014. The major difference between benefit-risk assessment for 510(k) applications versus those for PMA applications and *de novo* requests is the need to compare benefits and risks to those of the predicate device. As noted in that draft guidance, "This draft guidance addresses benefit-risk factors similar to those in the *PMA and De Novo* Guidance, but, unlike the benefit-risk determinations during the premarket review process for PMA applications and *de novo* classification requests which do not require a comparison to any other device, in evaluating the benefits and risks during a 510(k) premarket review, FDA considers the benefits and risks of the new device as compared to the predicate device."

Because patient preference assessment for regulatory purposes is a relatively new area, the MDIC PCBR Steering Committee hopes that this report will function as a valuable, early thought piece about how to incorporate patient preferences into CDRH regulatory approval decisions. This report does not purport to be the definitive document on the subject of patient centered benefit-risk analysis, but rather a document that helps further the early thinking in a nascent field. Moreover, this report is just the first version of what is envisioned to be a living document, periodically updated by MDIC as more experience is gained in collecting and using patient preference information in the regulatory context, as well as in marketing, reimbursement, and shared decision making.

It is also important to note what this report is not: it does not represent the opinion or policy of FDA and does not include any specific recommendations to the FDA regarding how to collect or use patient preference information in regulatory approval decisions. It is also not a substitute for FDA guidance documents or for direct discussions with CDRH staff regarding the incorporation of patient preference information into the approval process for a technology.*

Rather, in the absence of extensive experience collecting and using patient preference information, the major goal of this document is to help “sculpt the fog” around the concepts of patient-centeredness and patient preference information as applied in the regulatory context, thereby making these concepts more understandable and more useful to regulators, sponsors, patient groups, and other parties interested in these topics. In a world where health care decisions in general and medical device regulation specifically is increasingly “evidence-based,” this report is intended to further the understanding of patient perspectives through encouraging the collection of patient preference information, thereby helping discussions of the patient perspective regarding the benefits and risks of medical devices become more evidence-based. Towards MDIC’s goal of improving regulatory science to enhance medical technology innovation, the PCBR Steering Committee hopes that this Framework Report will be a valuable early discussion of patient preferences in the regulatory context that will encourage more work in this field and, thereby, encourage a more patient-centric approach to the development and regulation of medical devices.

* As of the date of publication of this report but independent of this MDIC effort, CDRH was developing a draft guidance regarding the collection and use of patient preference information that should be released in 2015.

Exhibit 1-1: Excerpt Regarding the Potential Value of Information on Patient Perspectives on Benefits and Risks from the “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,” CDRH, March 2012, Section 4.3, pp. 11-12

Patient tolerance for risk and perspective on benefit – if the risks are identifiable and definable, risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable* in exchange for a probable benefit. When making a benefit-risk determination at the time of approval or *de novo* classification, FDA recognizes that patient tolerance for risk and a patient-centric assessment of risk may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life. How data concerning patient risk tolerance and other patient-centered metrics are developed will vary depending on a number of factors, including the nature of the disease or condition and the availability of existing treatments, as well as the risks and benefits they present. FDA encourages any sponsor that is considering developing such data to have early interaction with the appropriate FDA review division.

When assessing such data in a PMA application or *de novo* petition, FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse. Therefore, FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others. It should also be noted that if, for a certain device, the probable risks outweigh the probable benefits for all reasonable patients, FDA would consider use of such a device to be inherently unreasonable.**

Different factors can influence patient risk tolerance, including:

- **Severity of disease or condition** – patients suffering from very severe diseases (i.e., those that are life-threatening) may tolerate more risk for devices used in treatment. For diagnostic devices, individuals might be more averse to the risk of a false negative result concerning a severe disease.
- **Disease chronicity** – some patients with chronic diseases who have adapted to their illness and minimized its interference with their daily lives may tolerate less risk and require risky devices to deliver a greater treatment benefit, whereas other patients who have suffered from a debilitating chronic illness over a long period of time may tolerate higher risk to gain less benefit.
- Availability of **alternative treatment/diagnostic options** (also see below) – if there are no other treatment/diagnostic options available, patients may tolerate more risk for even a small amount of benefit.

We recognize that patient-centric metrics such as validated quality of life measures can be helpful for health care practitioners when discussing treatment decisions with their patients, and may be used to demonstrate benefit for purposes of product approval. These types of metrics allow the physician to better quantify the impact of the device on the patient’s well-being and help the patient make a more informed decision. Moreover, it may be appropriate to approve a device where only a minority of the intended patient population would accept the risks as weighed against the benefits if the information necessary for patients and health care practitioners to make well-informed decisions is available and can be presented in a manner that can be understood by the practitioners and patients. Patient-centric assessments should take into account both the patient’s willingness and unwillingness to use a device or tolerate risk. Both preferences are informative and helpful in determining patient tolerance for risk and benefit and the benefit-risk profile of a device.

* 21 CFR 860.7(d)(1) states that: “The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.”

** For the purpose of this guidance the concept of “unreasonable risk” should be construed to mean a risk that no set of reasonable patients would be willing to endure to achieve a probable benefit.

Exhibit 1-2: MDIC PCBR Project Steering Committee Members

- Robert Becker, MD, PhD, FDA, Center for Devices and Radiological Health, Office of In Vitro Diagnostics and Radiological Health
- Randall Brockman, MD, FDA, Center for Devices and Radiological Health, Office of Device Evaluation
- Stephanie Christopher, Medical Device Innovation Consortium; MDIC PCBR Program Manager
- Jessica Foley, PhD, Focused Ultrasound Foundation
- Jim Gardner, MD, MBA, Cook Group, Inc.
- Andrew J. Greenfield, MBA, AbioMed
- Arie Halpern, Simulia
- Martin Ho, MSc, FDA, Center for Devices and Radiological Health, Office of Surveillance and Biometrics
- Telba Irony, PhD, FDA, Center for Devices and Radiological Health, Biostatistics and Office of Device Evaluation
- Ross Jaffe, MD, Versant Ventures and National Venture Capital Association (NVCA); MDIC Board Champion, PCBR Project
- Alethia Karkanis, WL Gore
- Richard Kuntz, MD, MSc, Medtronic
- Jack Lasersohn, JD, The Vertical Group and National Venture Capital Association (NVCA)
- Bennett Levitan, MD, PhD, Janssen R&D LLC, Johnson & Johnson
- Barry Liden, JD, Edwards Lifesciences
- Bryan Luce, PhD, MBA, Patient-Centered Outcomes Research Institute (PCORI)
- Kim McCleary, FasterCures
- Mimi Nguyen, FDA, Center for Devices and Radiological Health, Office of the Center Director
- Kathryn O'Callaghan, FDA, Center for Devices and Radiological Health, Office of the Center Director
- Bryan Olin, PhD, Cyberonics
- Anindita Saha, FDA, Center for Devices and Radiological Health, Office of the Center Director
- Diana Salditt, Medtronic
- Peter Saltonstall, National Organization for Rare Disorders (NORD)

Committee Advisors

- Marc Boutin, JD, National Health Council
- Scott Braithwaite, MD, MS, FACP, Department of Population Health, NYU School of Medicine
- Brett Hauber, PhD, RTI Health Solutions
- Bray Patrick-Lake, MFS, Clinical Trials Transformation Initiative (CTTI)
- Kelly Slone, National Venture Capital Association, Interim Project Manager for PCBR initiative
- Sean Tunis, MD, MSc, Center for Medical Technology Policy

Exhibit 1-3: MDIC PCBR Project Framework Working Group Members

- Scott Braithwaite, MD, MS, FACP, Department of Population Health, NYU School of Medicine
- Randall Brockman, MD, FDA, Center for Devices and Radiological Health, Office of Device Evaluation
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Exhibit 1-4: MDIC PCBR Project Catalog Working Group Members

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Section II: Patient Centered Benefit-Risk Assessment: Definitions and Background Concepts

The purpose of this section is to help ensure a common understanding of terms used in this Framework Report by providing definitions of important terms and background concepts regarding patient centered benefit-risk assessment and patient preferences. Several key terms in the Patient Centered Benefit-Risk (PCBR) Framework can be defined in multiple ways. This is especially true of terms that are used both in a technical manner and in conventional speech, such as *risk*, *preference*, and *judgment*, as well as terms with different meanings in different fields such as *risk tolerance*. This section of the report will:

- define important terms that will be used throughout the remainder of the report, and
- discuss several important concepts related to how patient preference information can be used to inform benefit-risk determinations.

Beyond the terms discussed formally in this section, definitions for other relevant terms can be found in Appendix B: Glossary of Terms.

Important Definitions

Benefit, Harm, and Risk

The terms “benefit” and “risk” are subject to considerable ambiguity that often leads to confusion in discussions of benefit-risk.² “Risk” in particular can refer to the concept of a harmful event, the probability of a harmful event, or the impact of that harmful event on a patient. To lessen this ambiguity, the MDIC PCBR Framework adopts terminology conceptually similar to that in the European Medicines Agency’s Benefit-Risk Methodology Project.³

A **benefit** is a favorable effect or desirable outcome of a diagnostic or therapeutic strategy.

A **harm** is an unfavorable effect or undesirable outcome of a diagnostic or therapeutic strategy.

Both benefits and harms are subject to uncertainty. In the Framework, the uncertainty in the occurrence of a benefit or harm will be characterized by **probability**, with the understanding that this probability may be described in a variety of ways, including by proportions, person-year rates, Kaplan-Meier rates, or related measures.

Risk is defined as the qualitative notion of the probability and/or severity of a particular harm. This definition accommodates how the term “risk” is used in much of the benefit-risk literature and prior FDA CDRH guidance.*

* It should be noted that this accommodation does lead to an unfortunate asymmetry in the definitions of “benefit” and “risk” as illustrated by the lack of a term to complete the analogy: “Harm is to risk as benefit is to X.” Since we

Preferences

The concept of “preferences” may be defined differently by different stakeholders. The definition of preference may also differ depending on the method by which preferences are elicited. For MDIC’s PCBR Project, **preferences** are defined as “qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions,” a definition consistent with the use of the term in the patient preference literature,⁴⁻¹¹ “**Attributes**” of a medical device are features such as effectiveness, safety, tolerability, means of implantation/use, duration of the effect, duration of use, frequency of use, lifestyle aspects of use, and other device characteristics that impact benefit-risk considerations.* This definition of preferences was developed to meet the following criteria:

- allows for characterizing preferences for desirable attributes (benefits) and acceptability of undesirable attributes (harms);
- includes the relative nature of preferences (i.e., allows for direct or indirect comparison across attributes);
- allows for qualitative and quantitative characterization of preferences;
- is flexible enough to include perspectives of all relevant stakeholders (e.g., patients, physicians, caregivers, payers); and
- enables comparative assessment with non-device therapeutic options.

Note that, while some of the language in this document refers to “preferences” as representative of a target population as a whole, preferences are heterogeneous and may vary considerably within any population or may differ considerably in different subgroups within the target population. The Catalog of Methods of Assessing Patient Preferences (the “Catalog”, attached as Appendix A and summarized in Section V) provides insights into the assessment and characterization of this preference heterogeneity.

It is also important to distinguish between preference and **judgment**. Preference refers to the tradeoffs that individuals consider or exhibit in making decisions or choices for themselves, while judgment refers to considerations of individuals in making decisions or choices for others. The methods described in the Catalog can be used to assess either preference or judgment, although most are used most commonly for preference elicitation.

While the focus of this report is on patient preferences, a variety of other stakeholders besides patients may have an interest in a medical decision. Physicians, other providers, family members, hospital

do not have a term for the probability and/or magnitude of a favorable event, we commonly use benefit in both contexts – to convey both the notion of a favorable event and as the descriptor of the probability and magnitude of a favorable event – and will do so in this Framework.

*Other terms for attribute in different bodies of literature are “features,” “objects,” or “criteria.”

administrators, and payers may have a stake in the decision and have a preference regarding which treatment is most appropriate. Assessing these preferences requires clarity on the decision being made and the role the stakeholder has in that decision. For example, when conducting “preference” studies with physicians, the assessment may be of the physician’s judgment about treatment for a patient, of the physician’s preference for their own treatment (actually a patient preference regarding their care), or their preference regarding the choice of instrument/device that they will use to perform a procedure (a preference regarding a purchase or use decision).

Patient Preferences

While the preferences of a variety of stakeholders can be assessed, the focus in the PCBR Framework is on those of the patient. **Patient preferences** are those expressed by patients with regard to decisions concerning their health care. In most situations, who is the patient and what decisions that patient faces are relatively clear. However, there are situations in which patients cannot express their preferences. Such situations include children, for whom parents are responsible for health care decisions, and those patients incapacitated in some way that impairs their ability to make decisions regarding their care, including patients with impaired consciousness (such as caused by delirium, coma, sedation) or impaired cognition (such as caused by dementia, traumatic brain injury, developmental disability, psychiatric illness). In these situations, preferences regarding health care decisions are generally expressed by those with decision responsibility for the patient, including parents, next-of-kin, guardians, or responsible health care providers.

While the perspectives of physicians or other providers involved in patient care may be useful in framing benefit-risk issues, the CDRH Benefit-Risk Guidance suggests that the patient’s perception of benefit and risk can be particularly helpful:

“Patient-centric assessments should take into account both the patient’s willingness and unwillingness to use a device or tolerate risk. Both preferences are informative and helpful in determining patient tolerance for risk and benefit and the benefit-risk profile of a device.”^{1(p12)}

The CDRH Benefit-Risk Guidance also emphasizes that if there is a distinct subset of patients who would accept the benefit and risks of a particular technology, even if a minority, then the product could potentially be approved for that subset of patients, so long as there is sufficient information for patients and health care providers to make well-informed decisions.^{1(p9)} The measurement of patient preferences is therefore distinct from that of other stakeholders and potentially valuable in the regulatory approval process for medical technology.

Risk Tolerance, Maximum Acceptable Risk, and Minimum Required Benefit

A key use of patient preferences is to assess how much of a risk an individual would accept for a given degree of benefit, or how much benefit an individual would require for a given degree of risk. These tradeoffs emerge directly from preference information. For example, consider devices that enable a person with a limp to walk. Device A always causes a rash but completely improves one's ability to walk. Device B always partially improves one's ability to walk but does not cause a rash or other adverse events. The choice between these treatments is based on the preferences for rash, partially improved walking, and completely improving one's ability to walk.

The PCBR Framework uses the terms "maximum acceptable risk" and "minimum required benefit" to characterize these tradeoffs. **Maximum acceptable risk** is the greatest increase in probability or magnitude of a harm that a patient would accept for a given benefit. **Minimum required benefit** is the smallest increase in probability or magnitude of a benefit that a patient would require to offset a given risk. Quantitative assessment of patient preferences can enable computation of these two metrics.

Consistent with prior use in CDRH guidance documents, the term "**risk tolerance**" is closely intertwined with the notion of maximum acceptable risk, as higher risk tolerance implies a greater maximal acceptable risk for a given benefit. Caution is required with the use of this term, however, because as described below, in the Decision Analysis literature, "risk tolerance" refers to the impact of uncertainty on decisions and applies to both benefits and harms. To avoid confusion from a potential clash in terminology, in the MDIC Framework, "risk tolerance" is a notion reflecting the degree to which a patient would accept greater probability or severity of a harm in exchange for a given benefit, while maximum acceptable risk and minimum required benefit are quantitative measures of this notion.

Note that both maximum acceptable risk and minimum required benefit can be applied to cases with no uncertainty, as in the walking example above. However, most therapies have harms and benefits that are probabilistic and require the introduction of an additional notion that reflects how uncertainty impacts patients' views on maximum acceptable risk and minimum required benefit.

Uncertainty Attitude

Uncertainty attitude is a reflection of the degree to which uncertainty in the attributes of a treatment alters one's decisions about use of the treatment.* It is independent of the preferences that an individual places on particular benefits or harms. Uncertainty attitude is highly relevant to medical decision making

* In the Decision Analysis literature, "uncertainty attitude" is referred to as "risk attitude," with "risk" referring to uncertainty for any attribute, beneficial or harmful. The PCBR Framework adopts the term "uncertainty attitude" to clarify that the concept applies equally well to benefits and harms and to avoid confusion between the term "risk tolerance" as defined above and "uncertainty tolerant" patients as defined in this section, who would otherwise be labeled as "risk tolerant."

because there is often uncertainty whether an individual patient will experience the benefits or the harms of a therapy. In medical terms, uncertainty attitude measures the enthusiasm or reluctance of a patient to choose a treatment that, if the benefits and harms of the treatment and alternatives were known with certainty, the patient would be indifferent about choosing.

Patients who are **uncertainty averse** react to uncertainty by decreasing their maximum acceptable risk for a given benefit, or by increasing their minimum required benefit for a given risk. The uncertainty regarding harms or benefits makes uncertainty averse patients less willing to take a chance on a treatment. In contrast, patients who are **uncertainty tolerant** react to uncertainty by increasing their maximum acceptable risk for a given benefit, or by decreasing their minimum required benefit for a given risk. The uncertainty for the harm makes these patients more willing to take a chance on a treatment. Patients whose maximum acceptable risk is not impacted by uncertainty are referred to as **uncertainty neutral**. Note that the concept of uncertainty attitude (along a spectrum from averse through neutral to tolerant) is distinct from the concept of preferences. Knowing a patient's uncertainty attitude helps estimate how preference tradeoffs change due to uncertainty.

As an example of risk attitude, consider the following two weight loss devices:

- Device A, that has 100% chance of resulting in a 10-pound weight loss, or
- Device B, that has a 50% chance of resulting in a 20-pound weight loss and 50% chance of resulting in no weight loss

Regardless of a patient's preference for weight loss versus other symptoms, uncertainty averse (avoiding) patients are more likely to choose Device A, unless their preference-based valuation of the additional weight loss potentially offered by Device B is overwhelmingly strong. Uncertainty tolerant patients are more likely to choose Device B as they are more willing to gamble that they will lose the 20 pounds.

There are formal means to assess an individual's uncertainty attitude, although in practice, the concept may be more useful than any formal measurement. It is often not practical to measure a person's uncertainty attitude, much less that of a population, but it is often valuable to know whether a group of stakeholders is more averse/tolerant to uncertainty than another group and whether differences in decisions between groups of patients are due to varied tolerance for uncertainty rather than varied preferences for benefits and risks.

Preference Sensitive Decisions

Preference sensitive decisions are those in which there are multiple diagnostic or treatment options, and the decision which option to pursue depends upon the particular preferences of the decision maker. This concept has an important role in assessing when patient preference information is of value, as will be discussed in more detail in Section III.

Preference sensitive decisions occur when a patient has multiple treatment options with at least one of the following characteristics:

- No option is clearly superior over a plausible range of preferences;
- The evidence supporting one option over others is considerably uncertain.

The first part of the definition is equivalent to stating that there is at least one realistic tradeoff. This is best demonstrated with an example, as illustrated in Exhibit 2-1 below. The exhibit shows five alternative devices that differ in reducing days in the hospital after a procedure (benefit) and in probability of infection (risk). The ideal device is the bottom right corner – large reduction in days with low probability of infection. The available Devices A – E have the tradeoffs shown and are not near the bottom right corner. In this case, it is clear that Device C is superior in both benefit and risk to all other alternatives, so it is said to “dominate” the other choices. Preference information is not needed to choose among these alternatives.

Exhibit 2-1



Now consider the alternative example in Exhibit 2-2 below. Even without knowing a patient’s preferences of the relative importance of the benefit and risk, a patient can still observe that Device A is better than Devices D and E in both benefit and risk. Similarly, Device C is better than Device B in both benefit and risk. Therefore, neither the choice of Device A over Devices D and E or the choice of Device C over Device B is preference sensitive since Devices A and C dominate the other devices to which each is compared. In contrast, choosing between Devices A and C is a preference sensitive decision. A patient cannot choose between Devices A and C without choosing which is more important, reducing hospital days or reducing the probability of infection. By measuring patient preferences regarding the relative importance of these two attributes, we can better understand how patients will choose between Devices A and C.

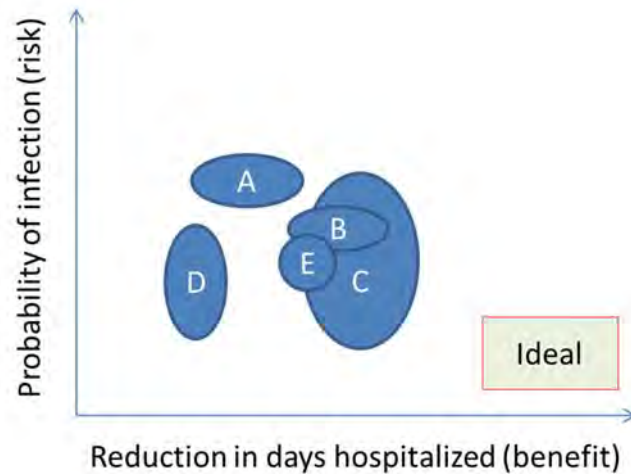
Exhibit 2-2



Considering a plausible range of preferences also impacts whether a decision is preference sensitive in practice. The choice between Devices A and C in Exhibit 2-2 is not preference-sensitive if the tradeoffs are so unbalanced as to be unaffected by preference information when considering a realistic range of preferences. For example, it is implausible that a person would not accept the risk of a brief, minor infection with no sequelae to avoid spending a year in a hospital. If the differences between Devices A and C involved such an unbalanced tradeoff, then the decision between the two is clear and not preference sensitive. This understanding of a realistic range of preferences reflects an important role for expert clinical judgment as a proxy for assessing patient preferences in regulatory benefit-risk determinations.

As noted in the second part of the definition of preference sensitive decisions, considerable uncertainty can magnify the importance of preference information. Uncertainty can even convert a decision with only one dominant solution into a preference sensitive decision that depends on a patient's uncertainty tolerance. Consider what happens when uncertainty about the measures of benefit and harm is included in an example similar to that in Exhibit 2-1. In Exhibit 2-3 below, the bubbles are stretched to represent uncertainty about the benefit and risk of each device. The benefit and risk for a device can lie anywhere within its bubble. It is now uncertain if Device C dominates Devices B and E, as their bubbles overlap to a great extent. For example, Device B may even be better than C in both benefit and harm, as C's bubble extends to larger risk and lower benefit than much of B's bubble. The actual benefit for Device C may be greater than, equal to, or less than that for Device B. An uncertainty neutral patient would likely regard Device C as the best option for the same reasons as given above, but an uncertainty averse patient who has preferences that strongly favor avoiding infection over reducing hospital days might choose Devices B or E over Device C, since the uncertainty in C's probability of infection extends to much higher probabilities than do B's and E's. Hence, in the face of considerable uncertainty about benefits and risks, Device C no longer clearly dominates Devices B and E.

Exhibit 2-3



Application of the Patient Preferences in Benefit-Risk Determination

A thought experiment may further illustrate the role that patient preference information may play in benefit-risk determination decision making. This example is not intended to specify an algorithmic approach to the use of patient preferences in benefit-risk assessment, as formal mathematical formulation of these problems in device approval situations may not always be feasible. Rather, it serves to connect many of the ideas expressed above in one conceptual example and to depict the resulting benefit-risk questions.

