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A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies

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ABSTRACT

Background: In response to 2012 guidance in which the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) stated the importance of patient-centric measures in regulatory benefit-risk assessments, the Medical Device Innovation Consortium (MDIC) initiated a project. The project was used to develop a framework to help the Food and Drug Administration (FDA) and industry sponsors understand how patient preferences regarding benefit and risk might be integrated into the review of innovative medical devices. **Methods:** A public-private partnership of experts from medical device industry, government, academia and non-profits collaborated on development of the MDIC patient centered benefit-risk framework. **Results:** The MDIC Framework examines what patient preference information is and the potential use and value of patient preference information in the regulatory process and across the product development life cycle. The MDIC Framework also includes a catalog of patient preference assessment methods and an agenda for future research to advance the field. **Conclusions:** This article discusses key concepts in patient preference assessment of particular importance for regulators and researchers that are addressed in the MDIC Framework for patient centered benefit-risk assessment as well as the unique public-private collaboration that led its development.

Keywords: patient-derived preferences, preference-based measures, preferences, regulatory.

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Introduction

Patient preferences or patient preference information can be used in a narrow sense to simply refer to the expression of preferences about the choice that patients face regarding which treatment option to use, for example, the preference of therapy with a device versus therapy with a drug, and has been used by drug and device companies as part of product development. Patient preference information, however, has a similar role in the regulatory process as it does during product development: defining how to frame benefit-risk issues so they are most germane for patient decision making, identifying preference subgroups for whom preferred decisions would be different, and supporting benefit-risk modeling to guide patient-centered decision making [1].

The Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) launched the Patient Preference Initiative [2] in September 2013 to examine ways in which it could broaden patient input in medical device regulation. This initiative stemmed from recognition in a landmark 2012 guidance [3] issued by CDRH that patients' perspectives on benefit-risk trade-offs will vary according to individual expectations and tolerance and should be considered by regulators for both premarket-approval applications and de novo petitions. A 2013 public workshop [4] convened experts in health economics, social sciences, patient advocacy, and the medical device industry for a robust discussion of methods and tools for measuring treatment preference as well as of gaps in the evidence base and tool set.

The learnings from this workshop helped shape the Medical Device Innovation Consortium's (MDIC's) Patient Centered Benefit-Risk (PCBR) project, which built a first-of-its-kind framework and catalog of patient preference methods on the basis of limited experience with regulatory patient preference studies. CDRH's pioneering study on patient preferences in obesity [5] as well as other experiences with patient preference assessment

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methods outside the regulatory context, such as health economics research, has fostered a vision for how the patient perspective can be integrated into medical device benefit-risk assessment [1].

Advancing the Science of Patient Preference Assessment through Collaboration

In September 2013, CDRH launched the Patient Preference Initiative to gather patient and stakeholder views on the best way to measure patient risk tolerance and benefit preference. The Patient Preference Initiative emerged from FDA's 2012 Benefit-Risk Guidance in which FDA stated the factors to consider in making a benefit-risk assessment [3], including collecting patient-centric metrics to measure benefit and ways of measuring a patient's tolerance for risks. The comments generated by the guidance, workshop, and dockets were clear—there needed to be a scientific way to study patient preferences and have FDA staff consider such data when making benefit-risk assessments for medical products. The medical device community, including FDA, determined that the development of the field would require a multistakeholder approach through public-private partnerships (PPPs) that include patients and researchers. In May 2015, CDRH released a draft guidance on including patient perspectives in regulatory submissions [6].

The growing interest in patient perspectives and the more active role of patients in health care decision making led to the development of MDIC's PCBR project. MDIC is the first PPP created with the intention and objective of advancing regulatory science around the development and approval of medical devices. MDIC was formed in 2012 to improve the understanding of medical device regulation and helps develop the tools, methods, and approaches used in medical device development. MDIC membership is open to organizations that are substantially involved in medical device research, development, treatment, or education or in the promotion of public health and have an interest in regulatory science [7]. MDIC is a nonprofit 501(c)3 organization, governed by a board of directors representing industry, FDA, the National Institute for Health, and the Centers for Medicare & Medicaid Services. MDIC member dues fund the MDIC infrastructure and provide seed funding for projects. Additional funding for projects comes from grants, contracts, and directed donations. The goal of the 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 this patient preference information into premarket and postmarket regulatory submissions and decisions. The PCBR project began in May 2013, starting with assembling an expert steering committee to flesh out the project. The MDIC PCBR group submitted a proposal to develop the Framework and Catalog to the FDA Broad Agency Announcement and was funded in April 2014 (BAA HHSF223201400011C, "Patient-Centeredness: Integrating Patient Preference into Regulatory Submission"). A working group was formed to develop the Catalog and the development of both the Framework and the Catalog was overseen by the PCBR Steering Committee.