Consider a simplified device approval case with the following characteristics:

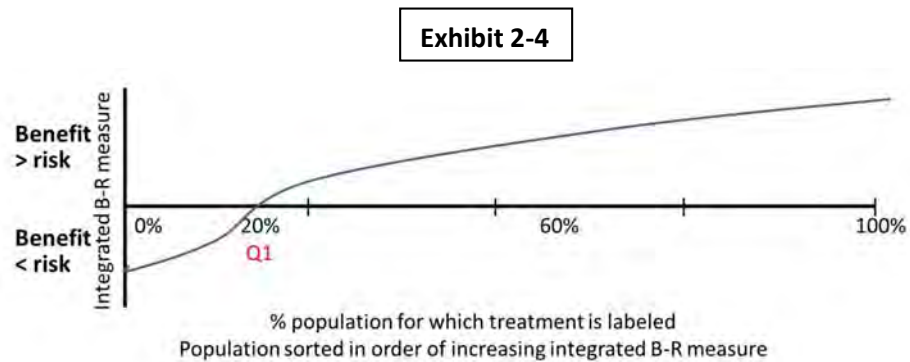
- The target population for the device is clearly specified.
- Probabilities for benefits are homogeneous for the population (i.e., the probabilities for the benefits for any member of the population are the same as that for any other member of the population).
- Probabilities for harms are also homogeneous for the population.
- Preferences and uncertainty attitude are known for the population and were assessed with validated methods.
- Preferences for benefits and harms are heterogeneous within the population (i.e., the preferences for the benefits and harms for any member of the population may differ from those of other member of the population).

The last two assumptions require more a more detailed explanation:

- We also assume that the characteristics above are measured precisely enough to calculate an integrated benefit-risk measure for the target population of the device. Integrated benefit-risk measures are means to merge the probabilities of benefits and harms, patient preferences, uncertainty aversion, and potentially other related data into a single, unified metric. The purpose of these measures is to augment clinical judgment by enabling a clear means to understand the interactions between many of the core elements in a benefit-risk decision.
- While this thought experiment will make use of an integrated benefit-risk measure, it is important to note that whether and how to use integrated benefit-risk measures in regulatory decision making is an evolving dialogue and these measures currently have a limited role in regulatory discussions.¹² As such, the use of the measure in this discussion is intended to be conceptual. The application of patient preferences to integrated benefit-risk measures for regulatory considerations is an area for further work related to patient preferences discussed in Section VIII. (Examples and discussions of integrated benefit-risk measures can be found in a number of studies.)^{11,13-19}
- The integrated benefit-risk measure in this thought experiment can roughly be considered a sum of differences in probability of benefits and harms, each weighted by their respective preference and by measures for uncertainty aversion.* A positive integrated benefit-risk measure indicates benefits outweigh risks, and a negative measure indicates risks outweigh benefits. The more the measure deviates from zero, the greater the difference from benefits and risks being balanced.
- Finally, we assume the benefits outweigh risks for a portion of the population due to preference heterogeneity. We also assume that no objective characteristics (such as demographics or diagnostic criteria) enable reliable prediction of the preferences for a given patient; i.e., no objective characteristics other than preference can be used to determine whether benefits outweigh risks for a particular patient. (If such a measure were available, a potential regulatory option would be to consider approval for patients with these objective characteristics.) Therefore, there is a distribution of values of the benefit-risk measure due to preference heterogeneity alone. As such, it would be possible to construct a curve that depicts a histogram of the benefit-risk measure's values across the target population.

The implications of this thought experiment are illustrated in Exhibit 2-4.

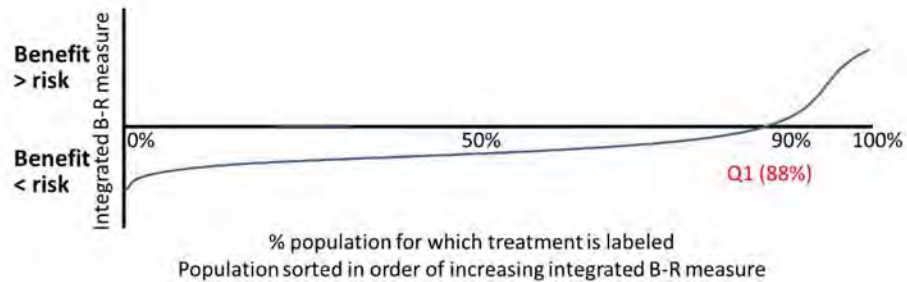
* This example uses a common, simple approach for integrated benefit-risk measures: the sum of probability differences for each benefit and harm times the corresponding preference weight for each harm; i.e., $net\ clinical\ benefit = \sum_{All\ attribute\ i} (preference\ weight\ for\ attribute\ i) \times (probability\ of\ attribute\ i\ for\ device - probability\ of\ attribute\ i\ for\ placebo\ device)$. The preferences are scaled to be per unit of probability for each attribute. This example measure does not incorporate uncertainty attitude.



The blue line shows the integrated benefit-risk measure, representing both probabilities of benefits and harms and patient preferences for them. The x-axis reflects the entire population for the device, with the population sorted in order of increasing integrated benefit-risk measure. The measure is negative for the portion of the population to the left of Q1 (20% in this example) and is positive for the remainder of the population. Q1 can also be defined as the proportion of the population for which benefits do not exceed minimum required benefit or for which risks exceed maximum acceptable risk. A regulatory decision based on these types of benefit-risk considerations alone may favor approval because the vast majority of the population has benefits exceeding risks, and no patients have risks overwhelmingly exceeding benefits.

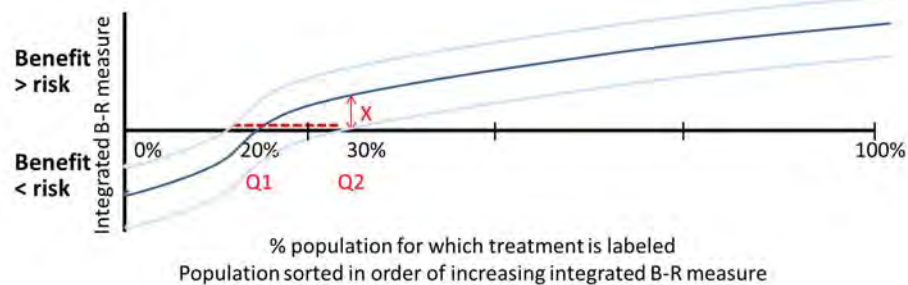
Exhibit 2-5 shows an alternative scenario. Here, benefits exceed risks due to preference for only 12% of the population, or risks are below maximum acceptable risk for only 12% of the population. Approval for the entire population could result in more risk than benefit for the population as a whole, yet the 12% may reflect a substantial number of patients who would choose to use the treatment were it available. In this case, a regulatory decision based on benefit-risk considerations alone might not approve the device for the entire population, but rather may indicate it for those patients whose preferences are such that benefits exceed risks. Such an approval would be for a subgroup of patients based on preference. These two examples demonstrate how regulatory knowledge of the distribution of patient preferences can potentially influence a regulatory decision.

Exhibit 2-5



One last step in this thought experiment is to extend the simple integrated benefit-risk measure depicted in Exhibits 2-4 and 2-5 to account for uncertainty. These exhibits show a single, deterministic measure for each patient, based on average rates (point estimates) for the benefits and harms and a deterministic set of preferences for each patient. Exhibit 2-6 below illustrates the effect of incorporating uncertainties for benefits, harms, and preferences into the integrated benefit-risk measure for the example in Exhibit 2-4.

Exhibit 2-6



Uncertainty in the integrated benefit-risk measure is represented by a band around the measure bordered by the light blue lines. The light blue lines can be considered a 95% confidence interval around the measure. Because of this uncertainty, the proportion of patients for which benefit exceeds risk (above Q1) could vary from 70% to 85%, with the range for the threshold Q1 represented by the dashed red line. If the decision were to use the treatment as long as the integrated benefit-risk measures' confidence interval excludes risk exceeding benefit, then the set of patients for which the treatment is appropriate shifts from above Q1 to above Q2. Effectively, benefits have to exceed risk by the threshold depicted as X in Exhibit 2-6 in order to account for the uncertainty. The portion of the population for which this criterion is met is 70% in this example. An alternative description is that, when the maximum tolerated risk is computed with uncertainty, the risk must be below the maximum tolerated risk by at least X to have confidence that benefits exceed risk.

Additional Comments

As stated above, the intention of this Framework Report is not to specify an algorithmic approach to incorporating patient preferences into FDA benefit-risk assessments. While benefit-risk analysis concepts originate from decision science, the most appropriate means for incorporating them into regulatory decision making is more a reflection of regulatory policy than decision analysis methods. Formal mathematical formulation of these benefit-risk problems in device approval situations will not always be necessary or feasible, nor will an algorithmic approach to incorporating patient preference information into regulatory benefit-risk assessments. Rather, the discussion of terms and concepts in this section of the Framework Report are intended to inform discussion of incorporating patient preferences into regulatory decisions, which in the end will require judgment on the part of both sponsors and FDA staff. The next section of this report, Section III: “Evaluating the Potential Value of Patient Preference Information in Regulatory Benefit-Risk Assessments of Medical Technology,” will build on the concepts outlined in this section to discuss in what situations patients preference information might be valuable in helping to frame benefit-risk assessments for regulatory purposes.

Section III: Evaluating the Potential Value of Patient Preference Information in Regulatory Benefit-Risk Assessments of Medical Technology

A key question regarding the use of patient preference information is how to identify situations in which patient preference information would help regulatory decision making. Patient perspectives on benefit and risks will be more valuable in regulatory evaluation of some clinical indications, benefit-risk scenarios, and technologies than in others. This section of the PCBR Framework Report discusses factors to consider in deciding in what situations patient preference information might be useful in regulatory decision making.

Factors to Consider in Determining if Patient Preference Information Could be Useful in a Particular Regulatory Decision

The decision to collect and submit patient preference information to help in the regulatory approval of that technology is at the judgment of the sponsor. In other situations, FDA staff may want to collect patient preference information to help them frame the thinking about the regulatory requirements in an emerging area of medical technology, as is illustrated by the study of patient preferences regarding weight loss technologies undertaken by CDRH and discussed throughout this report.⁴ The big issue facing sponsors or FDA staff is deciding in what situations collecting such information will be valuable in the regulatory process and worth the time, cost, and effort.

As described in Section II, one set of conditions under which patient preference information is likely to be of value is if the clinical decision to use the medical device is “preference sensitive” based on its benefits and harms. As discussed below, there are other conditions in which such information is potentially valuable as well. In developing a process for determining whether patient preference information could be useful in the regulatory approval of that product, the PCBR Project Steering Committee decided not to take an algorithmic or prescriptive approach. Rather, the approach outlined in this Report is to describe factors which suggest that patient preference information would be a meaningful addition to a regulatory submission.

The factors outlined below focus on the benefits and risks of specific technologies. Section 513(a) of the Federal Food, Drug and Cosmetic Act requires demonstration of reasonable assurance of safety and effectiveness for devices subject to premarket approval. Determination of reasonable assurance of safety and effectiveness involves weighing any probable benefits to health from use of the device against any probable risk of injury, in addition to other factors. CDRH’s Benefit-Risk Guidance for premarket approval and *de novo* classifications¹ recognizes a number of these other factors in addition to clinical data on benefit and risk, such as availability of alternative treatments and the importance of patient-centric assessment of benefit and risk. Information on how patients value a new technology compared to therapeutic alternatives provides context for benefit-risk decisions. In alignment with CDRH’s structure for benefit-risk assessment, preference is not limited to benefits and harms, but also includes attributes

such as means of implantation/use, frequency of use, lifestyle aspects of use, and other non-therapeutic outcomes. The PCBR Steering Committee acknowledges that benefit-risk decisions may be based on these characteristics in addition to therapeutic outcomes. However, the focus of this section is on preference information regarding benefits and risks due to the explicit relationship between benefit-risk assessment and the statutory approval standard.

Factors that are broadly relevant for preference-sensitive decisions and situations in which patient preference information could be valuable include: 1) factors related to the perspective of patients as stakeholders, 2) factors related to benefit-risk tradeoffs inherent in the use of a particular technology, and 3) factors related to regulatory novelty. While these three groups of factors may not capture all possible considerations about whether or not to collect patient preference information in a specific situation, they do represent a core set of factors that can be considered. Each of these three types of factors is discussed in more detail below.

None, some, or all of these factors may be relevant to a particular technology or clinical indication. While preference-sensitivity is a common denominator of whether preference information might be valuable, a useful “rule of thumb” is that the more factors that apply to a technology or clinical indication, the more important patient preference information is likely to be in a regulatory decision.

Factors Related to the Perspective of Patients as Stakeholders

Patient preferences 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. To the extent that technologies are used in such indications, patient preference information may be helpful in informing the benefit-risk assessment for regulatory approval. Specific factors related to the perspective of patients as stakeholders include:

- ***Differences in patient preferences or risk tolerance from that of other key stakeholders.*** Information on patient preferences might be useful when there is a suggestion that patients are willing to accept a different degree of risk or require a different degree of benefit than providers or regulators (have different maximum acceptable risk or minimum required benefit), and understanding that difference may alter the regulatory decision.
- ***Heterogeneity in patient preference.*** Patient preference information can be valuable when it illustrates the preferences of an “average” patient, but it is especially valuable if it illustrates the range of patient preferences across the population and the existence of a subgroup of patients with considerable differences in preferences. Preference information would be particularly valuable when there is a suggestion that these differences are important enough to alter the decision whether to approve a product for at least one subgroup of patients. Understanding the heterogeneity of patient preferences may help sponsors and regulators agree on label claims that appropriately identify the

patient population for which the technology is indicated. This characterization of heterogeneity by patient preferences can be considered a complement to efforts to elucidate heterogeneity of treatment effect by defining clinical factors (e.g., physical exam, biomarkers, imaging, disease severity measures) that enable more precise prediction by patient subgroup of the likelihood of the harms and benefits.

- ***Understanding the clinical experience requires considerable personal familiarity with the disease.*** Personal experience with the disease or condition might be necessary to understand the acceptability of benefits and harms or to report clinical endpoints for products with certain indications. For example, the perspective of the patient might be valuable in technologies addressing rare diseases or unmet medical needs or in submissions supported by subjective clinical endpoints.

Information on patient preferences might be particularly valuable in the following instances:

- *When the clinical experiences of key endpoints for the device are highly subjective (e.g. pain, fatigue, nausea, paresthesia, itch, depression), or when impact on quality of life is an important outcome measure.* The more subjective the outcome measures for benefits and/or risks of a technology are, the more useful patient preference information might be in interpreting and weighing those subjective responses. Quality of life (QOL) measures and Patient Reported Outcomes measures (PROs) are often used when measurement of the outcomes of a therapy are based on the subjective experience of the patient. PROs may be primary, secondary, or exploratory endpoints,²¹ and in many situations, provide information on the level of patient perception of an outcome (e.g., pain, shortness of breath, quality of life). In some situations, they measure patient satisfaction with the outcomes of a therapy (e.g., satisfaction with appearance after a dermatologic procedure or satisfaction with an orthopedic surgery). However, these subjective outcome measures do not provide information on the relative importance attributes to patients or how patients tradeoff off benefits and risks. Information from patient preference studies can provide information that complements subjective outcome information from PROs and QOL instruments by helping understand how patients value and tradeoff those outcomes.
- *When the key benefit is considered a “lifestyle” or fully elective benefit and decisions to use the product are patient-driven.* Patient preferences and risk tolerance are of particular interest for those classes of technologies that by their very nature are preference-sensitive, notably elective medical procedures or technologies that are used based on patient preference and not on severity of symptoms or other more objective medical needs. Information on how patients think about the benefits and risks might help in the regulatory evaluation of fully elective procedures to enhance appearance or lifestyle (e.g., for impotence, baldness, wrinkle-reduction, tattoo removal). Indeed, how patients select among multiple elective treatment options in the real world may explicitly or implicitly provide information regarding which benefits patients want and what risks they want to avoid among the available options.

Even when endpoints are subjective on the part of providers, rather than patients, information showing how patients assess and value the benefits and risks of the clinical approach relative to providers might be valuable in framing the benefit risk assessment for FDA staff. For example, dermatologic technologies are often assessed based on provider view of patient appearance change; similarly, wound healing technologies, are often assessed based on provider view of the quality of the closure of the wound. Demonstrating that patient perceptions of benefits and risks are consistent with (or, in other cases, are significantly different from) those of providers may be helpful in informing the regulatory benefit-risk assessment process when using subjective assessment of appearance or functional outcome endpoints.

- *In rare diseases or rare indications for which reviewers are generally less familiar with the clinical experience of the benefits or harms than they may be in more well-known disease states.* In diseases about which FDA staff have little to no experience, particularly rare diseases, preference information may illuminate how patients (or their caregivers, who may be the best available proxy for the patient) experience the disease state, and may prove particularly valuable in informing regulatory benefit-risk assessments. Indeed, a good example of how preference information can be developed to help inform FDA regulatory approaches to rare disease therapies is the study of treatment preferences expressed by parents of patients with Duchene’s Muscular Dystrophy undertaken by the Parent Project Muscular Dystrophy.²² Such cases are really a subset of those involving regulatory novelty, which is discussed in more detail later in this section.
- ***Patient involvement in use of the technology.*** Patient preference information may be particularly valuable in the approval of patient self-use products when the self-use product has a different benefit-risk profile than alternatives involving treatment of the patient by a health care provider. For example, in home dialysis, patients may accept more risk in exchange for benefits of convenience and better outcomes from more frequent dialysis compared to in-center hemodialysis.*

Factors Related to Benefit-Risk Tradeoffs Inherent in the Use of a Particular Technology

While there is a formal definition for preference-sensitivity, there are situations in which the use of a technology is almost certain to be highly preference sensitive even in the absence of formal analysis. Patient preference information could be particularly useful in regulatory decision making for products with

* In the evaluation of such patient self-use products, it is important to draw a difference between patient preference information and human factors information. Human factors information focuses on how patients or providers use a technology and on the user experience. The FDA will likely require sponsors of patient self-use products to present human factors studies to demonstrate that targeted patients can safely and effectively use the product. However, patient preference information focuses on the patient’s decision whether to use a technology given its benefits and risks relative to other alternatives. While human factors information is needed to show that most, if not all, patients are able to use the product, patient preference information may be useful in showing that a portion of the target patient populations would choose to use the product.

challenging benefit-risk scenarios, including products with marginal benefit-risk profiles or complex benefit-risk tradeoffs. Such situations include:

- ***Marginal benefit-risk scenarios (“close calls”).*** As illustrated in Exhibit 3-1 below, patient preference information is less likely to be useful for regulatory decisions where there are clear benefits and little risk to patients (top left box, green). The choice to use a medical technology in this situation would likely not be a preference sensitive decision as the benefits clearly exceed the risks. Benefit-risk assessment in other situations, illustrated by the other quadrants of Exhibit 3-1, can be less straightforward when it is less clear whether benefits exceed risks. In these more challenging to assess benefit-risk situations, the decision to use the technology is more likely to be preference sensitive and preference information more valuable in making the benefit-risk determination. Patient preference information may be particularly useful:
 - *When there is a clear benefit with serious risks (top right box, orange).* In this situation, patient preference information would be valuable to clarify that at least a portion of the patient population has a risk tolerance that would allow them to choose the therapy.
 - *When there is modest benefit but also modest risk (bottom left box, yellow).* For technologies with this benefit-risk profile, patient preference information would be valuable to make sure the technology delivers at least the minimum required benefits for the level of risk, as the low level of risk is not likely to exceed the maximum acceptable risk.
 - *When there is significant risk with modest benefit (bottom right box, red).* In this situation, a product is unlikely to be approved unless it addresses a clinical need for which the modest benefit with significant risk of the technology represents an attractive alternative to the other available treatment options. Patient preference information would be valuable to demonstrate that there is at least a subset of patients who would accept the level of benefit offered and for whom the harms do not exceed the maximum acceptable risk.

Additional factors, such as uncertainty about benefits and risks, can add complexity to benefit-risk assessments, particularly if the assessment is a “close call.” Studies that assess patient preferences in light of those factors can assist in sorting through the complexity of benefit-risk assessment in those situations. Situations in which complex benefit-risk tradeoffs arise may include those in which:

- *The technology is so different from existing therapies or so novel that either (1) incremental benefits and/or harms are likely to be large, or (2) there is little existing data that indicates the likelihood of benefits and harms.* Such situations overlap with those discussed under “regulatory novelty” below, and might occur when:

- *The technology is a therapy for a chronic condition traditionally treated with drugs.* The technology has a different benefit-risk tradeoff compared to the drug, for example where there may be lower efficacy with the technology but there are likely fewer systemic side-effects than the drug. Patient preference information might be useful in demonstrating that patients will want to use this technology instead of or in addition to drug.
- *The technology is less invasive.* The new technology and more invasive alternatives may have fundamentally different benefit-risk profiles (e.g., the minimally invasive approach is less risky but also less effective than the more invasive approach). Patient preference information might reveal if and how patients are willing to tradeoff off invasiveness for safety or efficacy differences.
- *The technology changes the provider or caregiver or the setting of care.* For example, the technology may enable patient self-care versus physician or nurse-provided care. If so, information on the patients' view of which setting they prefer may impact the regulatory benefit-risk assessment.
- *The technology is reversible.* Patients may prefer a reversible treatment that is less beneficial but which preserves future treatment options to an irreversible treatment that is potentially more beneficial, but which cannot be reversed if it fails.
- *Concern exists that an inherent risk (e.g., death) is so significant that few patients with plausible preferences (even those who are risk seeking) would take that risk for the benefit of the technology in that clinical situation.* Evidence that there is at least a subset of patients that would choose to use the technology given the benefits and risks might be needed to obtain regulatory approval in such cases.
- **Temporal tradeoffs.** An important component of patient perspective on benefits and harms is time preference. This is highly related to the construct of a "discount rate" in Decision Sciences, which quantifies the notion that people like positive experiences (including health) sooner rather than later, all else being equal. Individual's preferences vary greatly with respect to the discount rate, and some investigators have argued that eliciting an individual patient's time preference is a key component of eliciting other aspects of their preferences. Accordingly, patient preference information may be particularly valuable:
 - *when benefits occur early and harms occur much later; or*
 - *when harms occur early and benefits occur much later (e.g., using a treatment to delay onset or worsening of a disease).*

- **Substantial differences in benefits and harms from other alternatives.** If a technology under regulatory consideration differs greatly from existing treatment options in terms of benefits and harms, patient preference information may be useful to understand how patients view the different benefits and harms of the variety of treatment alternatives. As referenced in the bullet point regarding complex benefit-risk tradeoffs above, patient preference information may be particularly valuable:
 - *when the treatment is based on a new technology or mechanism of action which offers patients and/or providers the potential for a substantial improvement over existing technology, but different or potentially greater harms than existing technology (e.g., a non-invasive device compared to implantable devices, or vice versa);*
 - *when the treatment entails side effects that are quite different from accepted or standard treatment (e.g., use of a medical device instead of a drug, or vice versa).*
- **Non-compensatory tradeoffs.** Patient preference information can be particularly valuable to discover subgroups of patients for whom there are risks for which no benefit would compensate (e.g., for some patients, no degree of reduction in mild pain will compensate for an increase in mortality). While in some cases the importance of the risk (e.g., death) may be obvious, but in other situations patient preference information may be required to demonstrate that no patient would accept the risks of a technology (e.g., chronic pain or disability) for the benefits offered. A challenging aspect of regulatory decision making is that the full spectrum of these risks may not be known *a priori* or even after initial clinical trials.²³
- **Decision is preference sensitive due to uncertainty.** As discussed in Section II, an important component of patient preferences is uncertainty attitude, or how uncertainty about benefits and harms of a treatment affect patient decisions to use that treatment. There may be a subset of patients that prefer the possibility of a cure over the certainty of an improvement. For example, some risk-tolerant patients may be willing to accept the risk of a new treatment that offers a 50% chance of curing a chronic disease, whereas other risk-averse patients may not and would prefer an existing treatment that does not offer a cure, but would improve 100% of the patients. Accordingly, patient preferences are particularly germane to regulatory decisions when:
 - *the average benefit clearly exceeds the risks, but the probability of an individual patient experiencing the benefit or the degree of benefit experienced by an individual patient varies widely; or*

- *the average benefit clearly exceeds the risks, but it is unclear in an individual case whether the benefits will occur before the disease progresses or whether the patient might die before the benefit occurs.*

Factors Related to Regulatory Novelty

In addition to data that is required for regulatory decision making, there might be a large array of knowledge that exists *a priori* before additional data is collected. This knowledge, or the lack thereof, influences the understanding of sponsors, FDA staff, and others of the disease state, and of benefits and harms of a particular treatment approach, and therefore is directly relevant to discussions about the importance of incorporating patient preferences into regulatory decision making. The more familiar that clinicians, sponsors, and FDA staff already are with the benefits and harms of an existing technology, particularly with how patients perceive those benefits and harms, the less need they have for additional patient preference information. The less familiar clinicians, sponsors, and FDA staff are with a disease state or a new treatment approach, the more valuable that patient preference information may be in helping each of these groups understand how patients view the benefit-risk tradeoffs inherent in the use of the technology.

Additionally, in areas with a significant regulatory precedent, it is less likely that patient preference information will make a significant difference in the regulatory process, unless such information is needed to help change that precedent. The less regulatory precedent there is for the approval of a new technology, the more likely it is that patient preference information could help shape the benefit-risk determination for approval of that technology.

To illustrate, assume a novel technology emerges in a new clinical area in which there is not much existing knowledge regarding its benefits and harms or about patient preferences regarding the use of that technology. In this situation, patient preference information can be particularly helpful to sponsors and FDA staff in framing the benefit risk issues to be considered in the approval process. As mentioned earlier in this section, situations in which challenges of regulatory novelty might arise include using a device for a clinical indication that has traditionally been treated by drugs (e.g., a device treatment for hypertension) or a new less-invasive technology for a clinical area already served by a more invasive technology (e.g., percutaneous heart valves compared to traditional surgically implanted valves).

Sponsors might consider collecting and submitting preference information, and FDA might consider encouraging such collection based on:

- ***FDA staff familiarity with a particular clinical area.*** Patient preference information will be more useful in informing regulatory decisions in clinical areas with which the FDA staff have less familiarity than in areas where there is significant regulatory precedent and the staff have a good understanding of the clinical context of use of the technology.

- **FDA staff familiarity with the use of a particular technology.** Patient preference information can be useful in situations where it can help sponsors frame for reviewers the clinical context and clinical issues around the use of a new technology in an existing clinical area or the use of an existing technology in a new clinical indication.

The CDRH study of patient preferences regarding weight loss devices⁴ referenced throughout this report is the best existing example of patient preference information being used to identify the key benefits and risks important to patients and using that information to frame regulatory requirements in a clinical area. The preference information from that study was then used in the approval of a novel medical device, the Enteromedics Maestro™ Rechargeable System for patients with obesity.²⁴

When Patient Preference Information is Less Likely to be Valuable

In addition to thinking about when patient preference information might be valuable for CDRH benefit-risk determinations, it is also helpful to identify situations in which such information would likely not be of great value. Preference information is less likely to be valuable when decisions are not preference-sensitive. Such situations include:

- **When the patient is not a major decision maker or stakeholder.** This may be the case in situations in which it is primarily the preferences of others, particularly providers, that determines the use of a particular technology (e.g., the decision of a surgeon to use one particular surgical tool versus another). In such situations, information about the preferences of other key decision-makers may be much more useful than patient preference information.
- **When the disease state, technology, study design, and clinical inputs are generally understood by both sponsors and FDA staff, and there is significant regulatory precedent for approval.** In these situations, patient preference information may be nice to have, but would likely not be as valuable in the regulatory benefit-risk assessment process as it would in areas in which sponsors and FDA staff have less experience.
- **When the benefits of the technology are so high and the risks so low that approval is highly likely.** This is the situation illustrated in the upper left, green box in Exhibit 3-1. In such cases, the benefit-risk assessment is so straightforward based on clinical data that patient preference information will not add much information to the regulatory decision.
- **When the treatment is clearly superior to existing therapies such there is no benefit-risk tradeoffs compared to alternative therapies.** This situation can occur when the treatment is likely superior to all alternatives in terms of effectiveness with no tradeoff in safety; when the treatment is likely safer

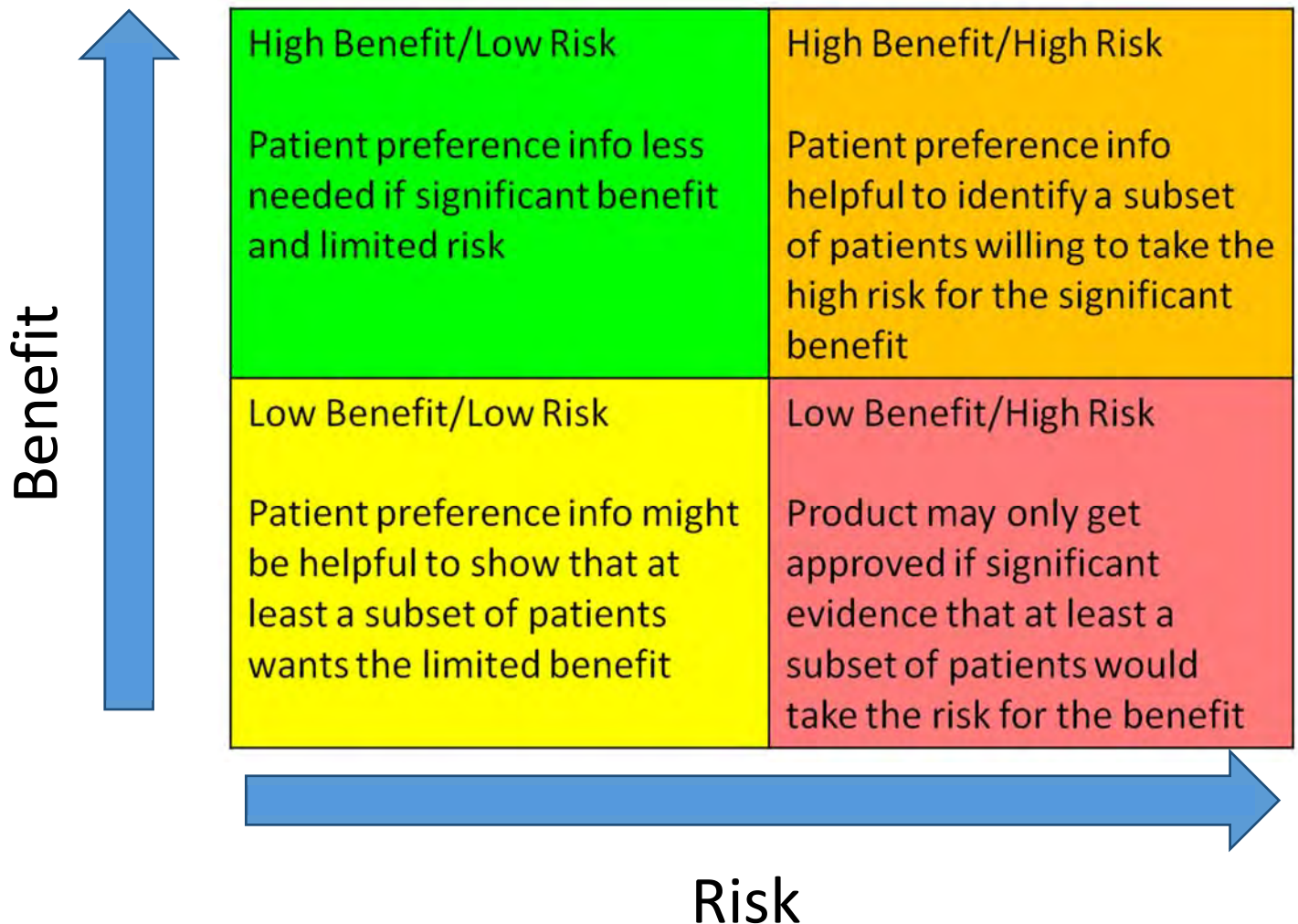
than all other alternatives with no loss of effectiveness; or when the treatment is likely superior in both safety and effectiveness to all other treatments.

- ***When the treatment addresses an unmet medical need with poor outcomes such that the risks of the treatment will not be greater than the risks of the untreated disease.*** In this case, the patient does not have treatment alternatives. From a regulatory approval point of view, the key benefit-risk issue is whether there are benefits to the patient of the treatment, and collecting patient preference information is less likely to be of value in the regulatory benefit-risk assessment process decision.

While collecting patient preference information in these situations might be valuable for other purposes such as reimbursement, marketing, or shared medical decision making, as discussed in Section VII, such preference information is not likely to be of significant value in the regulatory benefit-risk determinations in these situations.

Based on the factors outlined and summarized above, sponsors might decide that it would be helpful in the approval process for a specific technology to include patient preference information that can frame, for CDRH staff, patients' perspectives on benefits and harms of that technology. In particular, a sponsor might identify areas in which they want to collect and present to FDA information about patient preferences to strengthen their evidence supporting a positive benefit-risk determination, to help them identify subgroups of patients for whom the initial approval of a new technology is particularly compelling, or to better align the product labeling with the treatment decisions patient and providers will need to make once the product is in the market. FDA staff might decide to undertake their own evaluation of patient preferences to help them better understand the benefit-risk tradeoffs in a particular clinical area, particularly an emerging clinical area, as they recently did for medical devices used to treat obesity. Section VI of this Framework Report discusses the use of patient preference information in regulatory benefit-risk assessments. Patient preference information can have other value to sponsors as well. Section IV discusses the value of collecting patient preference information at different stages in the product lifecycle, and Section VII discusses the potential value of patient preference information beyond the regulatory process in marketing, reimbursement, and shared decision making.

Exhibit 3-1: The Value of Patient Preference Information as a Function of Benefit and Risk



Section IV: Potential Use and Value of Patient Preference Information in the Product Development Lifecycle

Section III discussed the factors to consider in deciding whether patient preference information would be useful in the regulatory approval process for a given technology. If patient preference would be useful, a question arises regarding the timing of collection of this information. This section of the Framework Report will focus on the basic uses of patient preference information in the regulatory process and how such information can be collected and used throughout the product development lifecycle. While this section focuses on the collection of patient preference information for regulatory process, it will also mention the potential use and value of patient preference information for other purposes, including product development, reimbursement, marketing, and shared clinical decision making, topics that will be discussed in more detail in Section VII.

What is the Role of Patient Preference Information in Regulatory Benefit-Risk Assessments?

The CDRH Benefit-Risk Guidance discusses the value of a patient-centric approach to benefit-risk analysis in identifying at least a subset of patients willing to accept the risk of a technology for the benefits it offers.^{1(p11)} As was discussed in the Introduction to this report and is discussed further in Section VI, information on patient preferences can help FDA reviewers understand patient perspectives regarding benefits and risks of a technology. Patient preference information can be useful to FDA reviewers in three major ways:

Framing benefit-risk issues. Patient preference information can help identify the key benefit-risk issues of a particular therapy and how patients trade off benefits and risks of the therapy. Patient preference information can elucidate how patients with a disease or clinical need perceive the benefits and risks of a particular technology for addressing that disease or clinical need. This information can help identify the full range of benefits or risks that are important to patients.

Beyond elucidating the benefits and risks important to patients, preference information can help reviewers understand how patients think about and trade off benefits and risks. As discussed in Section II, patient preference information can help identify the maximum acceptable risk and minimum required benefit that patients will accept in deciding whether to use the product. It can also help identify the amount of additional risk patients are willing to accept in exchange for a specific amount of benefit. Information on how patients think about the tradeoff of benefit and risk can help reviewers frame their benefit-risk assessment in a patient-centric way. This can be of particular value when patients are willing to accept more risk for a given benefit or less benefit for a specific level of risk than reviewers might otherwise expect.

Identifying subgroups of patients that would prefer a technology under review. Patient preference information can be helpful to identify subgroups of patients with decision-relevant differences in

preferences, particularly those subgroups who would be willing to accept the currently known benefit-risk tradeoffs of the technology under study. As outlined in the FDA Benefit-Risk Guidance, a key regulatory consideration is whether there is a significant subgroup of patients that is willing to accept the risks of a particular technology given the benefits that it offers. An important value of patient preference information in the regulatory process is helping to identify if there is a subpopulation of patients (if not all patients) that is willing to accept the benefit-risk tradeoff offered by a particular technology.

Subgroups of patients may be defined by traditional demographic or disease categories, such as age, gender, race/ethnic background, disease severity, trajectory of disease, or refractoriness to other treatments. Patient subgroups may also be identified by preferences themselves, particularly if there is a subset of patients with the disease that, because of greater risk tolerance, higher valuation of the benefits, greater tolerance for uncertainty, or some combination of those factors, would prefer a specific treatment when other patients would not. As is discussed in more detail in Section VI, if there is an identifiable subset of patients that would use the product that cannot be defined based on traditional demographic or clinical characteristics, but that can be identified based on preferences, such products might be labeled for those patients expressing that preference.

Building a quantitative benefit-risk assessment model. *Patient preference information is essential to bring the patient's perspective into cases where a quantitative benefit-risk model is used to inform a product approval decision.* While generally not needed in most regulatory situations, such quantitative benefit-risk models can be particularly valuable in those few complex cases where there is a mixture of several important benefits and harms, some favoring the study technology and some favoring the comparator, such that quantitative modeling is the best way to understand benefit-risk tradeoffs. The preferences can be used as weights to scale differences in probability or severity of benefits and harms to reflect their importance to patients.

By helping frame risk-benefit issues from the patient's perspective, the use of patient preference information in a benefit-risk assessment for regulatory approval can help ensure that such an assessment is "patient-centric" and reflects the patient perspective. By using patient preference information to help identify at least a subset of patients for which benefits exceed risks, patient preference information supports the approval of a product for that subset of patients even if the benefit-risk analysis for the "average" patient or for the majority of patients with the disease would not be indicated for the product. And for more complex cases, patient preference information can support quantitative benefit-risk modeling. Used in these ways in a patient-centric regulatory approval process, patient preference information helps ensure that products are appropriately approved for the subgroups of patients that would choose to use those products based on their benefits and risks.

Building a Body of Knowledge About Patient Preferences

The assessment of whether the benefits of a technology exceed the risks for a particular patient population is central to the decision to approve the product. Such a benefit-risk assessment is usually based not just on one study, but on a body of knowledge about the product that has been built over time. While a major pivotal trial may provide critical information on the benefits and harms of the technology, the design of such trials is usually based on knowledge derived from existing literature about the disease and its treatment, experience with other devices used to treat the same disease, and earlier pre-clinical and clinical studies of the device in question. Indeed, a key element of every product approval application is communicating to the reviewers the body of knowledge about the disease state, the current therapies available, and the demonstrated safety and effectiveness of the product under consideration.

Similarly, information about patient views of benefit and risk for a given technology can contribute to the body of knowledge about a product and thereby help inform this benefit-risk assessment. In essence, a body of knowledge about patient preferences can be a subset of the broader body of knowledge about the product. While one major preference study may provide critical information about patient preferences regarding a product, such a major preference study could, and probably should, be designed based on prior literature about patient preferences in the particular disease state, information on patient preferences about prior products, and information gathered earlier in the product development process about patient preferences. The application for approval could then communicate to reviewers the full body of patient preference knowledge about the disease state, about alternative products, and about the product under consideration to help inform the benefit-risk assessment for that product approval.

In building a body of knowledge around patient preferences for regulatory purposes, it might be helpful for the sponsor to “begin with the end in mind,” that is to start with the goal of obtaining regulatory approval for the product and consider the patient preference information that might be helpful to the benefit-risk assessment needed for that regulatory approval. The sponsor, perhaps with input from FDA staff, can then work backwards from the regulatory benefit-risk assessment to identify how a body of knowledge about patient preferences can be built up through the product development and regulatory processes, as will be discussed in more detail later in this section.

Before discussing this approach to building up the body of knowledge about patient preferences further, it is helpful to think about how patient preference information can be collected and used at each stage of the product lifecycle.

Patient Preference Information and the Product Lifecycle

The key stages of the Product Lifecycle can be described in terms of typical activities that occur during the product development process, including the relationship of each activity to steps in the regulatory process, such as design controls, that are required for regulatory approval. Exhibit 4-1, “Incorporating

Patient Preferences into the Medical Device Total Product Lifecycle,” is a diagram developed by CDRH staff to illustrate the major steps in the product development process and how patient preference information might be collected at each stage to enhance product development and help build the body of patient preference information that informs the regulatory approval decision as well as serve post-market purposes. Each step is discussed briefly below.

Discovery and Ideation. This stage often consists of basic market research, gathering key stakeholder (patient, payer, and physician) inputs through a variety of means to characterize clinical needs for a new product. This may include literature reviews of the safety, effectiveness, and gaps associated with existing procedures and therapies to understand benefits and risks. Informal, proof of concept testing in animals may occur to demonstrate feasibility and generate intellectual property. Information gathered from patients regarding their view of the disease and preferences regarding existing treatments can help innovators understand the clinical needs and the characteristics of the new technology required for success. This phase often includes a focus on understanding the clinical, commercial, organizational, and technical risks of the new opportunity and developing plans to address them.

Given that details on the full range of benefits and risks of a new technology are generally not known at the time of conceiving of the technology, much of the patient preference information that can be collected at this early stage in the product development process will likely be qualitative more than quantitative. Nevertheless, such information from patients, even if qualitative, can be quite helpful in defining important attributes or features of the product and in thinking about what additional information will need to be captured going forward through the product development process.

Invention and Prototyping. At this stage, the concept and market assessment is mature enough for an organization to commit resources to begin a formal development effort using design controls, often culminating in the execution of clinical studies. Key steps relevant to patient preferences include:

- *Design and development planning efforts to schedule key activities required to bring the product to market.* This planning stage will often include characterizing the clinical, regulatory, and reimbursement pathway to commercialization, including the need for clinical trials. Such planning can include considering what additional information about patient preferences might be valuable to framing benefit-risk issues and building the body of knowledge needed for the regulatory benefit-risk assessment of the technology.
- *Development of design inputs and specifications.* This includes **Invention** that contains further details on the concepts developed in the Discovery and Ideation phase and **Prototyping** of the proposed design to assess its ability to meet key stakeholder inputs using **Pre-Clinical Testing** techniques. Patient feedback on initial designs may be helpful in this process, not only on attributes of the products themselves, but also on how patients perceive the benefits and risks of

this technology versus other options. Much of this feedback may be qualitative, although some quantitative information may be captured at this stage as well.

- *Design Verification. Pre-Clinical Testing* (e.g., animal studies, modeling, electromechanical testing, and software testing) to show that the finished design meets the design specifications.
- *Design Validation. Pre-Clinical Testing* (modeling and simulation), risk analysis, and **Clinical Trials** to ensure that the finished device meets stakeholder (patient, payer, and physician) needs. Again, patient feedback from early clinical use, both qualitative and quantitative, is often very valuable in design iterations.

Clinical Testing. This stage begins when prototype products are moved into formal human clinical trials in the U.S. or abroad. Such testing may begin with feasibility studies, followed by one or more larger clinical trials to demonstrate safety and efficacy. Information collected on patient preferences and key concerns can help inform clinical trial design. Clinical trials can offer an opportunity to collect additional feedback from patients both on the technology itself and their preferences about the use of this technology compared to other alternatives. As data about the actual benefits and risks of a product increases based on clinical trial results, patient preference studies can become more specific to the product itself and more quantitative.

Regulatory Approval. When FDA issues an order approving a product for marketing in the U.S., it approves the specific product labeling and may also specify additional post-approval requirements. As discussed earlier in this section, patient preference information submitted for regulatory approval can help frame benefit-risk issues from a patient perspective, help identify a population of patients for whom the benefit exceeds the risk, and, if needed, help inform a quantitative benefit-risk tradeoff model.

Product Launch and Reimbursement. The scope of the product launch is dictated by company strategy and the availability of reimbursement for the new technology. A company may undertake a full market launch, or the initial product launch may be limited to a small group of initial physicians or hospitals to test marketing strategies, obtain additional stakeholder feedback, and develop additional longer-term outcome data to support reimbursement. Initial launch may be limited by reimbursement issues, particularly if new coding, coverage, and payment levels need be established before providers will use the technology. As will be discussed in Section VII, patient preference information may supplement clinical data on technology safety and effectiveness in such reimbursement discussions. Additionally, patient preference issues may help guide informed consent or shared decision making efforts around a new technology.

Post-market Monitoring. During commercialization, additional data on safety and effectiveness, as well as customer satisfaction, may be gathered by actively conducting post-market studies (including FDA-mandated post-approval activities) and seeking customer feedback about product use. Knowledge gained

during post-market monitoring may trigger product changes, leading back into the discovery and ideation phase (e.g., application to a new disease state) and the product development process (e.g., evolutionary design changes). In addition to clinical data and traditional customer feedback, formal studies of patient preferences may help inform product changes, regulatory considerations around expanding the indications/labeling for the technology, and perhaps the risk assessments underlying product recalls.

Exhibit 4-2, “Patient Preference Information and the Product Development Lifecycle,” provides additional thoughts on the role patient preference information (PPI) can play at each stage in the product development lifecycle. The table focuses on how information collected at each stage of the process can help inform each of the major uses of patient preference information in the regulatory approval decision: framing benefit-risk (B/R) issues, defining subpopulations for which benefits exceed risks, and informing quantitative benefit-risk tradeoff models. It also highlights other uses of patient preference information collected at each stage and offers some additional comments about patient preference information.

Early Planning for Collecting Patient Preference Information

As discussed above, the body of knowledge about patient views of benefit and risk for a given technology collected throughout the product development process can help inform the regulatory benefit-risk assessment for product approval. Again, it is reasonable for sponsors, perhaps with input of FDA staff, to consider the patient preference information that is needed for the regulatory approval decision, and then decide how best to collect this information during the pre-approval portion of the product lifecycle. Starting with consideration of what information about patient preferences would be helpful in the FDA regulatory approval decision, the sponsor, perhaps with FDA staff input, can work backwards through the product development cycle to identify opportunities earlier in the cycle to collect such information. To this end, sponsors need to make sure that the planning for obtaining patient preference information begin early in the product development lifecycle to make sure such information is available to inform later product development, regulatory approval, product launch, and reimbursement decisions. In the CDRH Benefit-Risk Guidance, the FDA “encourages any sponsor that is considering developing such data [on patient tolerance for risk and perspective on benefits] to have early interaction with the appropriate FDA review division.”^{1(pp11-12)}

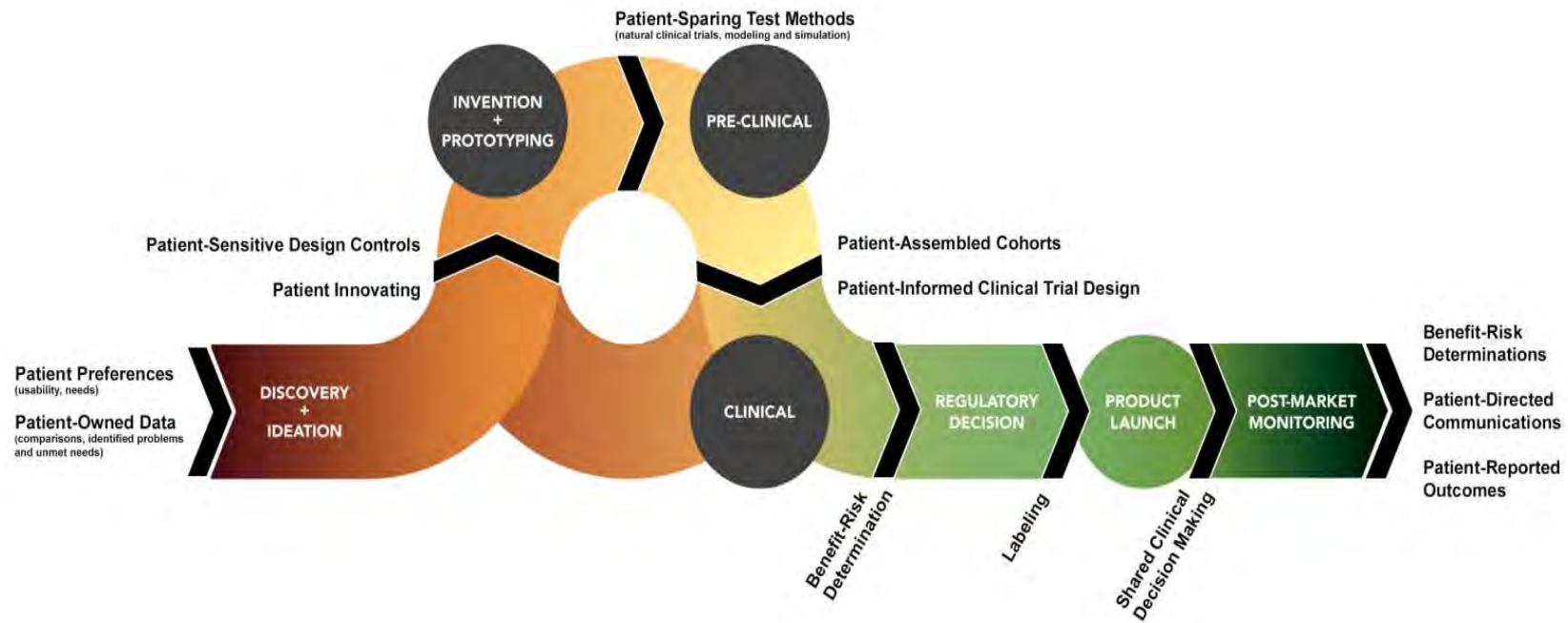
Sponsors may want to start understanding issues related to patient preferences long before their discussions with FDA staff. The Discovery/Ideation and Invention/Prototyping stages often occur before the sponsor has any interaction with FDA staff regarding the technology. Information on patient preferences collected prior to interaction with the FDA can provide valuable background information that can help inform initial discussions about regulatory requirements, clinical trial design, and what additional patient preference information might be valuable to the regulatory approval process. These early stages of product development can also be a good time to initiate interactions with the FDA regarding the product concept to discuss the appropriate regulatory pathway and the potential value of patient preference information.