MDIC's PCBR Framework

The MDIC PCBR Framework is intended to provide insight and suggestions for how the patient's perspective on benefits and harms might be incorporated into the regulatory approval process [8]. It reflects commonalities that were identified across the disparate missions and perspectives of industry, FDA staff, patient advocacy groups, and others. As such, the Framework covers a wide range of topics, including background concepts on benefit-risk assessment and preferences, conditions when patient preferences may be especially valuable to collect data, potential uses for preference information throughout the product development life cycle, practical considerations when conducting a preference study, roles for preference information in the regulatory process and postapproval, and a research agenda to improve approaches for collecting and using preference data. These sections of the Framework build on one another, although they can also be read independently. Although the Framework depends on quantitative measures of patient preference and clinical trial data, the Framework itself is qualitative and conceptual—requiring of the reader only familiarity with the product development cycle and clinical judgment.

The terminology that at present describes patient-centered benefit-risk is rife with ambiguity because of its simultaneous evolution in distinct professional settings. To reduce this ambiguity, the Framework defines *benefit* as a favorable effect or desirable outcome of a diagnostic or therapeutic strategy and a *harm* as an unfavorable effect or undesirable outcome [1]. *Risk* is defined as the qualitative notion of the probability and/or severity of a harm. These definitions align with both scientific literature on benefit-risk assessment and regulatory precedence, in particular CDRH usage [1]. *Preferences* are defined as qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions, whereas *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 [1].

A key concept in the MDIC Framework is the intuitive and scientifically supported notion that patients vary greatly in the degree to which they will accept risk for a given benefit. For a given device with well-characterized benefits and risks, even when these properties are uniform over a population, some patients may consider the benefits to outweigh the risks, whereas others may not. A patient preference study can assess preferences for a population overall as well as heterogeneity in preference and whether there are distinct subgroups whose preferences would lead them to make different decisions. A major role for preference information in development and regulatory decisions is to provide information for whether to consider approving a device for an entire population or only for those patients whose preferences are such that they regard benefits as exceeding risks.

It can be challenging to know whether and when resources, budget, and time should be allocated to a patient preference study. This is especially the case at present because patient preference information is not a requirement for approval of medical devices, and its inclusion in a regulatory submission is optional at the election of the sponsor. The MDIC Framework identifies a set of factors that suggest patient preference information could be valuable in supporting development or regulatory review (Table 1). These factors relate to the unique perspective of patients with the condition, benefit-risk trade-offs inherent in the device (Fig. 1), and novelty of the indication or technology.

The MDIC Framework describes many roles for patient preference information in device development and review. These roles fall into three categories: 1) framing benefit-risk issues, 2) identifying subgroups of patients with decision-relevant differences in preferences, and 3) providing information for quantitative benefit-risk modeling. Framing benefit-risk issues includes helping characterize medical devices on the basis of benefit-risk assessments of existing treatments, determining which issues and end points are most important to patients (and most relevant

Table 1 – Factors suggesting patient preference information will be valuable in supporting device development or regulatory review.

Factors related to the perspective of patients as stakeholders	• Patients are willing to accept a different degree of risk or require a different degree of benefit than do providers or regulators • Patient preferences vary across the population sufficiently that there are substantial subgroups that would make different decisions whether to use the product • Understanding the clinical experience requires considerable personal familiarity with the disease, for example, rare diseases, highly subjective end points (pain, nausea, itch), quality of life, lifestyle indications (baldness, impotence, wrinkle reduction) Self-use treatments vs. treatment by a health care provider (e.g., in-home dialysis)
Factors related to benefit-risk trade-offs inherent in a technology	• The benefit-risk trade-off is marginal ("close calls")—all but the upper left quadrant in Figure 1 • The device entails temporal trade-offs, such as early benefits with harms occurring much later or initial harms with benefits occurring much later (e.g., a treatment to delay onset of a disease, obesity device surgery) • The device results in benefits and/or harms that are substantially different from those in existing treatments (e.g., implanted device vs. oral drug) • When there is considerable uncertainty about the frequency and/or severity of benefits and harms of the new and existing treatments
Factors related to regulatory novelty	• Populations or indications with which FDA has limited regulatory precedent • New technologies in an existing clinical area or use of an existing technology in a new area

FDA, Food and Drug Administration.