It is important to recognize, however, that many of the risks that may occur with a particular technology may not be known until the end of pivotal trials. Conducting patient preference studies for the purposes of supporting a regulatory benefit-risk assessment without including all key risks can greatly hamper the use of the preference information in supporting an application. In some cases, it may be necessary to delay collection of patient preference information until after the pivotal study, but before submission for regulatory approval. The decision when best to conduct preference studies will depend on knowledge of the treatment's mechanism of action, information on prior treatments of the same class, results from studies conducted to date, and clinical judgment, and is an appropriate topic for sponsor/FDA discussions.

This section of the Framework Report has focused on when in the product lifecycle information on patient perspectives and preference can be collected and how that information might be used to help inform the product development process as well as regulatory approval decisions. Section V discusses the "how" of collecting patient preference information by summarizing Appendix A of this report, the "Catalog of Patient Preference Assessment Methodologies," which reviews the range of quantitative methods available to assess patient preferences, and discussing considerations in method selection for assessing patient preferences in a particular situation.

Exhibit 4-1

Incorporating Patient Preferences into the Medical Device Total Product Lifecycle



Source: FDA Center for Devices and Radiological Health (CDRH)

Exhibit 4-2: Opportunities for Collection and Use of Patient Preference Information during the Product Development Lifecycle

PPI = patient preference information; B/R = benefit-risk

<u>Lifecycle Stage</u>	<u>Framing B/R Issues</u>	<u>Defining Subpopulations</u>	<u>Other Uses (including Quantitative B/R Models)</u>	<u>Comments</u>
Discovery and Ideation	<ul style="list-style-type: none"> Characterizing the need for and important attributes of a new product by examining the B/R associated with existing procedures and therapies 	<ul style="list-style-type: none"> Identifying patients for whom new product might apply 	<ul style="list-style-type: none"> Using PPI and patient risk tolerance to frame B/R tradeoffs associated with existing procedures as an input to product design steps above 	<ul style="list-style-type: none"> Helpful to start thinking about patient preferences from the early days of need assessment
Invention and Prototyping	<ul style="list-style-type: none"> Understanding how patients think about B/R may lead to creative insights/ideas about product design 	<ul style="list-style-type: none"> Understanding perspectives of subpopulations with disease may lead to creative insights/ideas about product design 	<ul style="list-style-type: none"> Preliminary risk analysis from PPI drives patient-specific design controls as part of product specifications PPI gathered during “formative” testing of prototype usability* 	<ul style="list-style-type: none"> Early patient feedback can be valuable in prototyping phase and can help refine understanding of B/R issues important to patients
Pre-clinical Development	<ul style="list-style-type: none"> Seek early patient feedback on key design elements Seek early patient input on what outcomes are important 	<ul style="list-style-type: none"> Early patient feedback may identify patients subgroups particularly interested in product Preclinical testing might identify limits on 	<ul style="list-style-type: none"> Patient-specific design controls can be used during pre-clinical design verification testing 	<ul style="list-style-type: none"> Gather PPI during non-clinical trial validation studies involving users

* Usability engineering and testing is described in more detail by International Electrotechnical Commission (IEC) 62366:2007, Medical devices—Application of usability engineering to medical devices and American National Standard Institute / Association for the Advancement of Medical Instrumentation ANSI/AAMI HE75:2009, Human factors engineering –Design of medical devices.

		technology that affect the patient population targeted	<ul style="list-style-type: none"> Risk analyses finalized with results of formative testing 	
Pre-submission Interactions between Sponsor and CDRH Staff	<ul style="list-style-type: none"> PPI used to help define B/R issues identified as part of B/R process (as outlined in CDRH B/R Guidance) PPI can help sponsors and FDA understand the relative importance of different benefits and/or risks as well as how patient might tradeoff benefits and risks Identify gaps in PPI that would be valuable for regulatory decision 	<ul style="list-style-type: none"> PPI used to inform staff about heterogeneity of patient perspectives on benefit and risks Identification of gaps in understanding of how patient subpopulations think about B/R 	<ul style="list-style-type: none"> PPI can help identify need for quantitative B/R model in areas with significant B/R tradeoffs and inform design of such models Sponsors may identify gaps in PPI that would be valuable to fill for reimbursement, marketing, informed consent, and shared decision making (see Section VII) 	<ul style="list-style-type: none"> Most important decision during this phase is whether patient preference information would be valuable in regulatory evaluation of the technology in question per factors discussed in Section III; in many cases it, it is not needed.
Clinical Trial Design and Execution	<ul style="list-style-type: none"> PPI can be used to help define primary and secondary endpoints Clinical trial can be an opportunity to collect information on patient impression of B/R of product and whether patients would choose technology over alternatives 	<ul style="list-style-type: none"> PPI used to help define patient populations/enrollment criteria PPI used to define subpopulations for analysis 	<ul style="list-style-type: none"> Quantitative PPI used to supply weights for factor weights in quantitative B/R models. Identification/collection of information useful for reimbursement, marketing, future product development, and/or shared clinical decision making Patient-specific design controls, including instructions for use, 	<ul style="list-style-type: none"> Most efficient to collect information on patient preferences during clinical trials, but in some cases may have to wait until actual benefits and risks are known from clinical trial results

			validated from patient feedback gathered during clinical study and other “summative” testing of product design	
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Regulatory Approval Submission/Regulatory Decision	<ul style="list-style-type: none"> • PPI needed to bring patient perspective into B/R assessment • PPI can be used to identify B/R issues, measure relative importance of B/R issues to patients, and to show how patients tradeoff benefits and risks (see Section V) 	<ul style="list-style-type: none"> • Identify heterogeneity in patient risk tolerance and in valuing of benefits • Define subpopulations based on symptoms, severity, or other illness characteristic that would choose technology based on B/R • Define subpopulations based on preferences – need to specify how to inform patients and identify those that would choose the product 	<ul style="list-style-type: none"> • Quantitative B/R models may inform FDA decisions in areas with significant or complex B/R tradeoffs • PPI helps focus PMA conditions of approval or post-market surveillance requirements on important remaining B/R questions 	<ul style="list-style-type: none"> • Regulatory decisions incorporating PPI may be based primarily on a single preference study or may be based on body of knowledge about patient preferences that is built over prior steps in product lifecycle
Post-Approval				
Post-market studies	<ul style="list-style-type: none"> • PPI can help frame B/R issues and clinical value for post-market studies and regulatory evaluation • PPI can help in designing and interpreting trials on expanded indications 	<ul style="list-style-type: none"> • PPI can help in designing and interpreting trials in expanded target patient populations 	<ul style="list-style-type: none"> • Collect PPI to support reimbursement efforts, refine market strategy and messaging • Refine information for patients and providers, and to develop shared decision making tools 	

			<ul style="list-style-type: none"> Collect PPI to help identify areas for further product development 	
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Post-market Launch	<ul style="list-style-type: none"> Use PPI to identify/frame additional opportunities for label changes and/or new indications Use PPI to understand the significance of emerging safety issues and their impact on the product's B/R profile 	<ul style="list-style-type: none"> Use PPI to identify to expand subpopulations indicated Use PPI to identify opportunities for the technology in other disease states 	<ul style="list-style-type: none"> Marketing: help define target patient population, key messages, and launch strategy to optimize initial adoption and success rates Shared decision making: B/R information important basis of informing patients regarding product use decisions Actively and passively obtain PPI to identify new design features and design changes 	
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Section V: Factors to Consider in Undertaking a Patient Preference Study

Beyond issues regarding in what situation and when in the development cycle patient preference information might be helpful, a topic of critical importance is how to obtain information on patient preferences. While a detailed “how to” guide on designing and implementing patient preference studies is beyond the scope of the PCBR Project, this section of the PCBR Framework Report discusses issues to consider when planning to undertake a patient preference study. The section describes briefly the process of developing Appendix A of this report, the “Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies,” and summarizes the methods cataloged. It then discusses factors to consider in selecting a method for a patient preference study. This section also suggests questions that sponsors, FDA staff, or others should address when designing such a study.

Background on Appendix A: Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies (the “Catalog of Methods”)

There are many methods that can be used to elicit patients’ preferences. These methods have different theoretical foundations and have been developed and applied in different research disciplines. Some have originated in economics, others in consumer marketing, others in decision analysis, and several in health services research. Because benefit-risk preference analysis is an emerging field, researchers in this area may not be aware of the variety of assessment methods available, what they measure, how they are used, and important differences among them.

In undertaking the Patient Centered Benefit-Risk Project, the Steering Committee quickly realized that there is no compendium of existing methods to collect and analyze information on patient preferences regarding the benefits and risks of a medical technology. As described in more detail in Appendix A, the PCBR Steering Committee contracted with RTI Health Solutions to oversee the creation of a “catalog” of methods for assessing patient preferences. To oversee the work, the PCBR Steering Committee created the “Catalog Working Group,” the members of which are listed in Exhibit 1-3. RTI Health Solutions, in conjunction with the Catalog Working Group, created the “Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies.”

Both qualitative and quantitative methods can be used to elicit information about patients’ preferences for benefits and risks associated with medical technologies. Qualitative methods are designed to gain an understanding of patients’ thoughts, feelings, and experiences in an unstructured or semi-structured manner. While the concepts of interest are broadly defined before interacting with patients, patients are encouraged to share and provide input without restrictions. The most commonly used qualitative methods are individual interviews and focus groups, although open-ended survey questions and social media also provide the opportunity to capture qualitative data. Typically, information gathered using qualitative methods is organized using some form of thematic analysis. While qualitative methods may

also yield data that can be summarized numerically (e.g., the percentage of patients reporting a specific symptom, treatment benefit, or side effect), quantifying patient responses is not the primary objective of these methods.

Within the context of benefit-risk assessments, qualitative methods often are used to identify issues that are important to patients in managing their disease and in evaluating treatment options. In fact, qualitative research, particularly concept elicitation, is often an important early step in the development of more rigorous studies designed to quantify benefit-risk preferences. The development of most quantitative patient-preference studies relies heavily on qualitative research to help identify the important benefits, risks, and other factors that will be evaluated by the quantitative study. While qualitative methods may also provide an indication of patients' preferences among medical technologies, these methods are not optimal for quantifying the relative importance of treatment attributes or patients' willingness to trade off among attributes.

In contrast to qualitative methods, quantitative methods are structured, with the type of data to be collected clearly defined and the response options limited to permit statistical analysis. For example, benefit-risk preference studies are explicitly designed to provide quantitative estimates of preference weights or the rate at which patients are willing to trade off among the benefits and risks of a medical technology.

Quantitative and qualitative methods need not be used in isolation and may actually prove most powerful when used in combination. For example, a survey that is primarily quantitative may include open-ended questions that provide supplemental information that can be analyzed using thematic analyses, and quantitative tasks such as rating or ranking may be included within a qualitative study to provide numerical outputs.

While both qualitative and quantitative methods can be used to elicit patients' benefit-risk preferences, qualitative methods alone will likely not provide the level of information required to inform regulatory benefit-risk assessments. Therefore, the Catalog of Methods in Appendix A focuses on quantitative methods for collecting and analyzing patient preference data.

The first step in developing the Catalog of Methods was to develop a definition of "patient preference methods:"

Patient preference methods are methods for collecting and analyzing data that allow quantitative assessments of the relative desirability or acceptability to patients of attributes that differ among alternative medical treatment approaches.

As noted above, the preference methods included in the Catalog are quantitative. Desirability refers to preferences for positive outcomes or attributes (i.e., benefits). Acceptability refers to aversion to

negative outcomes or attributes (i.e., harms). In addition, benefit-risk preference measures are most useful when preferences for one attribute can be directly compared to preferences for all other attributes that matter to patients. Therefore, methods should provide information on “relative” preferences. Finally, because the ultimate purpose of benefit-risk analysis is to evaluate the benefit-risk balance between treatment alternatives, it is patient preferences for differences in the attributes of alternative medical treatments that matter most. While this Framework Report is focused on patient preferences regarding medical technologies, the definition more broadly includes assessing of preferences regarding medical treatments since technology-based approaches may be compared to drugs and other non-technology treatments.*

The definition of patient preference methods above focuses on methods that elicit relative preferences over attributes of a medical technology. However, there are preference methods that provide information about preferences for different medical technologies, but that do not provide information about relative preferences for or aversion to individual attributes of medical technologies. While these methods do not meet the strict technical requirements of the definition presented above, they are potentially valuable methods and are included in the Catalog for completeness.

The second step in developing the Catalog was to develop a set of principles that could be used to guide the selection of methods for inclusion in the Catalog. These principle are listed in Exhibit 5-1.

Exhibit 5-1: Principles for Including Methods in the Catalog

- The method should provide information on the relative importance of or tradeoffs among attributes that differ among alternative health interventions or diagnostic strategies, either directly or indirectly.
- The methodology, analysis, and interpretation of results of the method should be published in peer-reviewed literature.
- The method should have been applied previously to health interventions.
- The method should be able to be applied to eliciting patient preferences, even if the method is typically applied to elicit preferences or evaluations of stakeholders other than patients.

The methods identified in this step by the Catalog Working Group are presented in Exhibit 5-2. This list of methods was developed by the consensus of this working group with input from the Steering Committee. The Catalog Working Group did conduct informal searches of the literature to identify methods; however, a systematic review of the literature was not conducted. Therefore, some possible

* One treatment alternative that is available in all situations is to do nothing (i.e., no active treatment). In situations where there is no alternative therapy to the one under considerations, preferences can be assessed for the attributes of the medical technology compared with no active treatment.

methods for assessing patient preferences may have been overlooked or determined by consensus to be inappropriate for inclusion in the Catalog.

Exhibit 5-2: List of Methods Included in the Catalog

Group	Method
Structured-weighting	<ul style="list-style-type: none"> ▪ Simple direct weighting ▪ Ranking exercises ▪ Swing weighting ▪ Point allocation ▪ Analytic hierarchy process ▪ Outranking methods
Health-state utility	<ul style="list-style-type: none"> ▪ Time tradeoff ▪ Standard gamble
Stated-preference	<ul style="list-style-type: none"> ▪ Direct-assessment questions ▪ Threshold technique ▪ Conjoint analysis and discrete-choice experiments ▪ Best-worst scaling exercises
Revealed-preference	<ul style="list-style-type: none"> ▪ Patient-preference trials ▪ Direct questions in clinical trials

The final step in developing the Catalog was to evaluate each method against criteria identified by the Catalog Working Group as important to understanding the method and its ability to provide useful preference information for a patient-centered benefit-risk analysis of a medical technology, and how the usefulness of the methods depends on the stage of the product lifecycle. The criteria against which each method was evaluated address how the method is implemented, the type of patient sample in which the method can be implemented, the ability of the method to generate useful outputs, and the resources required to use the method. The evaluation of each method is not a rigorous or systematic review of the method. Neither is it intended to provide a detailed “how to” guide for implementing the method. Instead, it is intended to provide a high-level assessment and general characteristics of each method to sponsors, FDA staff, and others. Each method identified in Exhibit 5-2 is summarized and assessed based on these criteria in the Catalog of Methods in Appendix A.

The high-level evaluation of the methods contained in the Catalog should help those interested in pursuing a patient preference study to better understand the methods available and to identify the methods that might be of greatest value in their particular situation. The factors outlined below are designed to help sponsors, FDA, and others consider the important patient preference issues related to the area they want to study, which methods might best fit their research question, and what resources are required to undertake their studies.

Factors to Consider in Selecting a Method to Assess Patient Preferences

While the Catalog of Methods in Appendix A provides an overview of most methods available to assess patient preferences, the challenge for sponsors, FDA staff, or others who want to assess patient preferences is how and when to design and implement a patient preference study. Designing and implementing a preference study is dependent on numerous considerations, including the level of existing knowledge about benefits and risks in a particular clinical situation, the ability of each method to provide the type of patient preference information needed for the particular benefit-risk assessment, and the resources and experience of the organization undertaking the study. Designing and implementing a patient preference study does not follow a cookbook process, but requires judgment on the part of the organization undertaking the study.

Rather than providing a prescriptive approach, this section outlines three sets of factors to consider when undertaking a patient preference study:

- Factors related to defining the research question;
- Factors related to the fit of particular methods to the research question;
- Factors related to the resources available to undertake a patient preference study.

Each set of factors is discussed in more detail below.

Factors Related to Defining the Research Question

A critical first step in designing a patient preference study is defining the research question, specifically what are the benefit-risk issues for which patient preference information is needed and from which patient population such information is needed. The greater the clarity on the benefit-risk issues and the patient population that needs to be studied, the more straightforward it will be to design a patient preference study.

Role of preference patient preference information. The choice of method depends critically on whether the preference information is intended for use in defining strategic requirements for a device, informing the design of a clinical study (e.g., endpoint selection), providing evidence for a transparent and defensible regulatory benefit-risk assessment, identifying subgroups of patients with decision-relevant differences in preferences, or providing information to support reimbursement.

The requirements of a preference study intended to support strategic planning and informing the design of a clinical trial will generally be less than those required to support a regulatory benefit-risk assessment. Preference methods used in strategic planning or trial design often can be simpler (e.g., smaller sample size, less need for statistical rigor) or potentially qualitative in nature. In contrast, the

standards required of studies used for regulatory purposes likely will be higher than those for non-regulatory purposes, including greater emphasis on statistical rigor and the ability to audit and validate the study results. Indeed, the requirements of patient preference studies used for regulatory purposes may be similar to the standards required of clinical trials.* Identifying subgroups will typically require large sample sizes and methods that provide statistically meaningful measures of the differences between the subgroups. Such generalizations about sample sizes and methods might not apply to specific situations, however. In the end, the specific requirements for a patient preference study will need to be assessed on a case-by-case basis reflecting the goals of that study and the way the information from that study will be used.

Current level of knowledge of the benefits and harms of the medical technology. The current level of knowledge of the benefits and harms of a medical technology will influence the type of patient preference method that may be useful. Fundamentally, the purpose of a patient preference study is to provide context around objective data regarding the benefits, harms, and related attributes of a medical technology. The more information that is currently known about benefits and harms, the more straightforward the selection and application of a study method will be. Knowledge of benefits and harms can be divided into four broad categories:

- *Very little or nothing is known about the actual benefits and harms of the device.* When little is known about the outcomes or attributes of a device, identifying the potential attributes that matter to patients will provide much greater value than any attempt at quantitative preference assessment. It likely is not necessary to quantify how important each of these attributes is or the tradeoffs that patients are willing to make among them. Therefore, qualitative research methods will have a much greater role (such as to identify the benefits and harms that matter to patients as well as those that do not matter) than will quantitative methods.
- *There are known potential benefits but little is known about the potential harms of the device.* Often the actual or expected benefits of the device are well-known. However, the potential harms associated with a device may not be known because of novelty of the device, the novelty of its application, or because clinical studies have not been completed or those studies completed to date were not powered to detect or quantify potential harms. In this case, if there are a number of potential benefits, assessing the relative importance of the benefits can be instrumental in determining a device development strategy and selecting primary and secondary endpoints in future trials. Quantitative methods would be useful for assessing the relative preference for benefits. It may also be important to identify which potential harms matter to patients and which do not. Identifying harms that matter may be easier in this case than in the previous case because the

* As of the date of publication of this report but independent of MDIC PCBR Project, CDRH was developing a draft guidance regarding the collection and use of patient preference information that will likely address the requirements for patient preference information used in the medical device regulatory process. It is anticipated that this draft guidance will be released in the spring of 2015.

harms may be limited to those that, alone or in combination, could potentially offset the known or expected benefit.

- *The benefits and possibly some of the harms are known, but the probability of benefit is uncertain and the full range of potential harms and their probabilities are unknown.* In this case, as above, qualitative evidence may be sufficient to identify harms that matter. However, having information about the actual or expected magnitude of the benefit, even if data on the device are highly uncertain, provides an opportunity to quantify the harms' importance when weighed against the actual or expected level of benefit. In this case, it may be desirable to quantify the relative importance of harms, both known and potential, compared with different levels of expected benefit. Depending on the purpose of the study, it could also be important to elicit detailed information about the degree to which patients are willing to tradeoff benefits and harms over the ranges of possible benefits, known or expected harms, and hypothetical harms, even if the probability of occurrence of the hypothetical harms is very low or unknown. Quantitative methods will be valuable in this case.
- *The benefits and harms and the probabilities of each benefit and harm are well known.* When benefits and harms and the probabilities with which these occur are well known, it is possible to use advanced methods to understand the degree to which patients are willing to trade off among these outcomes. The more the benefits and harms are understood, the more targeted a study can be in eliciting detailed preference information. The level of detail required of a benefit-risk preference study under these circumstances will depend on how the study results will be used.

A clear understanding of the current level of knowledge regarding benefits and risks will help clarify the research question under consideration, and therefore, which methods might best address those research questions. The process of assessing patient preferences becomes more straightforward as more is known about the actual benefits and harms of a technology based on clinical experience.

Patient sample to be studied. A clear definition of the patient sample from which patient preference information needs to be gathered is essential to designing a patient preference study. There are two primary considerations when determining the patient sample to be studied:

- *Inclusion and exclusion criteria.* In a broad sense, the patient population for which the sponsor intends the product to be indicated will define that patient sample. However, there is often a distinction between the clinical trial population that meets study inclusion and exclusion criteria and the population that will use the product after launch. This distinction is well-understood for clinical efficacy and safety measurements, but likely will also be the case for preferences. For example, patients willing to enroll in a clinical trial may have different views on the benefits and harms associated with the treatment of their illness than those who are not willing to enroll. In addition, exclusion criteria may induce a bias in preference for the trial sample relative to the

general population. Finally, information obtained by patients during the screening process may result in preference changes. In some cases, sponsors or FDA staff may want to define the sample frame for a preference study more broadly to better assess a wide range of patient preferences and to collect information that may support not only the current approval but also the potential for label expansion. The decision as to whether preferences should be elicited by patients enrolled in a clinical trial, before or after screening for a clinical trial, or from patients recruited through an alternative source (e.g., a patient panel or patient advocacy group) will require consideration by the sponsor and FDA staff of the particular needs of the patients, the inclusion and exclusion criteria used in the clinical study, and the difficulty of recruiting patients through different means.