to a regulatory decision), assessing the relative importance of end points, and determining the maximum acceptable risk for a given benefit or the minimum required benefit for a given risk. This can be of particular value when demonstrating that patients are willing to accept more risk or less benefit than reviewers might otherwise expect. Identifying subgroups on the basis of preferences may have a role in identifying the population for approval, as noted earlier. Patient preference subgroups also can suggest new markets for a present indication and related disease states to which a technology may apply. Finally, although not needed in most regulatory situations, quantitative benefit-risk models can be valuable in complex cases. Preferences data can be used as weights to scale differences in probability or severity of benefits and harms to reflect their importance to patients. These three roles for patient preference information manifest in discovery, prototyping, preclinical development, presubmission sponsor/FDA interactions, clinical trials, submission and review, and postmarket activities.

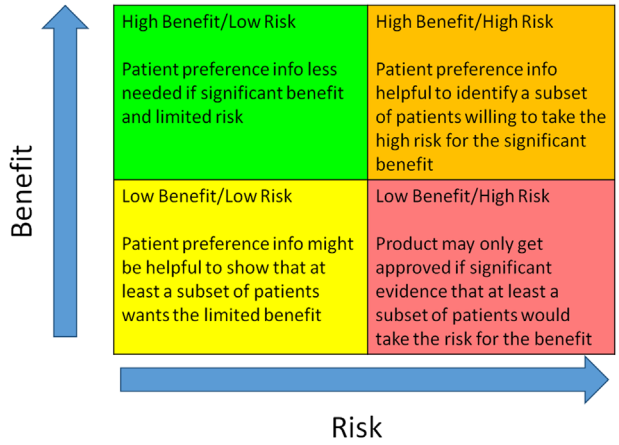

Fig. 1 – The value of patient preference information as a function of benefit and risk.

The MDIC Framework also addresses the question of which preference assessment method is most appropriate to use. This is a complex issue for which there is no algorithmic approach, although there are a number of important factors that have an impact on the decision. The Framework describes how the method selection depends on the research question being addressed, the present level of knowledge of the benefits and harms for a technology, how well the population being studied can be defined and obtained, the diversity of the population, the roles intended for the preference information, previous experience by the sponsor with applying methods to similar problems, and the budget, expertise, and time available.

Patient preference information has a similar role in the regulatory process as it does during product development: defining how to frame benefit-risk issues so they are most germane for patient decision making, identifying preference subgroups for whom preferred decisions would be different, and supporting benefit-risk modeling to guide patient-centered decision making. An important application of characterizing patient preferences is how patient preference information could be included in product-approval labeling. A comprehensive discussion of label issues is beyond the scope of the Framework, but several points are noted. It may be valuable to include preference information in the label if that information played an important role in the approval decision. If, as discussed earlier, a product is approved for a subgroup defined in part by their preferences, information that helps patients identify the preference subgroup to which they belong will be especially important for the label. Nevertheless, in contrast to subgroups defined by demographic or diagnostic information, preference studies generally do not allow a direct, prospective inference of preferences for an individual patient. Dealing with these issues will require addressing the role

of shared medical decision making and decision support tools, and validating and auditing preference data.

The Framework concludes with a research agenda on the use of patient preferences that may further efforts to make CDRH benefit-risk assessment more patient-centric.

MDIC's Preference Assessment Methodology Catalog

Patient preference assessment is a nascent yet evolving scientific discipline. To facilitate uptake of collecting and using patient preference data among major stakeholders (researchers, industry sponsors, and FDA staff) to support development, regulatory, and postmarketing decisions related to medical technologies, the MDIC has created a catalog of patient preference methods for them to consult when considering which patient preference methods could be used. MDIC created a working group consisting of academia, industry, and subject matter experts to develop the Catalog.

The MDIC Methods Catalog's objective is to identify a range of available methods to quantify patients' benefit-risk preferences. The Catalog aims to provide a general overview, not a systematic review, of these methods, and serves as a starting point for understanding the range of approaches available to assess patients' preferences.

Created within the context of medical product life cycle, the Catalog operationally defines patient preference methods as "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." The methods to be included in the Catalog were divided into four groups: structured weighting, health-state utilities, stated preference, and revealed preference. The grouping reflects the nature of the method (e.g., stated vs. revealed), the present application of the method (e.g., whether used as part of a decision-analysis method), and the underlying theoretic framework (e.g., ordinal- or random-utility-theoretic methods for most stated-preference methods). These methods are listed in Table 2.