- *Diversity of the patient sample.* Diversity* of a sample may be necessary to ensure that the sample matches the diversity of the population whose preferences are relevant for the study. Diversity in a population also is necessary to conduct analyses of subgroups of patients. Diversity can be imposed on the sample by setting targets or quotas for achieving a sufficient sample of patients with a specific characteristic or sets of characteristics to be able to quantify preferences for that group of patients and to compare that group of patients with another group of patients. Characteristics that can be used to stratify a sample could be related to patient demographics (e.g., age or gender), related to health history (e.g., disease stage, prior treatment), or related to patients' experience with a particular technology. Even if diversity is not imposed on the sample, having a diverse sample will allow for the post hoc testing of the effect of observable patient characteristics on preference.

A key challenge in sample selection is avoiding bias in the sample. There are many potential sources of bias, many of which are similar to those in clinical trials and are amenable to the same solutions used in clinical trials. One of the biggest challenges in finding the right sample for a patient preference study is avoiding bias that could be introduced through self-selection. In part, this is unavoidable because patients participating in clinical research or a patient-preference study must consent to participate, though the nature of voluntary patient panels and self-reporting of diagnoses often used for preference studies may require special consideration. It may be that those who choose to participate may have preferences that differ systematically from those who choose not to participate. Another potential source of bias is that patients who have chosen to use a medical technology may be more inclined to believe that the benefits of the device outweigh the risks than patients who have not. Therefore, including only patients who have chosen to use a medical technology in a sample for a benefit-risk preference study may bias the results in favor of the technology. While a full discussion of all the

* The term diversity is used here to describe diversity in characteristics of the population that are known. Diversity is related to preference heterogeneity to the extent that subgroups of patients with a specific characteristic or set of characteristics may have preferences that differ from patients without those characteristics or with different characteristics. This concept differs from unobserved preference heterogeneity, in which that heterogeneity is not explained by observed patient characteristics. The ability of a method to detect unobserved preference heterogeneity is, at least theoretically, independent of the diversity of the sample.

potential sources of bias in sample selection are beyond the scope of this report, it will be important for sponsors and others undertaking patient preference studies to consider potential sources of bias in their selection of a patient sample and how this sample differs from those in associated clinical trials.

Factors Related to the Fit of a Particular Method to the Research Question

Patient preference methods yield information that can be valuable in informing benefit-risk assessments. However, different methods yield different types of preference information. As noted above, some methods provide information about what attributes are important to patients without quantifying the relative importance of these attributes. Some methods provide quantitative measures of the relative importance of different attributes, but do not provide information about the tradeoffs patients are willing to make among these attributes. Finally, some measures yield quantitative measures at the rate at which patients are willing to trade off changes in one attribute for changes in other attributes. In addition to the types of information provided by the different methods, different types of methods require different commitments of time and money as well different expertise to implement.

Type of information needed. The specific research question will help define the type of information needed. Patient preference assessment methods can be used to provide three general types of information, each of which is described below.

- ***Attributes.*** This type of information indicates what matters to patients; that is, which attributes of a medical technology are important to patients when they weigh benefits and risks. This type of information often can be obtained using qualitative methods; however, simpler quantitative methods such as ranking can also be used to separate those attributes that matter to patients from those attributes that do not.
- ***Relative importance.*** This type of information indicates how much each attribute matters to patients. Obtaining this type of information requires using quantitative methods that provide a weight for each attribute. While these weights can be used to infer the tradeoffs patients are willing to make among attributes, this type of information does not necessarily require an in-depth understanding of the tradeoffs.
- ***Tradeoffs.*** This type of information indicates both how much each attribute matters and what tradeoffs patients are willing to make to obtain or avoid a given attribute. While this type of information can be approximated by comparing the weights that patients assign to each attribute, obtaining accurate trade-off information may require quantitative methods designed explicitly for this purpose.

Exhibit 5-3 lists the patient-preference methods included in the Catalog, stratified by the type of information they provide. This categorization of methods is meant to be a guide, because some methods can provide multiple types of information. In general, qualitative methods and simple ranking methods often are sufficient to identify attributes. More quantitative methods used to estimate the relative importance of attributes can be used to determine which attributes are important and which are not, in addition to providing weights for those attributes. If we assume that relative importance of attributes is a reflection of the tradeoffs patients are willing to make between attributes, then methods used to estimate relative importance can also provide trade-off information.²⁵ Methods used to explicitly estimate tradeoffs among attributes can also be used to estimate relative importance²⁶ and to determine which attributes are important to patients and which are not.²⁷

Exhibit 5-3. Patient-Preference Methods Grouped by the Type of Information They Provide

Type of information	Methods
Attributes	Qualitative methods (concept elicitation)
	Ranking
Relative importance	Simple direct weighting
	Ranking (if converted to relative importance scores)
	Outranking
	Time tradeoff
	Standard gamble
	Rating questions
	Best-worst scaling (case 1)
	Best-worst scaling (case 2)
Tradeoffs	Swing weighting
	Analytic hierarchy process
	Threshold technique
	Conjoint analysis and discrete-choice experiments
	Best-worst scaling (case 3)

Revealed preference methods and direct-elicitation methods are not included in Exhibit 5-3 because these methods often provide only an estimate of the extent to which one profile or medical technology is preferred to another. These methods typically do not provide information about the relative importance of individual attributes or about the tradeoffs that patients are willing to make among these attributes. These methods are often supplemented with other patient preference methods to tease out the relative importance of different attributes to the observed decision. These methods could also be used to validate the conclusions implied by other patient-preference methods.

The type of patient-preference information needed probably varies across the product lifecycle. In general, using patient-preference methods to identify attributes will be important in earlier stages; quantifying relative importance will become more important later in the product lifecycle; and quantifying tradeoffs is most important when used to support a formal benefit-risk assessment as part of a regulatory submission. Understanding differences in preferences across a group of patients or identifying subgroups of patients with different preferences may be important in several stages of the product lifecycle, but may be especially important as part of regulatory submissions for products that are preference sensitive or raise challenging benefit risk issues.

Ability of a particular patient population to provide the preference information needed. In general, the more quantitative and complex the method, the more detailed and complicated the process of collecting information from patients becomes. In designing a preference study, it is important to make sure that the patient population can provide the information needed. Children, patients with debilitating health problems, those with cognitive impairment, and those with significant handicaps that limit their ability to read, write, or use a computer to respond to questions, for example, may have challenges providing the information needed for complex, quantitative patient preferences studies. In these cases, eliciting preferences from parents, caregivers, or other proxies for patients are important options to consider.* In determining which patient preference assessment method to choose in a particular situation, it is important to factor in the ability to collect needed patient information.

Factors Related to the Resources Available to Undertake a Patient Preference Study

All preference studies require a commitment of resources and some experience with collecting patient preference information. Studies using most of the patient preference methods in the Catalog require primary data collection. Therefore, a study sponsor and other decision makers should consider the level of resources available for conducting a study and weigh the costs of the study against the expected benefit of completing a patient-preference study before determining which method to use. There are

* The Parent Project Muscular Dystrophy's study of parent preferences regarding treatment for children with Duchenne's muscular dystrophy is a good example of the use of a parent as a caregiver proxy for a child in preference studies.²⁸

basic resource constraints that must be taken into account when determining which method to use when conducting a patient-preference study, as below.

Time available to obtain patient preference information. Most patient preference methods described in the Catalog require primary data collection. Even the simplest studies using primary data collection can take weeks or months to complete. Studies using more sophisticated survey methods can take many months – 6 to 9 months being typical, depending on prior experience with similar preference studies and the availability of sponsor experts to work on the project during survey development. Clinical trials can take years. Therefore, it will be important to determine how much time is available to complete a study before the results are needed. In addition, designing the appropriate study and getting agreement from relevant stakeholders regarding the research objectives and study design will, in and of itself, take time. The time needed for study design and approval should also be factored into evaluating the time required to complete a patient preference study. Rough estimates for the time needed for the different methods are included in the Catalog, but the time needed to plan and complete a patient preference study needs to be evaluated on a situation-specific basis.

Budget available to conduct a patient preference study. Even simple studies using existing data or simple surveys require an investment of time by staff or a research partner. Developing surveys for primary data collection require resources for developing the survey instrument and collecting and analyzing the data. Costs for these types of studies can range from tens of thousands of dollars to hundreds of thousands of dollars depending on the complexity of the study and the cost of collecting data from a sample of patients. Rough estimates for the cost of the different methods are included in the Catalog, but, as noted above, the time and expense of undertaking a patient preference study needs to be evaluated on a situation-specific basis.

Prior experience with conducting patient preference studies. Many sponsors and decision makers are unfamiliar with the full range of patient preference methods that can be used to answer any given research question. Even if a sponsor or decision maker is familiar with one method, he or she is likely unfamiliar with alternative methods for assessing patient preferences. Prior experience is not necessary for conducting a patient preference study; however, greater experience with one or more preference methods can increase the level of confidence that a sponsor or other decision maker has with undertaking the study and using its results. Prior experience will also generally reduce the time and budget needed to complete a successful preference study.

Expertise required to conduct patient preference studies and interpreting and applying patient preference information. Even sponsors and stakeholders who have experience with one or more preference methods may lack the necessary expertise to conduct a patient preference study of sufficient quality to inform a benefit-risk decision. There is also a benefit to having external experts involved in the design, conduct, and analysis of a preference study, as it provides an additional layer of objectivity in the process. When a sponsor or other decision maker lacks the expertise to conduct a study or evaluate

its results, it may be necessary to bring external experts into the process. The availability and cost of outside consultants for specific methods may be an important factor in deciding what method to select for a particular preference study.

How to Use These Factors in Selecting Among Methods

As mentioned in the introduction to this section, the Catalog is not intended to provide a cookbook approach to conducting a benefit-risk preference study. However, there are some broad characteristics of methods that may assist sponsors, FDA staff, and other stakeholders think about the appropriate quantitative method to use in a given situation.

Generally speaking, the complexity of a patient preference study is related to the type of information the study is designed to generate. As described above, there are three different types of outputs:

- Information regarding which outcomes or attribute of a medical technology are important to patients and which are not (Attributes);
- Information regarding the relative importance of different outcomes or attribute of a medical technology (Relative importance);
- Information regarding the tradeoffs among outcomes or attributes that patients are willing to make (Tradeoffs).

Identification of attributes provides less information than relative importance, and relative importance provides less information than tradeoffs. Therefore, these three types of outputs can be placed on a continuum from a low level of information (identification), through a medium level of information (relative importance), to a higher level of information (tradeoffs). Similarly, although with a number of exceptions, the complexity of the methods required to elicit patient preference information increases as the level of information provided by the methods increases.*

The conceptual relationship between the information provided by a method and the complexity of a study using the method is meant to help sponsors and other decision makers think about each method when determining which method(s) will be most useful in achieving their study goals and allowing them to complete the study. However, the relationship between the information provided by a method and the complexity of the method is imprecise and variable based on the specifics of the situation. Therefore, sponsors, perhaps in consultation with FDA staff, will need to evaluate in each situation how well a particular method provides the information needed, and how challenging it will be to complete the specific study given each method that may apply, and then decide which method they want to use in that situation.

* Generalization about relative the complexity of methods or the challenges of using methods is difficult, however, because the complexity or challenge is highly dependent on how the study is implemented.

In addition, sponsors planning to submit patient preference information as part of a regulatory submission should consider the level of burden such a submission represents. Given the goal of a least burdensome path to regulatory approval, sponsors can work with FDA staff to determine the level of information needed to inform the regulatory decision and then determine the study design, including the method to be used, that can provide this level of information in the most efficient or least-burdensome way possible.

Questions for Sponsors and Reviewers to Consider when Deciding on a Preference Methodology

As mentioned in the introduction to this section, the Catalog is intended to present the range of methods that can be used to assess patient preferences, how each method is implemented, the type of patient sample in which the method can be implemented, the ability of the method to generate useful outputs, and the resources required to use the method to collect benefit-risk preference information. Below is a list of questions that sponsors and other stakeholders might consider when choosing among the available patient preference methods.

- *What is the purpose of the patient preference study?* Patient preference information may be useful in guiding internal decisions regarding product development or positioning. They may also be useful in providing data to be communicated externally to other stakeholders, not only FDA staff but also patients, payers, or purchasers of a technology, as discussed in Section VII. As a general rule, data used to guide internal decisions by sponsors may require less statistical rigor than data used to support decision making by external stakeholders, particularly the FDA.
- *Are the data being used to evaluate a single technology against one standard of care, or are they intended to be used to evaluate multiple technologies?* Patient preference methods can be used to evaluate a decision regarding a single technology or to evaluate multiple potential technologies in a given therapeutic or diagnostic area. Using patient preference methods to evaluate a single technology provides an opportunity to target the research to the known or expected benefits and harms, and thus, gain a deeper understanding of patients' preferences for that technology. However, the results of such a study may not be easily applied to other technologies in the same therapeutic or diagnostic area if the attributes of those other technologies differ substantially from those of the technology for which the preference study was developed. In contrast, the results from a preference study designed to evaluate multiple potential technologies may provide information relevant to multiple decisions but may not provide everything a sponsor or other stakeholder may want to know about a specific technology.
- *What are the characteristics of the sample from which patient preferences will be elicited?* Determining the sample from which to elicit patient preferences is key to developing a patient preference study and has substantial implications for the applicability of study results to any given research question. Samples chosen to match the population for which a technology is indicated

provide evidence of the preferences of the group of patients for whom the technology is intended. However, a narrowly defined sample limits the applicability of the study results to other patients for whom the technology may eventually be indicated or other patients who may use the technology in the real world. Conversely, eliciting preferences of a broad sample of patients may allow you to understand the preferences of a broader, and perhaps more realistic, population, but it may not provide sufficient information about a specific subgroup of patients unless the sample includes sufficient numbers of patients in that subgroup.

- *What type of patient-preference data is required for the benefit-risk preference study?* Before designing a preference study, it is critical that a sponsor or FDA determine whether the study is designed to identify benefit-risk issues, designed to assess the relative importance of benefit-risk issues, or designed to assess how patients trade off benefits versus risks around the use of a particular technology.
- *How important is the preference study to the regulatory or market success of the medical technology?* In the end, the decision regarding whether or not to undertake a patient preference study and the method to use in a patient preference study should be determined by the business need, particularly the value in the regulatory approval process. While a patient preference study may provide interesting and potentially useful information, conducting such a study may not make sense if the patient preference information obtained from such a study does not make a significant difference in the assessment of the technology by FDA or other stakeholders.
- *How much time and money is available to support the preference study?* As discussed earlier in this section, the amount of time and money available to support a study will be an important determinant of which methods are feasible to undertake in a given situation and which are not.
- *What expertise is available to assist in undertaking the preference study?* Organizations considering a patient preference study need to assess if they have the expertise in-house or whether they will need to contract with outside experts to undertake the study. If outside consultants are required, the availability and expense of such consultants may be an important determinant of what methods are selected and how the study is designed.

As stated earlier, there is no algorithmic or cookbook way to design and implement a patient preference study. Consideration of the questions above should help organizations think about the research question to be answered, the patient population to be studied, the method to be used, and the time and expense of the study.

Beyond the collection of patient preference information for regulatory purposes, there are a variety of issues to consider about how to use such information in the regulatory process. Section VI of this report

explores a range of questions about the use of patient preference information in the regulatory approval of medical technology.

Section VI: Considerations in Using Patient Preference Information in the Regulatory Process

As outlined in Section I, the MDIC Patient Centered Benefit-Risk (PCBR) Project grew out of FDA and MDIC interest in how patient preference information could be better collected and integrated into CDRH product approval decisions. Previous sections of this report have discussed background concepts regarding patient perspectives and preferences; outlined factors to consider in determining whether collecting patient preference information might be useful in the regulatory evaluation of a particular technology; discussed how patient preference information could be collected at different points in the product development cycle; and discussed considerations in selecting a method to collect information on patient preferences. The purpose of this section of the Framework Report is to discuss the potential use of patient preference information in the regulatory process, particularly key elements, timing, submission, and use of patient preference information in product approval decisions.

This section of the PCBR Framework Report does not take a prescriptive approach regarding how to use patient preference information in regulatory decisions. The regulatory decision making process for approving medical technology is the purview of the CDRH. As discussed in Section I, this report is not intended to make recommendations to CDRH regarding how FDA staff should use patient preference information in benefit-risk assessments. Rather, this section addresses several general considerations in the use of patient preference information in the regulatory process that might be helpful for FDA, industry, and others to consider. Topics addressed by this section of the report include:

- What roles can patient preference information play in informing CDRH benefit-risk determinations regarding product approval decisions?
- How could patient preference information be included in product approval labeling?
- How could patient preference information be included in post-market studies?
- Is patient preference information optional at the election of the sponsor?
- How could patient preference information submitted as part of an approval process be validated and audited?
- When is the right time in the product development cycle to determine if patient preference information should be collected?
- How could patient preference information be collected and used to better understand important benefit-risk issues in new or evolving areas of medical technologies, and thereby help frame development of expectations regarding clinical effectiveness in such areas?

These topics, discussed in more detail below, represent initial questions that arose from PCBR Steering Committee discussions. Additional considerations in the use of patient preference information in the regulatory process will likely arise with greater experience on the part of FDA staff, industry, physicians, patients, researchers, and others with the collection and use of such information.

What Roles can Patient Preference Information Play in Informing CDRH Benefit-Risk Determinations Regarding Product Approval Decisions?

Collecting and using patient preference information can help ensure that the CDRH benefit-risk determination process is patient-centric by helping to identify those benefits and harms most important to patients, by framing the benefit-risk issues and tradeoffs from the patient perspective, by helping to identify whether there are subgroups of patients that would choose to use the technology over other alternatives, and by supporting quantitative benefit-risk modeling.

Outlined in the CDRH Benefit-Risk Guidance, “Patient tolerance for risk and perspectives on benefits” are important factors in FDA benefit-risk determinations regarding the PMA or *de novo* approval of new medical device technologies. The guidance acknowledges the heterogeneity of patient preferences that may exist regarding the use of a technology, and that there may be subgroups of patients that may want to use a particular technology given its benefits and risks even if many other patients would not:

“When assessing such data in a PMA application or *de novo* petition, FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse. Therefore, FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others.”^{1(pp11-12)}

The CDRH Benefit-Risk Guidance goes on to state that if the benefits outweigh the risks for a subpopulation of patients, the product may be approved so that it is available for that subpopulation of patients to be able to use:

“... it may be appropriate to approve a device where only a minority of the intended patient population would accept the risks as weighed against the benefits if the information necessary for patients and health care practitioners to make well-informed decisions is available and can be presented in a manner that can be understood by the practitioners and patients. Patient-centric assessments should take into account both the patient’s willingness and unwillingness to use a device or tolerate risk. Both preferences are informative and helpful in determining patient tolerance for risk and benefit and the benefit-risk profile of a device.”^{1(p12)}

The CDRH Benefit-Risk Guidance recognizes the importance of patient-centric assessment of benefits and risks and the potential value of patient preference information in helping to inform CDRH’s benefit-risk determinations. It goes further to state that if there is a meaningful subgroup of well-informed patients who will accept the benefits and risks of a technology, even if that subset is a minority of

patients, that technology can be approved if patients can work with their health care providers to make informed decisions about the use of that technology. Such technology should be safe and effective and would still be expected to meet the statutory standard for approval, and CDRH's benefit-risk determination takes into account several other factors in addition to patient-centric assessments.

As outlined in Sections IV and V, patient preference information can be useful in informing CDRH's benefit-risk determinations in several major ways:

- to help identify from a patient's perspective what are the important benefits and risks of a technology used to treat a particular clinical condition;
- to assess what is the relative importance to patients of different benefits and risks, and to clarify how patients think about the tradeoffs of these benefits and risks of a technology;
- to help understand the distribution/heterogeneity of patient preferences regarding the use of a particular technology versus other available treatment alternatives; and whether a group of patients exist with the preferences and risk attitudes such that they are expected to choose to use a technology over other options given the benefits and risks of those technologies;
- in situations with complex benefit-risk tradeoff issues, to help develop weights for specific benefits and risks as input into quantitative benefit-risk models. While generally not needed in most regulatory situations, such benefit-risk models can be developed for those few complex cases in which there is a mixture of several important benefits and harms, some favoring the study technology and some favoring the comparator, such that quantitative modeling is a useful way to evaluate benefit-risk tradeoffs. Patient preferences can be used as weights to scale differences in probability or severity of benefits and harms to reflect their importance to patients.

These uses of patient preference information are discussed in more depth below.

Patient preference assessment can help identify which benefits and harms are important to patients, and elucidate how patients think about the tradeoffs of those benefits and harms of a technology.

The CDRH Benefit-Risk Guidance acknowledges the importance of a patient-centric approach to benefit-risk assessment.^{1 (pp11-12)} The guidance acknowledges that patient perceptions of the important benefits and harms of a technology may differ from those of others who do not have the clinical condition, notably FDA staff or physicians. While FDA staff and physician advisors have historically helped define the issues of safety and effectiveness about which sponsors are asked to provide data in the approval process and ranked their relative importance, neither group actually experiences the disease state, is responsible for the ultimate decision whether or not to use the technology, nor bears the consequences of those decisions and actually experiences the benefits and harms of the technology.

From this patient-centric point of view, the CDRH Benefit-Risk Guidance discusses aspects of benefits and risk assessment in which patient preference information can play an important role. First, the

guidance focuses on “probable benefits” and “probable risks” supported by valid scientific evidence, not theoretical benefits and risks.^{1(pp5-6)} This emphasis on probable rather than theoretical benefits and risks based on valid scientific evidence indicates an important role for formal studies of patient preferences which could help FDA reviewers identify what benefits and risks are important from a patient’s point of view.

Second, the guidance explicitly anticipates the collection and submission of information on patient preferences and risk tolerance. Appendix B of the CDRH Benefit-Risk Guidance contains a “Worksheet for Benefit-Risk Determinations” that is designed to help FDA reviewers document the information that forms the basis of CDRH benefit-risk determinations. This worksheet contains areas for summarizing clinical information regarding the types of benefits and harms, the magnitude of benefits and the harms, the probability of the patient experiencing the benefits and the harms, the duration of the benefits and harms, and the level of uncertainty about the clinical data and the generalizability of the results. Much of this information is anticipated to be collected from clinical studies rather than patient preferences studies, but patient preference information could potentially inform some of those categories as well, and potentially be collected within the same clinical studies. Indeed, the worksheet includes a section for information on “Patient tolerance for risks and perspective on benefits,” which includes questions on disease severity, disease chronicity, and a “patient-centric assessment.” This “patient-centric assessment” includes how patients perceive the benefits-risk issues raised by the technology, how they tradeoff benefits and risks, and whether they would accept the risks for the benefits.^{1(pp24-29)} This worksheet explicitly anticipates the collection of information on patient perspectives about the benefits and risks of new technologies, including patient preferences regarding those benefits and risks.

The CDRH Benefit-Risk Guidance summarizes well the types of information that can be collected to help inform CDRH benefit-risk determinations, as listed in the guidance’s Appendix B, the “Worksheet for Benefit-Risk Determinations.” Beyond the questions listed under the section titled “Patient tolerance for risk and perspective on benefit(s),” however, information gleaned from patient preference studies might inform a variety of other categories listed in the worksheet. There are some additional categories of information not included in the guidance worksheet that might be useful as well, which are also discussed in this section.

The following discussion of how the patient perspective can be brought into a variety of the categories of information used in benefit-risk determinations is not intended to be prescriptive about what patient preference information is required for a submission. It is also not meant to imply that, for a given technology, patient preference information needs to be collected in any particular category or that one or more patient preference studies needs to be undertaken. Rather, it is intended to discuss the possibilities for using patient preference information to bring the patient’s perspective into each category of information listed in the CDRH Benefit-Risk Guidance. In the end, sponsors, with or without FDA staff input, will need to decide what information about patient preferences to include in their applications for approval.

Patient preference information can help bring a patient-centric view to the following categories of information:

- *Type of benefits and harms.* While the probable benefits and harms of a new technology may generally be clear to all parties – patients, physicians, FDA reviewers, and sponsors – there may be situations in which patient perceptions of benefit and harms may be different from those of other parties. In particular, physicians and reviewers may not perceive the lifestyle benefits or challenges of a particular technology that might be very important to patients in their consideration of using a particular technology. Collecting information on patient perception of benefits and harms may help ensure that all the probable benefits and harms of a technology that may affect its use are identified and factored into a benefit-risk determination.
- *Magnitude and probability of benefits and harms.* As discussed in the CDRH Benefit-Risk Guidance, the magnitude and probability of the benefits and the harms of a particular technology are central to the benefit-risk assessment process. While clinical trial and observational studies are needed to quantify the magnitude and probability of benefits and harms, studies of patient preferences may provide information useful for understanding the minimal level of benefits and maximum level of harms that are acceptable to patients.
- *Duration of benefits and of harms to patients.* While the CDRH Benefit-Risk Guidance explicitly discussed the importance of assessing the duration of benefits and harms, it does not discuss how the value placed on the duration of benefits or harms may differ between patients, health care providers, and sponsors. Additionally, patients may differ in their willingness to accept lower benefits of longer duration versus higher benefits of shorter duration, or in their willingness to accept lesser harms of long duration versus greater harms of short duration than providers or sponsors might expect.
- *Effect of disease severity.* The CDRH Benefit-Risk Guidance notes that disease severity may affect how patients view the benefits and risks of a treatment. Patient preferences may be influenced significantly by severity of disease. For example, patients more severely affected by a disease may tolerate more risk or accept less benefit than patients less affected by the condition. Understanding how disease severity affects patient preferences may be important in benefit-risk assessment of some technologies.
- *Effect of disease chronicity.* The CDRH Benefit-Risk Guidance discusses how patient adaptation to chronic disease may affect their perspective on benefit and risk. Patient adaptation to their disease can be gleaned from direct patient reporting and from preference studies conducted longitudinally. Such studies may show how this adaptation to chronic disease can change patient tolerance of risk or perception of benefits over time.

- *Effect of disease trajectory and prognosis.* While not explicitly discussed in the CDRH Benefit-Risk Guidance, the trajectory of the disease, particularly whether the disease is stable, worsening slowly, or worsening rapidly will likely affect patients' acceptance of risk or valuing of benefits. Additionally, patients' perception of their prognosis will likely affect patient perspective on risk and benefits, with patients with poor prognosis willing to accept greater risk for a given level of clinical benefit than patients with better prognosis.
- *Patient benefit-risk tradeoffs.* The CDRH Benefit-Risk Guidance places how patients view benefits and risks and whether they would choose to use the technology under the category of "Patient-centric Assessment" information. Clearly, information on how patients trade off benefits and risks to make a decision whether or not to use a technology is essential to a patient-centric benefit-risk assessment. Physicians, FDA staff, or sponsors may have a different view of the tradeoff of benefits versus risks than patients. For example, physicians, FDA staff, or sponsors may be primarily concerned with mortality risk or other objective measures of benefit or harms whereas patients may be more concerned about quality of life issues. People without the disease also may have a different view of the time tradeoffs of benefits and risks than patients. For example, patients could have a different view of the tradeoff between near-procedure stroke risk versus longer-term mortality benefit in the use of percutaneous heart valves than physicians. Patient preference information that not only identifies the relative importance of benefits and risks to patients, but also elucidates how patients think about benefit-risk tradeoffs can help FDA staff take a more patient-centric approach to their benefit-risk determinations for regulatory approval. Additionally, as discussed in Sections IV and V, quantitative information on how patients trade off benefits and risks can be used to develop factor weights for quantitative benefit-risk models that could be particularly useful in complex benefit-risk situations.
- *Informed decision making.* The "Patient-centric Assessment" category in the Benefit-Risk Guidance worksheet includes information about how well patients can understand the benefits and risks of a technology, and what information it takes to enable patients to make an informed decision about the use of the technology. Patient preference studies can provide information that is valuable for this "patient-centric assessment."
- *Availability of alternative therapies.* The CDRH Benefit-Risk Guidance worksheet notes the importance of reviewers understanding the benefits and risks of other treatment alternatives for patients. Beyond the clinical data about the benefits and risks of other treatments, understanding how patients view the benefits and risks of alternatives will help reviewers better understand the minimum level of benefit and the maximum levels of risk that might prompt a patient to choose the new technology over the alternatives. It would also help to identify

whether there is a group of well-informed patients who would choose the new treatment over the other options available.

- *Uncertainty.* The CDRH Benefit-Risk Guidance worksheet notes the importance of understanding the uncertainty of (or the inverse, the confidence in) the clinical results used in benefit-risk determinations. Clearly, FDA reviewers need to understand how confident they can be in the information they are using in their decision making, not just the clinical data, but also the information on patient preferences. Several methods for preference studies provide measures of uncertainty in preference overall or within subpopulations. Additionally, as noted in Section II, patient uncertainty about the likely outcomes of using a technology – the probable benefit and risks – can affect their uncertainty attitude. Understanding how uncertainty concerning benefits and risks affects patient choice about whether to use a technology may be important in regulatory benefit-risk determinations, and also in designing post-approval studies to help improve patient confidence in the use of a technology.

In summary, the CDRH Benefit-Risk Guidance recognizes the value of taking an approach that is more patient-centric when assessing the importance of benefits and risks for regulatory approval. Since it is ultimately the patient that takes on the risks for the promise of the benefits, collecting patient preference information helps FDA staff, sponsors, physicians, and others understand what benefits and risks are important to patients, how they view the value of specific benefits or the concerns about harms, and how they think about benefit-risk tradeoffs. Such information can help ensure a patient-centric approach to the benefit-risk determinations that are core to CDRH approval decisions.

Patient preference studies can help understand the heterogeneity of patient preferences and thereby identify whether there is a subgroup of patients willing to accept the benefits and risks of a particular technology. As outlined in the CDRH Benefit-Risk Guidance, it may be appropriate to approve a product if a minority subgroup of patients that would view that the benefits of a technology exceed the risks, if the information necessary for well-informed decision-making is available and can be presented in a manner that enables a well-informed choice by the patient. Traditionally, subgroups of patients that are indicated for a technology have been defined on patient demographics, such as age and gender, or disease characteristics, such as specific diagnosis, specific physiological parameters, or disease severity. Patient preferences may indeed vary by such demographic or disease characteristics. For example, older patients may view mortality or quality of life issues differently than younger patients do. Alternatively, patients with a more severe form of disease may tolerate greater risks or accept lower benefits than do less severely affected patients. Patient preference information can therefore be helpful in identifying whether there is a subgroup of patients defined by demographic characteristics or disease severity that might choose to use a technology based on the benefits and risks that it offers.

Beyond demographic or disease characteristics, patient preference differences may inherently define a group of patients willing to use a technology. Within a group of patients with a disease that is

potentially indicated for a device, there may be a subset of patients who are sufficiently risk tolerant or who value the benefits so highly that they would choose to use the technology. Identifying that subgroup of patients would require some form of patient preference study that describes the distribution of patient preferences in the targeted patient population and shows a clear delineation of a subset of patients that would choose to use the device.

Patient preference assessment can help support quantitative benefit-risk modeling when valuable to inform benefit-risk assessment. Benefit-risk assessments for regulatory purposes generally do not require quantitative modeling. Most assessments are conducted by assessing the clinical data and other scientific evidence in light of the nature of the disease and medical need, potentially informed by patient preference information. However, there are cases where disentangling the net effect of multiple endpoints, dealing with endpoints that manifest at different times, or interpreting important endpoints that are subjective make benefit-risk assessments challenging. In these more complex situations, quantitative benefit-risk models can sometimes be highly informative. Generally, these models require a combination of statistical data from clinical trials and information from preference studies, with the preference information used as weights to scale differences in probability or severity of benefits and harms to reflect their importance to patients. While a detailed discussion of quantitative benefit-risk modeling in the regulation of medical devices is beyond the scope of this Framework Report, an exploration of the use of such quantitative models in the regulatory process might represent a useful area for future work by CDRH, MDIC, and others.*

In summary, collecting and using patient preference information can help ensure that the CDRH benefit-risk determination process is patient-centric by helping to identify those benefits and harms most important to patients, by framing the benefit-risk issues and tradeoffs from the patient perspective, by helping to identify whether there are subgroups of patients that would choose to use the technology over other alternatives, and by supporting quantitative benefit-risk modeling.

How Could Patient Preference Information be Included in Product Approval Labeling?

As is common with benefit-risk information collected from clinical trials, it may be valuable for patient preference information that is important to a product approval decision to be communicated to providers and patients through the product labeling. Such inclusion may be particularly useful when patient preference information helps define the population of patients indicated for the product in the label or has an important role in the approval decision. If the product is approved for use in a subset of patients defined in part by patient preferences – those patients that would choose to use the product when appropriately informed of the product’s benefits and risks – it may be appropriate for the labeling

* The European Medicines Agency (EMA) undertook a project to explore the use of quantitative benefit-risk modeling in the regulatory assessment of pharmaceuticals, with the results of that project published in 2012.^{38,39}

to include specifics about informing patients of the benefits and risks to help ensure that patients make an informed choice about whether they want to use the product.

Members of subgroups based on demographics or disease characteristics can be readily identified by health care providers, while members of subgroups based on preference will generally require self-identification through provider or sponsor elicitation of preferences from patients. Preference studies may provide information on the distribution of preferences in the study population and in subgroups of patients within that population, but they do not allow a direct, prospective inference of preferences for an individual patient.

In specific situations in which potential risks to a patient are substantial, benefits quite limited, or preference studies indicate that only a small group of patients out of the larger population might choose the treatment, the FDA could consider making documentation of this informed consent process a formal part of the labeling. Such an informed consent approach could help assure that only appropriately informed patients receive the therapy, which also might help mitigate risks that the product be used inappropriately by limiting use to appropriate patients. It is important when considering such an informed consent approach to understand that this would represent a significant burden to sponsors and physicians, and may be most appropriate in limited scenarios in which it is particularly important to identify those patients and to ensure they are well informed.

Such product labels could specify the key elements for informing patients of the benefits and risks of the technology. Such labeling might: 1) make it clear that patients be informed of specific benefits and risks of a technology identified in clinical and preference studies that are important to patient decisions around that technology; 2) include specific FDA-approved information that be presented to patients; and 3) perhaps include an additional FDA-approved instrument to document the patient's choice based on that information. In other words, the label may specify that the indicated population is defined, in part, based on preferences, where appropriate patients are identified by involvement in pre-defined informed consent/decision making process that assures that they are clearly informed of the probable risks as well as probable benefits to them, and have the information needed to make an informed choice whether or not to use the product. *

* An example of such an approach identified during the PCBR Project is the Vision Care Implantable Miniature Telescope (IMT) for vision impairment due to age-related macular edema. The PMA approval letter dated July 1, 2010 includes a requirement for distribution of an informed consent document:

“Informed Consent Process:

3. As part of your formal decision process, you must distribute your approved Acceptance of Risk and Informed Decision Agreement, which will serve as a collective source of information (including patient labeling) for the patient. Both the physician and the patient are intended to sign designated sections in order to best assure that a patient has obtained the labeling in an adequate enough time prior to surgery

Labeling may specify how information about risks and benefits about a technology are communicated to patients. A comprehensive discussion of how best to communicate benefit and risk information to patients is beyond the scope of this report. As discussed in Section VIII, a review of current best-practices for communicating information on benefits and risks to both patients and providers might be a valuable future project for MDIC, FDA, or others. While the information communicated to patients will be situation-specific and depend on the disease state, the technology, and other factors, members of the PCBR Steering Committee did note a few important approaches to such communication. Risks and benefits should generally be conveyed using absolute rather than relative measures since varying baselines make comparing relative measures potentially very misleading. Absolute risk changes may be communicated textually using “common language” phrases that have been shown to correlate with the level of uncertainty corresponding to the absolute risk change. For communication with physicians, forest plots and effects tables are valuable means to summarize such information. For communication of risk and benefit information to patients, well-validated graphical risk communication methods may be useful. **,

How Could Patient Preference Information be Included in Post-Market Studies?

The collection and analysis of patient preference information may be valuable as a part of post-market studies.

Post-market studies are sometimes required as part of FDA approval, particularly for technologies that address a significant clinical need but for which there is remaining uncertainty about benefits and harms, such as long-term performance or rare events. The purpose of those studies is to confirm the value of the technology in the indicated patient population and develop more evidence to reduce the uncertainty regarding the potential risks and/or benefits of the technology. Additionally, sponsors may

to read it and has understood the risks and other information associated with the Implantable Miniature Telescope™”.

This Vision Care IMT informed consent labeling helps to assure that physicians inform patients of the benefits and risks of a technology using an FDA-approved information document that is intended to be signed by both the physician and patient to show that the patient was informed in a timely manner and that the patient understands the risks of the technology. The Vision Care IMT PMA approval letter dated July 1, 2010, p. 3. as downloaded from http://www.accessdata.fda.gov/cdrh_docs/pdf5/p050034a.pdf

* For example, in a grid of 100 or 1000 faces, the proportion of patients with benefits but no risks can be shown with faces that have positive emotions, the proportion of patients with harms but no benefits can be shown with negative emotions, proportion of patients with both benefits and harms can be shown with conflicted emotions, and the remaining proportion of patients with neither harms nor benefits can be shown with non-emotive faces. Other graphical techniques are available as well.

** For an overview of several ways to communicate risk information to patients, see Fagerlin A., Zikmund-Fisher, B. J., Ubel, P. A. (2011). “Helping Patients Decide: Ten Steps to Better Risk Communication.” *J Natl Cancer Inst* 103: 1436-1443.

initiate studies post-approval to support expanded clinical indications or the use of the technology in additional patient populations. Post-market studies generally fall into one or more of the following categories:

- post-market studies to obtain more information about the general benefits and risks of a product;
- post-market studies to examine a particular risk or benefit of the product;
- additional sponsor-initiated studies to evaluate an expanded clinical indication; or
- additional sponsor-initiated studies to evaluate an approved clinical indications for an additional patient population (e.g., pediatric studies of a device approved in adults for the same clinical indication).

Similar to the value of patient preference information discussed for pre-market studies, patient preference information might be helpful in each type of study listed above, whether an FDA-mandated post-market approval study or sponsor studies initiated after approval. As previously discussed, there is no statutory requirement for incorporating patient preference information into FDA decisions. Similarly, there is no requirement for incorporating patient preference information into post-market studies. Rather, sponsors, with or without FDA encouragement, can choose to include patient preference information if they believe it will help better inform post-approval regulatory decisions and enhance the decision processes.

As with the initial FDA approval decision, patient preference studies might enhance post-market assessment and adoption of a particular technology by:

- helping clarify which risks and which benefits are most important to patients;
- helping assess the relative importance of these benefits and risks to patients;
- identifying a population of patients that, based on the benefits and risks of the technology, prefer the technology over other treatment alternatives;
- supporting quantitative benefit-risk models.

Patient preference information may also be valuable should there be a discovery of a different or larger risk in other post-market studies that impacts benefit-risk considerations of the study technology. Patient preference can help frame those risks and whether the patient population would have an interest in continuing to use the product given the new risk information or treatment alternative. Similarly, new information on greater or additional benefit derived from post-market studies may result in the benefit and risks of the technology appealing to a larger patient population, thereby potentially supporting an expanded labeled indication. If sponsors are considering the potential use of such patient preference information collected as part of post-approval studies to support expanded indications for a technology, they may want discuss their plans for post-market collection of patient preference information with the appropriate CDRH staff.

Is Patient Preference Information Optional at the Election of the Sponsor?

Patient preference information is not currently a requirement for FDA PMA, 510(k) or de novo approval, but such information can be viewed as a means of enhancing regulatory submissions to help ensure that benefit-risk determinations are patient-centric. Patient preference information can be included at the option of the sponsor, perhaps based on a suggestion or request from FDA staff.

Patient preference information is not currently a requirement for FDA PMA, 510(k), or *de novo* approvals, so any patient preference information submitted would be at the election of the sponsor. Patient preference information can be considered additional information the sponsor can choose to submit to enhance the benefit-risk assessment process in specific situations. Additionally, as illustrated by the CDRH obesity study⁴ and discussed in more detail later in this section, the FDA might decide to undertake patient preference studies to better understand benefit-risk issues in emerging areas of medical technology.

As noted in the CDRH Benefit-Risk Guidance, when sponsors are considering the use of patient preferences for their submission, it would be helpful to discuss with FDA staff their plans for collecting patient preference information and how that might help in understanding benefit-risk issues around a new technology and/or in identifying subpopulations of patients that will choose the technology given their preferences and uncertainty attitudes.^{1(pp11-12)}

For patient preference information to have significant value in the regulatory process, it would be important for FDA to develop sufficient knowledge and experience with the collection and analysis of patient preference information to provide guidance to sponsors in these discussions. Given that the collection and use of patient preference information is a nascent area in regulatory decision making, it is unlikely in the near term that most FDA reviewers will have much experience with the collection or analysis of such patient preference information. Sponsors, investigators, patient groups, and others bringing such information into regulatory submissions on their own may not only increase the likelihood of approval of a specific medical technology or improve the understanding of patient preferences in a particular disease state, but also help to increase FDA staff familiarity and appreciation of the value of patient preference information.

How Could Patient Preference Information Submitted as Part of an Approval Process be Validated and Audited?

Patient preference data might be audited and validated in a manner similar to how other pre-clinical and clinical data submitted to FDA approval process are audited and validated.

As noted earlier, the CDRH Benefit-Risk Guidance makes it clear that the benefits and risks considered as part of the FDA approval process are those that are based on valid scientific evidence, not just unsubstantiated reports or opinions. Indeed, the guidance states:

“FDA relies on valid scientific evidence in making risk and benefit determinations, including the critical issue of identifying ‘probable risks’ and ‘probable benefits’ in the first place. In general, a ‘probable risk’ and a ‘probable benefit’ do not include theoretical risks and benefits, and instead are ones whose existence and characteristics are supported by valid scientific evidence.^{1(p7)}

Beyond the focus on traditional pre-clinical and clinical data as the source of evidence for benefit-risk determinations, the guidance implies that other information about benefits and risks, such as information on patient preferences, needs to be scientifically valid as well.

As with other pre-clinical and clinical data, patient preference data submitted to the FDA will need to be collected, analyzed, and presented in ways that are consistent with established methods or best practices to be considered as valid scientific evidence. Sponsors can consider patient preference information as another form of clinical data, subject to the same data handling and quality system requirements as other clinical data. The source data for patient preference information submitted to the FDA should be available to be examined by FDA auditors, if so requested. Such patient preference data need to be collected in a way that is acceptable to the FDA, meeting standard data handling requirements, software requirements, patient confidentiality requirements, etc. CDRH is developing a guidance document regarding patient preference information that is expected to discuss issues related to the collection and use of patient preference information data.* Best practices for the collection and presentation of patient preference data is beyond the scope of this report, but should be considered as an area for future work by FDA, MDIC, or others.

When is the Appropriate Time in the Product Development Cycle to Determine if Patient Preference Information Should be Collected?

There is no “right time” in the product development life cycle for collecting patient preference information. Rather, each sponsor will need to decide if such information is needed and then determine when and how to collect that information. The timing for collection of patient preference information can be assessed when the sponsor believes there is a sufficient understanding of the benefits and risks expected with the particular treatment to identify if patient preference information might be valuable in

* As of the date of publication of this report but independent of this MDIC effort, CDRH was developing a draft guidance regarding the collection and use of patient preference information that should be released in the spring of 2015.

the development or regulatory process. Sponsors should consider whether it would be helpful to collect some patient preference information before initial interactions with the FDA staff as background information for those discussions. It may be helpful for sponsors to begin discussions with FDA staff regarding the collection of patient preference information early in the interactions between the sponsor and CDRH, likely before finalization of plans for a pivotal clinical trial, rather than leave such discussions until after pivotal clinical trial results are available and the sponsor is filing its application for approval.

As discussed in Section IV, patient preference information can have value throughout product development life cycle. The appropriate timing for collecting patient preference information for regulatory purposes will depend on the characteristics of each technology and the disease(s) it addresses. In general, thinking about the potential value of patient preference information early in the planning for regulatory approval is better than waiting until late in the process, particularly after pivotal clinical data are collected. As described in Section IV, it may be helpful early in the product development process to consider what benefit-risk information will be required for regulatory approval and how patient preference information might enhance that benefit-risk determination. Thinking backwards through the clinical and development steps that will lead up to an approval decision is one approach to identifying the best stages in the development process for collecting patient preference information about that product.

Early discussions between the sponsor and FDA can help assess whether the current understanding of benefits and risks is sufficient to guide patient preference studies about a technology. Preference studies conducted early in development, often with qualitative or less rigorous methods, may be helpful in the product development process as well as in framing the benefit-risk issues to be addressed in the regulatory approval process. It is important to recognize, however, that early patient preference information collected before there is significant clinical experience with a technology may not address the full range of risks or benefits identified later in development after more extensive clinical experience. More rigorous (and more time-consuming and costly) preference assessment methods would be more appropriate for later in development when the clinical benefits and risks are identified and the potential value of preference information in assessing those benefits and risks for regulatory approval is better understood.

On the other hand, conducting preference studies after pivotal trials are completed may be challenging due to limited time between the unblinding of clinical results and the filing the application for approval. Such post-pivotal trial preference studies may be feasible and valuable, however, depending on what issues are identified during pivotal clinical trials and on how much preference information is required. It may be particularly valuable for a pivotal trial itself to include pre- and post-evaluation of patient preference regarding outcomes in both treatment and control arms to give a better understanding of how patients view the benefits and risks of technology changes in both arms of the study. In those situations in which it is difficult to collect patient preference information until after the completion of a clinical trial, each sponsor will need to decide if it would be better to delay the filing of an approval

application to collect patient preference information than to submit the application without that information.

How Could Patient Preference Information be Collected and Used to Better Understand Important Benefit-Risk Issues in New or Evolving Areas of Medical Technologies, and Thereby Help Frame the Development of Regulatory Standards for Clinical Effectiveness in Such Areas?

The FDA, industry, patient groups or other interested organizations, or a collaboration among these groups, might proactively undertake patient preference studies to help enhance the understanding of patient preferences and risk tolerance in emerging or changing clinical areas.

The process of obtaining regulatory approval in emerging or rapidly changing clinical areas can be challenging given uncertainty about which benefits and harms are most important to patients as well as other stakeholders. Recent examples of such emerging clinical areas include transcatheter heart valves, device interventions for hypertension, invasive neuromodulation devices, and devices for treatment of obesity. In such areas, FDA staff and industry may have differing views on the clinical outcome and safety issues that should drive benefit-risk assessments and which will be important considerations in regulatory approval decisions.