The MDIC Methods Catalog describes each method and provides examples of its previous use. To help the stakeholders to understand and distinguish different methods, the Catalog poses questions for them to consider when considering different methods for their specific research needs. These questions relate to methodology, sample, analysis, and output considerations. Each method is also reviewed using the presented factors. In addition, the Catalog identifies a number of general considerations related to the implementation of patient preference studies that are common across methods. These include sample representativeness and generalizability of results, heterogeneity of patients' preferences, validity of patient preference methods, and resources required to conduct a patient preference study.

The Catalog concludes with the following forward-looking research agenda for investigators to consider:

1. Comparing performance of some patient preference methods relative to other potential methods in some given situations;
2. Developing some guidelines to determine the sample adequacy;
3. Conducting a benefit-risk preference study designed to determine the impact of changing the list of attributes with any given method; and
4. Developing approaches to validate patient preference studies.

Table 2 – List of methods included in the Catalog.

Group	Method
Structured weighting	• Simple direct weighting • Ranking exercises • Swing weighting • Point allocation • Analytic hierarchy process • Outranking methods
Health-state utility	• Time trade-off • Standard gamble
Stated preference	• Direct-assessment questions • Threshold technique • Conjoint analysis and discrete-choice experiments • Best-worst scaling exercises
Revealed preference	• Patient preference trials • Direct questions in clinical trials

Implications of the Framework and Future Work

The MDIC Framework is intended to be a living document, not meant to be static, and will be updated and edited with regularity by the PCBR Steering Committee as more evidence and additional tools, methods, and approaches are evaluated and added. This first version was based on limited experience with regulatory patient preference studies, primarily CDRH's obesity study [5], as well as other experiences with patient preference assessment methods outside the regulatory context, such as health economics research. Additional patient preference studies for regulatory submissions, conducted by sponsors, patient groups, and perhaps CDRH, will add to the depth and experience of this nascent field.

Patient preference information is not intended to be a substitute for safety and clinical effectiveness evidence, but it is meant to be an additional form of evidence included in the development and regulatory submission of a device. Patient preference information provides additional data for consideration, but it does not eliminate the need for clinical and safety data. As stated in Section 2.2 of the CDRH draft guidance Patient Preference Information—Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling, "If FDA determines the device would expose patients to unreasonable or significant risk of illness or injury, or the benefits do not outweigh the risk for some definable target population, FDA would not approve such a device" [6].

Although the MDIC Framework was created to aid decision making regarding medical devices, it may be of interest to stakeholders in other therapeutic domains including pharmaceuticals and biologics. Indeed, other organizations, including FasterCures [9], the Biotechnology Industry Organization [10], the Drug Information Association [11], and the European Patients' Academy on Therapeutic Innovation [12], have provided programming targeted at various stakeholder groups including pharmaceutical and biologics companies about the importance of and methods for eliciting and documenting patient preference in medical product development. The patient preference assessment methods also have potential applications beyond the regulatory context, such as in marketing, reimbursement decisions, and shared medical decision making [1].

The development of the MDIC PCBR Framework comes because patient perspective is increasingly a key part of the conversation on medical innovation in medical devices, drugs, and biologics. The importance of the patient perspective in both the regulation and the development of innovative medical

technologies was included in the 21st Century Cures Initiative, a bipartisan congressional effort to speed access to medical innovation [13]. It is already gaining traction in patient and disease-specific groups that are advocating to have patient preferences considered as part of the regulatory review of new medical technologies. Other academic or public-private groups and regulatory agencies in Europe and Canada are exploring methods for assessing patient preferences. These efforts will provide ripe ground for cross-collaboration and opportunity to advance the field of patient preference assessment for the benefit of researchers, sponsors, regulators, and most of all patients.

As the MDIC Framework gains traction throughout the medical device community, it is intended to spark conversations among industry and CDRH about the role of preference information in the regulatory submission process and across the medical device product life cycle. Additional experience with regulatory patient preference studies and the Framework will reveal the success of this first endeavor and whether there are additional factors that should be addressed in future versions. MDIC will not directly conduct patient preference assessment studies but will encourage its device company members and other organizations to do so by providing tools and resources, such as best practices documents, references to existing studies, and advancing patient preference methodology research.

What began as a component of patient advocacy is beginning to evolve into an important piece of the growing science of understanding patient preferences for benefits, harms, and related treatment characteristics and incorporating those preferences into the processes of developing, regulating, and delivering medical devices and drugs. MDIC, through its public-private partnership, has developed an initial thought piece cataloging selected methods of patient preference assessment and how patient preference information can illuminate the patient perspective across the medical device product life cycle.

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