Patient preference information may be particularly helpful in such scenarios to frame the development of regulatory standards for clinical effectiveness by providing evidence on how patients view the benefits and harms of a new technology in a particular disease state, and thereby help clarify what patients may view as minimum acceptable benefit or maximum acceptable risk for that technology. As discussed in the introduction to this report, historically, FDA has received information on patient preferences anecdotally from patient comments during open public hearing sessions in advisory committee panel meetings or letters from patients or patient advocacy groups. However, such anecdotal information is limited in its ability to inform regulatory decisions because it is challenging for FDA staff:

- to assess the representativeness of these testimonies;
- to know how well informed about a device's benefit-risk profile these patients are;
- to determine what proportion of patients would consider the benefit-risk profile acceptable;
- and
- to formally assess maximum acceptable risk and minimum acceptable benefit from the patient perspective.

Indeed, it is hard to consider individual statements or letters of endorsement as “scientifically validated evidence” as described in the CDRH Benefit-Risk Guidance.^{1(p7)}

As CDRH staff developed the Benefit-Risk Guidance, they became aware of the need for more effective, scientifically rigorous ways to assess patient preferences to inform benefit-risk determinations. Therefore, they looked for an opportunity to survey a group of patients regarding a relevant disease state as a proof of concept for incorporating patient preferences into regulatory considerations for new technologies. FDA staff decided to undertake the study of patient preferences in obesity referenced throughout this report. This CDRH-sponsored study of patient preferences and risk tolerance for weight-loss devices is an example of how quantitative patient preference information can be used to understand the benefit and risk issues important to patients; develop a quantitative model of how patients tradeoff key benefits and risks; and use such information to help inform regulatory assessment in a specific product area.⁴

The CDRH obesity study is described in more detail elsewhere in this report. The results of this discrete choice experiment (DCE) survey and conjoint analysis helped FDA:

- clarify which risks and benefits were most important to the obese patients surveyed;
- understand the heterogeneity of preferences across the obese patient population;
- develop a benefit-risk “tool” that quantifies how patients tradeoff key benefits and risks to help inform reviewers of the minimum clinical effectiveness (weight-loss and weight-loss duration) that should be required of a device by patients, given its benefit attributes and risks;
- develop a model based on preferences to help understand the proportion and characteristics of a subpopulation willing to accept specific levels of risk in exchange for the benefits; and
- to quantify maximum acceptable risk and minimum acceptable benefit from a patient perspective.

Of note, the CDRH obesity preference study was not focused on a specific medical device but on the range of potential devices in terms of benefits and risks, and thereby helped frame an emerging area so as to better enable FDA staff to determine the regulatory standards for approval for weight-loss devices as pre-IDE requests and IDE applications are submitted. This particular patient preference study in obesity has helped FDA develop a benefit-risk based framework for thinking about clinical trial requirements for a variety of weight-loss technologies with different levels of risk and potential weight loss. Beyond showing the value of patient preference information, this study illustrates the value of proactive assessment of patient preferences in an emerging area of medical technology.

Indeed, the first obesity product approval informed by this obesity device framework is the Enteromedics Maestro Rechargeable System, an implantable vagal stimulator for obesity. Despite the fact that the additional weight-loss provided by the device compared to diet and exercise was lower than expected, it received PMA approval in January 2015 based on the positive benefit-risk assessment by an FDA advisory panel and the FDA reviewers. The pivotal study suggested that the additional weight loss provided by the device as compared to diet and exercise was lower than expected but still clinically

meaningful, and the patient preference study suggested this would still be important to obese patients. As noted in the FDA press release about the approval:

“The [Enteromedics] clinical study did not meet its original endpoint, which was that the experimental group lose at least 10 percent more excess weight than the control group. However, an [FDA Advisory Committee \(the Gastroenterology and Urology Devices Panel\)](#) found the 18-month data supportive of sustained weight loss, and agreed that the benefits of the device outweighed the risks for use in patients who met the criteria in the device’s proposed indication.

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.²⁹

This PMA approval represents the first example among medical devices in which patient preference information played an important role in informing a regulatory benefit-risk-based approval decision. Given limited funding and personnel, however, FDA cannot be expected to undertake patient preference studies in a wide range of fields. An individual company may want to undertake a patient preference study regarding a specific technology on its own to present to FDA to help frame regulatory standards for approval for that technology. For emerging clinical areas, there will likely be opportunities for FDA, industry, and other interested groups such as PCORI, NIH, and patient advocacy groups to work together on patient preference studies.

While FDA-sponsored patient preference studies regarding a clinical indication in an emerging area of technology can be valuable, as the CDRH obesity study and Enteromedics Maestro Rechargeable System approval has demonstrated, they do take time to plan, execute, analyze, and report. Again, identifying early in the regulatory process if patient preference information would be valuable in the assessment of a particular technology would help sponsors plan ahead for their own studies of patient preferences as well as identify situations in which a broader, multi-sponsor patient preference study may be important to frame the benefit-risk issues in a clinical area.

The comments in this section are offered as “considerations” rather than recommendations given the limited experience in using patient preference information in the regulatory approval process for medical devices. As has been discussed throughout this Framework Report, the use of patient preference information in regulatory benefit risk assessments is a nascent area with much to be learned as sponsors, FDA staff, and others work to identify situations in which patient preference information would be useful, collect such information, and use it in the regulatory process. Additional work is needed to improve the regulatory science around the use of patient preference information in benefit-

risk assessment. The final section of this report, Section VIII, discusses unanswered questions in current methods for assessing patient preferences and topics for this additional work that have been identified during this PCBR Project that might help further efforts to make CDRH benefit-risk assessment more patient-centric.

Section VII: Potential Value of Patient Preference Information Beyond the Regulatory Process

This MDIC PCBR Framework Report has focused primarily on the use of patient preference information in benefit-risk assessments for regulatory approval. Section IV also discusses at a high level the potential value of patient preference information in the product development process. Beyond product development and the regulatory approval process, information on how patients view the risks and benefits of a technology may be useful for other purposes, notably reimbursement, marketing, and shared medical decision making. While an in-depth discussion of how patient preference information might be useful in each of these areas is beyond the scope of this report, this section will discuss briefly how patient preference information might be useful in each of these areas and how future work in each of these areas might be useful.

Patient Preference Information and Reimbursement

Patient preference information regarding the potential risks and expected benefits of a medical device could be useful in reimbursement decisions, but, at present, such information is not explicitly sought or considered as part current of coding or coverage decisions processes. For example, evidence of clinical effectiveness is central to coding and coverage decisions, but information on how patients view a new treatment option, particularly compared to other treatment options, is not explicitly mentioned in either American Medical Association (AMA) Current Procedural Terminology (CPT) Code application process or the CMS National Coverage Decision (NCD) process.^{30,31} While the CMS NCD process does provide opportunity for public comment, such comments are usually in the form of statements by individual patients or by patient advocacy groups, not quantitative information from formal studies of how patients view treatment options.

Payers are interested in reimbursing technology that leads to effective clinical care for patients, as demonstrated by clinical evidence of improved patient outcomes. Patient outcomes are typically measured in clinical studies as the mean or median of one or more physiological, functional, or patient-reported parameters across a representative sample of the patient population. Such studies may or may not examine the heterogeneity of patient outcomes or patient preferences about those outcomes across the patient population. Payer staff involved in coverage decisions may not fully understand how patients see the benefit-risk tradeoffs of a given procedure or technology, and how patient perceptions of the value of a technology may differ from those of physicians or other providers. If a patient preference study reveals that many patients, or even a significant minority of patients, have a strong preference for new product given its attributes, payers may be persuaded to cover that product which otherwise would not be covered based on available clinical data alone.

As patient preference information is developed for regulatory purposes, it may be beneficial to make sure that such information is published and becomes part of the clinical literature that supports the use of the technology. Such published studies may provide additional perspective on the value of a new

technology that may influence coverage decisions, particularly if they identify a subset of patients that prefer a less expensive technology with a different benefit-risk profile than the average patient prefers. Submission of patient preference information may also help make sure that coverage decisions are more patient-centric, not just based on payer and provider perception of benefits and risks.

Again, given its regulatory emphasis, the MDIC PCBR Project did not focus significantly on the use of patient preference information in the reimbursement process. Indeed, the MDIC PCBR Steering Committee does not include significant payer or provider representation. In the future, MDIC or other groups might consider convening a group of interested stakeholders, including payers as well as industry and patient groups, to discuss how patient preference information might be valuable in coding, coverage, and payment decision processes.

Patient Preference Information and Marketing

Patient preference information can be used throughout the entire product lifecycle to help characterize a market opportunity, identify target patient populations for the technology, identify key technology attributes that are important or problematic for patients, and develop patient-facing marketing materials.

As described in Section IV of this document and illustrated in Exhibit 4-1, information on patient preferences regarding clinical needs for diagnosing or treating a disease state can be collected at each stage of the product development lifecycle. In early development, companies can obtain qualitative information through focus groups and structured interviews, and may work to obtain more quantitative information through some of the methods described in Appendix A. These efforts can inform the needs assessment and initial product description used as the basis product development activity, as well as product design and clinical testing efforts. Some of the most useful information that can be collected relates to patient-perception of the risks and benefits of established treatments and the risk profile of the target patient population, as well as their desired outcomes. Patient preference information about existing treatment options can provide an important benchmark against which the new technology may be compared through the rest of the product development process, identifying potential issues that need to be solved to make the new product successful in the market.

With more developed prototypes available during pre-clinical and clinical development, patients can provide even more direct feedback about the potential value of a new technology compared to existing treatment options. For patient self-use technologies, focus groups and clinical trials offer the opportunity to obtain direct patient feedback regarding specific features of the technology as well as information regarding patient preferences for the new technology versus others treatment options. While pre-approval clinical trials are often designed to look at issues of safety and effectiveness of the product, they also offer an opportunity to collect preference information from patients who have experienced the technology. For technologies that require clinical trials for which it may be difficult to

randomize patients, “preference trial” methodologies described in Appendix A may offer a way of obtaining both clinical and preference information about the technology.

After regulatory approval, marketing departments routinely collect and analyze preference information aimed at understanding and engaging patients and other customers. Data collection strategies range from simple analysis of social media sites and focus groups to more sophisticated analysis of patient preferences using some of the methods described in Appendix A. This patient-derived information, used in conjunction with preference information collected from physicians or other important stakeholders, can be used to help optimize advertising and promotional material as well identify new feature sets and other product changes that would be important to patients.

Preference information can be used to develop patient-facing marketing material to facilitate adoption. The validity of such marketing material is enhanced by using information evaluated during the regulatory approval process, both clinical outcome data as well as patient preference information. Developing materials that help patients understand the potential benefits and risks of a technology or treatment so that they can make an informed decision about its use will become increasingly important in a more “patient-centric” health care system that encourages shared medical decision making. Exploring better ways of communicating benefit and risk information to patients, particularly in complex medical decisions, represents an important area for future research in regulatory science that may be valuable in marketing efforts as well.

Given the evolving health care system and the changing way in which medical products are being marketed, companies might think about how patient preference information can enhance their marketing efforts as well as facilitate regulatory approval. The investment they make in collecting patient preference information for regulatory purposes may prove valuable in their marketing efforts as well. The application of patient preference information in marketing is outside the regulatory science purview of MDIC, and is perhaps best explored by individual companies or an industry group if there is such interest.

Patient Preference Information and Shared Medical Decision Making

The concept of incorporating patient perspectives on benefit and risk into regulatory decision making is consistent with broader efforts to incorporate patient perspectives into clinical decision making. In the end, it is the patient who is the ultimate consumer of medical care and has the choice of what medical care to receive. The shared medical decision making (SDM) movement has grown out of a desire to ensure that patients have the appropriate information they need to make major decisions about their medical care.

The process of shared decision making involves providing patients with accurate, unbiased, and clear information about the risks and benefits of a procedure or treatment that the patient, in collaboration

with his/her provider(s), can use to make a decision about the best course of action. As outlined by the Informed Medical Decision Making Foundation:

“Shared decision making (SDM) is a collaborative process that allows patients and their providers to make health care decisions together, taking into account the best scientific evidence available, as well as the patient’s values and preferences.
SDM is particularly important when it comes to preference-sensitive care, where there is more than one clinically appropriate treatment option for the condition, each with benefits and drawbacks, and in which the patient’s values and preferences should be critical in determining the chosen intervention.

Unfortunately, patients often make decisions about medical treatments without completely understanding their options. Decision aids present the various treatment options in an unbiased, balanced way to patients so they can make an informed choice. These tools, which are designed to complement, rather than replace, counseling from a health care provider, can be used to facilitate a shared decision making conversation between patient and provider.”³²

The methods used to assess patient preferences for benefits and potential risks have the potential to be useful in the realm of shared decision making. Certainly patient preference information collected on new technologies can help confirm whether the use of the technology is preference sensitive and therefore a good candidate for shared medical decision efforts. Patient preference information that is used as a basis for a regulatory approval decision may be important information to present to patients to assist in their decision making about the use of that product, particularly if it is incorporated into the product label. As discussed in Section VI, for a technology with significant risks, CDRH may include in labeling the use of approved informed consent materials to ensure that patients are adequately informed of the risks and benefits of that technology. Additionally, as health care providers increase the use of shared decision making as a way of assuring that only desired and appropriate care is provided to their patients, the preference 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. Of importance to providers and companies, shared decision-making processes may help reduce potential liability by assuring that patients receive consistent and clear about the benefits and risks of a particular technology and that their decision to use the product is well documented.

Given the focus of the MDIC PCBR Project on the regulatory use of patient preference information, the PCBR Steering Committee did not explore in depth the use of patient preference information in the context of shared decision making. MDIC, PCORI, patient groups, or others may want to convene a group of experts in shared decision making as well as representatives of industry, FDA, patients, providers, and payers to further explore the use of patient preference information in shared medical

decision making and the use of patient preference information collected for regulatory purposes in such efforts.

Reimbursement, marketing, and shared decision making are areas where patient preference information collected for regulatory purposes might also have value. Additional experience with collecting patient preference information along with additional thought and research is needed to explore the possibilities of using patient preference information in these areas and to establish best practices for the collection and use of such information. Section VIII discusses the unanswered questions regarding methods to collect, analyze, and present patient preference information.

Section VIII: Future Work in the Collection and Use of Patient Preference Information for Regulatory Purposes

As outlined in the Introduction of this report and emphasized throughout, the field of patient preference assessment for regulatory purposes is relatively new. This Framework Report is intended to be an early thought piece about how to incorporate patient preferences in the regulatory approval process. This report does not purport to be the definitive document on the subject of patient centered benefit-risk analysis, but rather a document that helps further the thinking in a nascent field. Moreover, it is envisioned that this report is the first version of a living document, updated periodically by MDIC, likely with the help of FDA and other organizations, as more experience is gained in collecting and using patient preference information in the regulatory context, as well as in marketing, reimbursement, and shared decision making.

In the process of developing this Framework Report, the PCBR Steering Committee identified several areas where additional experience, thought, or analysis would be valuable to improve the ability to collect and use patient preference information in the regulatory process. Additionally, in the process of developing the Catalog of Methods, the Catalog Working Group identified areas in which additional work might improve our understanding of the properties of patient-preference methods and their use in benefit-risk assessments.

The purpose of this section of the Framework Report is to discuss areas for future work that would improve the ability of FDA, industry, and others to collect and use patient preference information in the regulatory process and in the total product lifecycle. The section begins with a summary of the outstanding issues identified during the development of the Catalog of Methods, and then highlights several additional areas for future work identified during the course of the MDIC PCBR Project.

Areas for Future Research Regarding Patient-Preference Methods

The Catalog Working Group identified a number of questions regarding patient-preference methods and their application in benefit-risk assessments for which there were no clear answers. These questions reflect those that arose during the development of the Catalog as well as questions raised during review by members of the Patient Centered Benefit-Risk project Steering Committee, CDRH staff, and Medical Device Innovation Consortium (MDIC) member companies. These questions fall into four broad categories: 1) the choice of method; 2) the sample; 3) the development of a study; and 4) the validity of the method. Suggestions for future research are provided to address each question. The suggestions for future research are only suggestions and are not meant to be prescriptive nor exhaustive. There may be other approaches to providing information to address these questions.

These questions and suggested areas for future research on these questions are discussed below. Additional information regarding these questions and suggestions is provided in Section 6 of Appendix A: the Catalog of Methods.

Choice of Method

Once a sponsor has identified the type of patient preference information required and the point in development when the information can best be collected, it is not always clear which methods are the best option among the alternative methods available. A key question is whether using different methods to answer the same research question will yield similar and consistent results. There are only a few studies comparing the outputs of different patient-preference methods applied to the same underlying research question.^{28,33,34} An area for future research would be applying multiple patient - preference methods to answer the same research question. Such studies will enable users to directly compare and contrast the performance of different patient preference methods and the relative advantages and limitations of any given method in a different situation.

Sample Selection

There is no clear guidance on whose preferences should be measured in a patient preference study. Representativeness is evaluated entirely by comparing the sample with the population of interest, which is determined, in large part, by the research question. The research question may involve understanding the preferences of a population with well-defined characteristics (e.g., a clinical trial population for which there are well-defined inclusion and exclusion criteria). In this case, recruiting a representative sample is relatively straightforward. However, the research question may be broader and involve understanding the preferences of the population that will be exposed to the medical technology in the future. In this case, recruiting a representative sample may be difficult because the characteristics of the overall population of interest may not be well understood. For example, a medical technology may be indicated to treat a given condition, but the number of patients with that condition and the distribution of ages and genders of patients in that population may not be known with any degree of certainty. Even if observable characteristics of the population are known, it is impossible to ensure that the preferences of any sample are representative of the overall population because differences in preferences may not be completely explainable by observable characteristics. Another complication is that preferences can change over time, such as patients with chronic illnesses often learn to adjust to their illness and may show different preferences later in life, so that chronicity of disease may need to be factored into sample selection considerations

Because it is difficult to know how the representativeness of a sample is likely to affect the results of a patient preference study, one research project might be to conduct the same patient preference study with different samples with different characteristics. Such a study would provide evidence regarding the sensitivity of the results obtained with specific patient preference methods to the choice of sample and

may provide evidence of systematic biases resulting from sampling choice or the degree of sensitivity of some methods to the choice of sample when compared with other methods.

Another issue in sample selection is whether prior experience with treatment biases preferences relative to patients who have not been treated for the condition. Of particular interest is whether people with prior experience with the medical technology or a similar technology have preferences that vary systematically from those people who do not have such experience. Whether prior experience influences patients' preferences for medical technologies in any case, every case, or only in cases with certain properties is unknown. To better understand these issues, a study of patients' benefit-risk preferences for medical technologies might be conducted with samples of patients who have prior experience with a medical technology as well as patients who may potentially be eligible for a medical technology to provide evidence of the extent to which people with prior experience have systematically different preferences from those who do not. This type of study might be repeated for different types of medical technologies to provide evidence regarding the extent to which such differences in preferences may or may not exist for different technologies.

Alternatively, a patient preference study could be conducted among patients who would be eligible for a medical technology but who have no prior experience with the medical technology. The same patient preference study could then be conducted among patients who receive the medical technology once the medical technology becomes available. Information on differences in preferences between these groups would provide both an understanding of the effect of an experience on patient preferences and may also provide a method for validating the premarket patient preference study (see suggestion for future research under Study Validity).

Development of a Study

There is no definitive guidance on the selection of device attributes to be used in a preference study. For some studies, the primary objective is to identify the attributes of the medical technology that are important to patients. However, in studies in which the objective is to quantify the relative importance of attributes or to quantify the tradeoffs patients are willing to make among attributes, the choice of specific attributes among those available is critical to study design. Sometimes the attributes that are identified as important by patients during qualitative research are used in quantitative studies. Other approaches to identifying the attributes for a study include asking a group of medical or regulatory experts to identify those attributes that are most important to a regulatory decision, or conducting a literature review or review of product labels to determine those attributes that distinguish one medical technology from alternative medical technologies or a standard of care. Benefit-risk frameworks such as the BRAT Framework and ProACT-URL also provide guidance on attribute selection.^{11,14,35-38} However, these approaches to selecting attributes are applied inconsistently across patient preference methods and across patient preference studies using a given method.

To better understand how best to select product attributes, a patient preference study could be designed to determine the impact of changing the list of attributes with any given method. Such a study could have two arms in which patients are assigned randomly to see different sets of attributes developed using different approaches to attribute identification. A key component of such a study would be to ensure that a number of attributes (perhaps half) are common to both studies. The results of such a study could provide an understanding of whether differences in attribute selection result in comparable weights or tradeoffs for a common set of attributes or whether the inclusion of different attributes affects patients' evaluations of the common set of attributes.

Another challenge with defining attributes for a patient preference study is how best to define those attributes for patients to understand them. There is no definitive guidance on how to assure that patients understand attributes. Differences in the description of attributes may lead to different estimates of relative importance or different measurements of how patients make tradeoffs. The extent to which differences in attribute definitions and patients' comprehension of those definitions affect patient preference estimates are not well understood.

One way to better understand how different definitions of attributes might influence preference measurement would be to design a patient preference study that examines the impact of changing definitions of attributes. Such a study could include two arms in which patients are assigned randomly to one of two sets of attribute definitions. The results of such a study could provide an understanding of the extent to which patient preference estimates are sensitive to the way in which attributes are described. In addition, comprehension questions could be included to evaluate patients' understanding of the definitions presented in the survey, and the data could be analyzed to test whether differences in the level of comprehension systematically affect patient preference estimates.

Study Validity

There is also no definitive guidance on how to assure a patient preference study is valid. In addition, it is not yet clear what regulators or other users of patient preference data would need to be comfortable with using patient preference study results. While there are academic standards for good design and conduct of conjoint analysis preference studies and there are internal consistency tests that can be used in these studies, there currently is no clear definition of what constitutes a valid patient preference study. Unlike in patient reported outcomes (PRO) research, there is not a standard set of validity tests that can be applied to patient preference studies. A review of standards and methods for assuring validity in other types of clinical studies, such as studies using PROs, might identify principles that could be used in developing analogous, but likely different, approaches to validating patient preference studies.

Stated-preference methods typically involve scenarios in which patients are asked to make hypothetical choices without actually experiencing the consequences of that choice. Therefore, it is unknown

whether patients would actually do what they say they would do. Often hypothetical choices are necessary because observing actual choices is impossible or observing actual choices does not provide sufficient variation in attributes and attribute levels to tease out the rates or levels of severity at which patients would be willing to trade off among attributes. Despite providing experimental control over the attributes and attribute levels that are considered in treatment decisions, the hypothetical nature of the choice from which patient preference data are derived may weaken the validity of patient preference estimates.

Although some methods exist for evaluating the consistency of hypothetical choices when patients are asked to make multiple choices in the same study, there is little evidence as to what level of consistency would be required for a study to be considered valid. One method for establishing the validity of patient preference methods is to determine whether the hypothetical choices patients make are consistent across choice scenarios. A review of existing patient preference studies to examine the consistency of responses using hypothetical choices might provide some guidance as to the level of consistency that can be expected from such studies.

As noted above, stated-preference methods typically involve scenarios in which patients are asked to make hypothetical choices, and it is unknown whether patients would actually do what they say they would do. A patient preference study designed to generate information that can help validate the evidence collected through premarket patient preference studies and to understand the effect of experience on patient preferences could be conducted (see suggestion for future research under Sample). One study could be conducted among patients who would be eligible for a medical technology but who have no prior experience with the medical technology. The same patient preference study could then be conducted among patients who receive the medical technology once the medical technology becomes available.

Each of these issues and suggestions for future research is discussed in more detail in Appendix A: The Catalog of Methods.

Opportunities for Future Work in the Use of Patient Preferences Information for Regulatory Purposes

During the process of developing this Framework Report, the PCBR Steering Committee noted several areas where additional thought, experience, and analysis would be valuable in improving the ability of FDA staff, industry, patient groups, and others to collect and use patient preference information. Additionally, feedback from MDIC members on the draft of this report confirmed the need for additional work in some of these areas and identified other areas as well. These areas are discussed below. These opportunities for future work fall into three broad areas:

- gaining additional experience with collecting and analyzing patient preference information;
- effectively communicating benefit and risk information to patients and providers; and

- using patient preference information in the regulatory process.

Each of these areas is discussed in more detail below.

Gaining Additional Experience with the Collection and Analysis of Patient Preference Information

The most significant need in the field of assessing patient preferences for regulatory purposes is simply gaining more experience with doing such studies and applying them in the regulatory context. In its work, the PCBR Steering Committee could only identify one study of a patient preference study being used as part of the CDRH regulatory process: the study of patient preferences in obesity initiated by the FDA.³⁹ The use of this study to develop to a benefit-risk framework for thinking about clinical requirements for medical devices for obesity⁸ and the recent approval of Enteromedic's Maestro Rechargeable System for obesity⁴⁰ illustrate the potential value of patient preference information in the regulatory process. Its singularity also highlights need for more examples of the collection and use of patient preference information in the FDA process.

The value to FDA, industry, and others of additional patient preference studies goes beyond the use of the specific results of those studies. The value of additional preference studies might also include:

- gaining more experience with the variety of methodologies described in the Catalog of Methods:
 - obtaining greater insight into how best to elicit the full range of benefits and risks that need to be assessed in a particular clinical indication;
 - learning how to best define benefits and risks and describe their level and probability to patients in order to conduct useful patient preference studies;
 - comparing the results of different methods of assessing patient preference information for the same technology or clinical indication;
 - validating the use of various methods of patient preference elucidation;
 - gaining a better understanding of the comparative strengths and weaknesses of different patient preference assessment methods and best practices for applying each method.
- gaining more experience with using patient preference information in regulatory benefit-risk analysis:
 - better understanding the study pre-specification, statistical, and validation considerations that are important in assuring accurate and useful preference studies;
 - learning how best to compare patient preferences for the benefits and risks of different types of therapies, such as devices vs. conservative care, invasive vs. non-invasive devices, acute vs. longer term therapies, devices vs. drugs;
 - learning how best to evaluate preferences and preference changes over time.

- learning how to most efficiently and cost-effectively design and execute patient preference studies.
- learning how to best communicate the results of patient preference studies to patients, providers, FDA staff, industry staff, the public, and others.

As experience with additional studies is gained, the ability of FDA, industry, and other groups to collect and use patient preference information to enhance benefit-risk assessments should improve.

As noted in Section VI, the collection and incorporation of patient preference information is not an FDA requirement, and is currently elective on the part of the sponsor of a particular FDA approval application. Therefore, gaining additional experience with patient preference studies will result from sponsors thinking about the potential value of patient preference information in a particular situation, perhaps using the factors outlined in Section III; deciding to take on collecting such information; and then publishing the results of such studies or referencing them in publically available materials such that others in industry and the FDA can learn from that experience. As noted in Section VII, similar to the publication of clinical studies publication of patient preference studies may support marketing, reimbursement, and shared medical decision making efforts as well as enhance the knowledge of the medical device ecosystem about the potential value and best practices around assessing patient preferences. Beyond the value of such discussions in a specific situation, the collective experience with such discussions may enhance future discussions about patient preferences in other situations and help all involved figure out the most efficient and cost-effective way to collect such information.

Collaboration on Studies of Patient Preferences in Emerging Areas of Medical Technology. In addition to the value of additional patient preference studies to support FDA applications for specific technologies, patient preference studies may be particularly helpful to both FDA and industry in framing benefit-risk issues in emerging or important areas of medical technology. The obesity study used throughout this report is an excellent example of using a patient preference study to better understand patient benefit-risk tradeoffs regarding technology use in one clinical area – devices for obesity -- that has helped shape the thinking about regulating new devices that in that area. The value of such broad studies of patient preferences regarding treatment options in a particular disease state is that they are not tied to consideration of the benefit and risks of a particular technology. Rather, they can help understand patient perspective on benefit-risk tradeoffs in a clinical area independent of a specific technology, and thereby help to assure a clear and fair approach to establishing regulatory requirements for the full range of technologies, and possibly drugs, attempting to address the particular clinical problem.

While the CDRH undertook by itself a broad study of patient preferences in obesity, the FDA cannot be expected to undertake all such studies in other clinical areas as they arise. Rather, other interested

parties might be better positioned to undertake or collaborate on similar broad studies of patient preferences in particular clinical areas. Such collaborations might take the form of a group of companies working together to use a patient preference study to help define clinical requirements in a particular area; an FDA-industry collaboration on a particular area, perhaps through a group such as MDIC; an effort led by an independent research organization such as PCORI, an academic study undertaken with government or foundation funding support, a project undertaken by one or more patient advocacy groups in a particular area; or some combination of the above. A good example of a broad patient preference study sponsored by a patient advocacy group to help shape the regulatory requirements in a particular area is the study sponsored by Parent Project Muscular Dystrophy regarding caregiver (parent) preferences regarding therapies for Duchenne's Muscular Dystrophy previously mentioned in this section.^{22, 28}

Areas of emerging technology in which broad patient preference studies might be particularly useful include:

- *Less invasive alternatives to existing invasive procedures:* The obesity study represents one important example of studying patient preferences in an area in which many of the emerging technologies being pursued are less-invasive alternatives to existing surgery procedures. As noted in Section III, patient preference studies might be particularly helpful when the benefits as well as the risks of less invasive approaches are less than those of the more invasive options.
- *Device alternatives to drugs:* Patient preference studies might be particularly useful when there is a fundamental difference in treatment paradigms, such as a device-based alternative in disease states traditionally treated with drugs. One example is when a single procedure is being developed as an alternative to chronic treatment with drugs, such as renal denervation as an alternative to medication in treating hypertension. A different example might be the use of an implantable device as an alternative to chronic treatment with drugs, such as implantable neurostimulation for Parkinson's disease as an alternative to drug therapy. Devices, which generally work locally at an anatomic or end-organ level to influence disease, may raise fundamentally different issues of risk than drugs, which generally work at a molecular or cellular level and often go throughout the body. Patient preference studies in clinical areas traditionally treated with drugs in which device approaches are emerging might be particularly valuable to help regulators and sponsors think about the important benefit-risk tradeoffs for drug vs. device therapies.

Development of a Repository of Patient Preference Studies. One approach to improving the collective understanding of how to collect and use patient preference information might be to establish a repository of patient preference studies. A patient preference registry might be similar in concept to the Cost-effectiveness Analysis Registry run by the Center for the Evaluation of Value and Risk in Health at

Tufts University.* Such a repository might include a centralized database that contains a broad range of published patient preference studies, including those regarding specific medical devices, drugs, and diagnostics as well as more general studies of diagnostic or treatment approaches to specific disease states. The repository might include studies undertaken by industry, FDA, academics, or others, whether used in the regulatory process or undertaken for other purposes. It might also include patient preference studies by industry or others that are submitted to the registry but that have not been formally published. The repository might be sponsored and operated by a public entity, such as FDA, NIH, or PCORI; a public-private partnership such as MDIC; a private entity such as a particular university or foundation; or some combination of these organizations.

Such a repository of existing patient preference information might prove valuable as a “one-stop shop” for FDA staff, industry, or others looking for existing information on patient preferences so as not to have to undertake a new study. It would also offer prior examples of patient preference studies to help inform the design and implementation of new patient preference studies. Additionally, a repository might also facilitate periodic assessment of the field of patient preference measurement, particularly the comparison of different methodologies for collecting and analyzing patient preference information. By bringing a focus on patient preference studies, a central collection of patient preference research should help advance this emerging field of regulatory science.

Development of Tools to Help Parties Considering Patient Preference Studies. In feedback to the draft of this report, several MDIC members highlighted the potential value of having worksheets or other tools to help those considering undertaking a patient preference study to decide if such a study would be useful, decide when in the development process to undertake such a study, decide how to design such a study, and how to present such information for use in the regulatory process. They cited the value of the worksheets provided by FDA in the Benefit-Risk Guidance document as a precedent for such tools for helping in the process of collecting and using patient preference information.

As an initial thought piece on the collection and use of patient preferences in regulatory benefit-risk assessment and given limited experience with the use of patient preference information in the regulatory process, the PCBR Steering Committee specifically avoided taking a “cookbook” or checklist approach to the decisions that would be involved in designing, undertaking, and using the results of a patient preference study, choosing instead to offer ways of thinking about the issues and a “factors to consider” approach in several sections of this report. With additional FDA and industry experience with patient preference information in the regulatory process, however, the PCBR Steering Committee envisions developing worksheets or other tools for facilitating the process of undertaking patient preference studies and using such information in the regulatory process, potentially in collaboration

* The Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts University analyzes the benefits, risks and costs of strategies to improve health and health care. In addition to their work as a research and training center on cost-effectiveness research, CEVR has developed and maintains two databases that are resources for health care stakeholders: the Cost-effectiveness Analysis (CEA) Registry and the National Coverage Determinations Database. For more information on the CEA Registry, see: <https://research.tufts-nemc.org/cear4/Home.aspx>

with other public-private partnerships, academic, or related groups. Down the road, based on experience with additional patient preference studies and their use in the regulatory process, MDIC might consider developing such tools as part of updating this report; FDA might consider developing such tools as part of developing guidance on patient preference information; or other groups might consider developing such tools on their own.

Effectively Communicating Benefit and Risk information to Patients and Providers

As discussed in Section VI, informing patients of the potential benefits and risks is necessary to be able to elicit their preferences regarding the diagnosis or treatment of a disease, a large topic that has a considerable body of literature. Given the focus of the report on the patient preferences themselves, this report does not address how best to inform patients regarding benefits and risks. And while the report discusses the potential value of patient preference information in the regulatory labeling of a technology, it does not discuss best practices for communicating benefits and risks to patients and providers so as to assure that patients can make a well-informed choice about the use of a particular technology.

Review of Best Practice for Communicating Benefit-Risk Information to Patients and Providers. A follow-on project coming out of this report might be to review the best practices for communicating benefit and risk information to both patients and providers in the context of the elicitation of patient preferences, informed consent, and shared medical decision making. Such a report might review the existing literature on how to effectively communicate such benefit and risk information to patients and providers, and then summarize the best practices for doing so. While several important issues in communicating benefits and risks to patients were discussed at a high level in Section VI, there is an opportunity for MDIC, FDA, and others to independently or in collaboration undertake a more in-depth project to assess the literature in this area and develop list of recommended best practices to help inform industry, FDA, and others. Beyond the potential value in informing FDA practices around labeling, understanding the best ways for providers to communicate benefits and risks to patients to assure that the patients can make well-informed choices about their medical care may be of significant value to providers and industry in reducing medico-legal liability.

Development of a Framework for Incorporating Patient Preference Information into Product Labeling.

As discussed in Section VI, patient preference information might support labeling claims for a product in which the indicated population to use the technology is based on patient preferences in addition to or instead of more traditional demographic or disease severity characteristics. Similar to the label for the Vision Care Implantable Miniature Telescope (IMT) approval referenced in Section VI, such labeling might include specific informed consent requirements along with documentation of the patient's choice (i.e., expressed preference) in order for the patient to be eligible for the technology. Building on the review of best practices for communicating benefit and risk to patients, MDIC, FDA, and patient groups might collaborate on a project to think through issues related to incorporating patient preference

information into product labeling. Beyond issues of when and how preference information is presented in labeling, this project could consider issues related to how labeling information is used in informed consent and shared medical decision making to facilitate providers' ability to help patients make well-informed choices about the use of medical technology.

Using Patient Preference Information in the Regulatory Assessment Process and Beyond

In addition to gaining experience in collecting and analyzing patient preference information and understanding how best to communicate benefit and risk information to patients, further thought and experience around how to actually use patient preference information in the regulatory process would be valuable to FDA, sponsors, patient groups, and others. There are several possible projects that might contribute to this understanding of how to best use patient preference information in the regulatory process, including gaining experience with using quantitative benefit-risk models. Beyond the value of patient preference information in the initial approval of medical devices, it may be valuable to explore the value of such information in the drug and biologic approval processes and in the post-market setting.

Use of Quantitative Benefit-Risk Analysis in the Regulatory Process. As noted in Section VI, while most benefit-risk assessments can be performed using clinical judgment applied to study data, there are cases where the interaction between multiple benefits and harms, the diversity of views of the relative importance of treatment attributes, or the need to make a defensible argument make a quantitative model for benefit-risk highly informative. An example of such a quantitative approach is used in several figures in Section II of this Framework in which a quantitative benefit-risk measure is used to illustrate the relationship between benefits and risks over the population. There are numerous quantitative approaches to benefit-risk assessment, many of which incorporate weights that reflect the relative importance of benefits, harms and other attributes^{8,39-40}; however these approaches currently have traction only in academic and health economic types of applications. The tool developed based on CDRH's obesity preference study is a good example of such a quantitative model.⁴ As noted elsewhere in this report, the quantitative model has allowed CDRH to apply the preferences to help establish the regulatory requirements for new obesity technologies as well as has influenced the approval of at least one medical device, the Enteromedics Maestro Rechargeable System.^{24,29}

There is a significant opportunity for additional work to explore the value of quantitative benefit-risk assessment in the regulation of medical devices and drive towards consensus amongst stakeholders on the use of such models. Sponsors, perhaps in consultation with FDA staff, might undertake studies not only to assess patient preferences, but also to develop quantitative benefit-risk models that can be submitted as part of the information supporting the application of a novel device for FDA approval. Examples where patient preference information is used in quantitative benefit-risk assessments would build experience with such approaches, providing insights on how such models might be used for both internal sponsor purposes as well as regulatory purposes.

Use of Patient Preference Information in Post-Market Studies. While much of the emphasis on the value of patient preference information in the initial approval of a product, such information may have value in post-approval studies as well. As discussed in Section VI, patient preference information collected in the post-market setting might help clarify which risks and benefits are of most importance to patients; help assess the relative importance these benefits and risks; help identify additional patient populations that might prefer the technology over other treatments; and support the development of quantitative benefit-risk models discussed above, particularly models that might be useful beyond the regulatory process in reimbursement, marketing, and shared decision making.

With the growing interest in post-market data collection on the outcomes and risks of a technology in routine use, one area to explore is capturing patient preference information as part of registries and other post-market studies. Beyond the potential value of such information in obtaining expanded indications for a product, companies may want to explore the use of post-market patient preference information for other purposes, notably reimbursement and marketing. Post-market patient preference studies will further build the overall experience with undertaking patient preference studies and further understanding of how best to collect and use preference information.

Use of Patient Preference Information in the Regulatory Process for Drugs and Biologics. Given MDIC's focus on regulatory science related to medical devices, this Framework Report has focused on how patient preference information might be used in the regulation of medical devices. Yet such preference information may be valuable in the regulation of pharmaceuticals and biologics as well. Incorporating patient preferences into the development of drugs as well as devices has become an important area of regulatory focus, as illustrated by Title I of the 21st Century Cures Initiative currently before Congress emphasizing the importance of incorporating the patient's perspective into the regulatory process for both drugs and devices.⁴¹ In response to Federal Register Notice FDA-2014-N-1698, "FDA Activities for Patient Participation in Medical Product Discussion," both the Biotechnology Industry Organization (BIO) and *FasterCures*, a center of the Milken Institute, submitted letters that discuss the potential value of patient preference studies among a number of other approaches to bring the patient perspective into CDER's and CBER's approval processes.^{42,43} The Parent Project Muscular Dystrophy's preference study in Duchenne's disease referenced earlier in this section is one early example of a patient group-initiated preference study intended to help guide the regulation of drugs and biologics in a specific disease state.^{22,28} This interest in bringing the patient perspective into pharmaceutical regulation is not limited to the U.S. The Innovative Medicines Initiative, a public-private partnership in Europe to promote the development of new therapeutics, has proposed "Patient perspective elicitation on benefits and risks of medicinal products, supplementing benefit risk assessments by regulators and HTAs (health technology assessments) from development through the entire life cycle" as a new initiative under its IMI 2 proposal for its next phase of projects.⁴⁴

The methods evaluated in the Catalog are not tied to specific types of therapy, so this compendium of patient preference assessment methodologies should be of value to those interested in collecting patient preferences regarding the use of pharmaceuticals and biologics. However, the product development lifecycle and the process of evaluating drugs and biologics is somewhat different than that for devices, so how patient preference information might be used in the CDER and CBER approval processes may be different than how it would be used the CDRH approval process. While some of the considerations discussed in this Framework Report may be useful in thinking about drug and biologics, a separate consideration of how best to incorporate patient preference information in to the drug and biologic approval process may be valuable to both FDA and industry. FDA, perhaps in conjunction with industry organizations, patient groups, and other interested parties, might consider undertaking their own “framework” project regarding how to use patient preference information in the CDER and CBER regulatory approval processes.

Additional Opportunities to Improve the Incorporation of Patient Preferences into Regulatory Decision Making

The list of opportunities for further work in the collection and use of patient preference information in regulatory process contained in this section is based on the PCBR Steering Committee’s review of its work and of initial feedback from MDIC members based on an initial draft of this Framework report. This list of areas for possible future work should be considered a starting point. Additional ideas regarding both the content of this report as well as areas for additional work will emerge as this Framework Report is reviewed over time by both MDIC members and by others outside of MDIC. MDIC and the PCBR Steering Committee welcome constructive feedback on this report and ideas for further work in the field of patient preference assessment.

While it is important to be aware of the areas where more knowledge and experience would be valuable to enhance the ability to undertake patient preference studies and use them to inform the regulatory process, these areas should not be viewed as obstacles to undertaking patient preference studies for regulatory or other purposes. To the contrary, there is an important need for more studies of patient preference to expand industry, FDA, patient groups’, researchers’ and others’ experience with such studies. The MDIC PCBR Steering Committee hopes that this Framework Report and the Catalog of Methods will be helpful to those considering undertaking patient preferences studies, and thereby encourage the continued growth and maturation of this field.

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Appendices

Appendix A: Catalog of Methods of Assessing Patient Preferences – Circulated as a separate document

Appendix B: Glossary

There are a number of terms related to patient-centered benefit-risk analysis that have been used in the Framework and Catalog that may be new to users of these documents. In addition, some of the terms used in these documents may have different meanings to different people in different contexts. This glossary of terms is intended to define each of the terms as they are used in the Framework and Catalog. These terms may be defined differently in other documents and as used for other purposes. In addition, this glossary of terms does not include descriptions of each patient-preference method included in the Catalog. For descriptions of individual patient-preference methods, see Table 3 in Section 2 of the Catalog.

Attribute: A general characteristic of a medical technology such as effectiveness, safety, tolerability, or method of use.

Attribute level: A specified value of an attribute. For example, if response rate is an attribute describing efficacy, the actual probability (e.g., 78%) is the level of that attribute.

Benefit: A favorable effect or desirable outcome of a diagnostic or therapeutic strategy.

Consistency: The extent to which repeated choices made by a patient do not vary illogically or in violation of expectations.

Diversity: The degree to which patients in a sample have differences in observed characteristics such as age, gender, or disease experience. Diversity is related to preference heterogeneity to the extent that subgroups of patients with a specific characteristic or set of characteristics may have preferences that differ from patients without those characteristics or with different characteristics.

Generalizability: The extent to which the results derived from a sample can be applied to the population of interest.

Harm: An unfavorable effect or undesirable outcome of a diagnostic or therapeutic strategy.

Health-state utility: A quantitative measure of patient preferences for a health state or an attribute of a medical technology bounded by 0 and 1 in which 0 represents death and 1 represents perfect or normal health. It is a measure of the desirability or acceptability of a health state or an attribute of a medical technology relative to death and perfect health.

Heterogeneity: Differences in preferences among a sample. Preference heterogeneity can be explained (differences in preferences are correlated with known characteristics of the patients) or unexplained (differences in preferences are not correlated with any patient characteristics for which data are available).

Hypothetical scenario: A hypothetical decision context presented to patients that is used to motivate the need to make a choice or judgment that does not require any action that will result in experiencing the consequences of the decision (see also, stated preference).

Judgment: Considerations of individuals in making decisions or choices for others.

Latent-class analysis: A method for identifying segments of patients with similar preferences that are distinctly different from other segments and where the segmentation is defined by preferences.

Maximum acceptable risk (MAR): The greatest increase in probability or magnitude of a harm for which a patient would accept a given benefit.

Minimum required benefit (MRB): The smallest increase in probability or magnitude of a benefit for which a patient would require to offset a given risk.

Patient-preference method: Qualitative or quantitative assessment of the relative desirability or acceptability of attributes that differ among alternative medical technologies.

Population: The group of patients whose preferences are intended to be represented by patient-preference data.

Preference: Qualitative or quantitative statement of the relative desirability or acceptability of attributes that differ among alternative health interventions. Preference refers to the tradeoffs that individuals consider or exhibit in making decisions or choices for themselves.

Preference-sensitive decision: A decision in which there are multiple diagnostic or treatment options, and the decision of which option to pursue depends on the particular preferences of the decision maker.

Profile: A combination of attributes or attribute levels intended to represent a possible state of the world or medical technology.

Qualitative patient-preference method: A patient-preference method designed to gain an understanding of patients' thoughts, feelings, and experiences in an unstructured or semistructured manner. Although qualitative methods may also yield data that can be summarized numerically (e.g., the percentage of patients reporting a specific symptom, treatment benefit, or side effect), quantifying patient responses is not the primary objective of these methods.

Quantitative patient-preference method: A patient-preference method that is structured, with the type of data to be collected clearly defined and the response options limited to permit statistical analysis.

Relative importance: A quantitative measure of the level of desirability or acceptability of an attribute of a medical technology.

Representativeness: The extent to which the sample represents the population of interest on some selected characteristics of interest.

Revealed preference: A choice or behavior made by a patient in the real world that reflects an action that results in experiencing the consequences of the decision.

Risk: The qualitative notion of the probability and/or severity of a particular harm.

Risk tolerance: A qualitative term reflecting the degree to which a patient would accept greater probability or severity of a harm in exchange for a given benefit.

Sample: The group of patients whose preferences are measured in a patient-preference study.

Segment: A group of patients in a sample with similar preferences that are systematically different from other groups.

Subgroup: A group of patients in a sample with a common observable characteristic or set of observable characteristics. Subgroups can also be referred to as strata.

Stated preference: A preference expressed by a patient that does not require any action that will result in experiencing the consequences of the decision (see also, hypothetical scenario).

Structured weighting: A group of patient-preference methods typically used in multicriteria decision making.

Subgroup: A group of patients in a sample defined by a common characteristic that distinguishes one group of patients from another group of patients.

Tradeoff: A measure of the extent to which a change in the level of one attribute of a medical technology is offset by a change in another attribute of that technology.

Uncertainty attitude: The degree to which uncertainty in the attributes of a treatment alters one's decisions about use of the treatment. It is independent of the preferences that an individual places on particular benefits or harms.

Uncertainty averse: A term used to describe a patient who reacts to increases in uncertainty by decreasing his or her maximum acceptable risk for a given benefit or by increasing their minimum required benefit for a given risk. Increases in uncertainty regarding harms or benefits make uncertainty-averse patients less willing to take a chance on a treatment.

Uncertainty neutral: A term used to describe a patient whose maximum acceptable risk is not impacted by increases in uncertainty.

Uncertainty tolerant: A term used to describe a patient who reacts to increases in uncertainty by increasing his or her maximum acceptable risk for a given benefit or by decreasing their minimum required benefit for a given risk. Increases in uncertainty regarding harm make these patients more willing to take a chance on a treatment.

Validity: The extent to which quantitative measures of relative importance or tradeoffs reflect the true preferences of patients.

Weight: A quantitative measure of relative importance.