ACRP Regulatory Affairs Committee Review of FDA Draft Guidance Document

Patient Preference Information – Submission, Review in PMAs, HDE Applications and De Novo Requests, and Inclusion in Device Labeling

What is the guidance?
This guidance is to help Sponsors and other stakeholders make informed decisions on whether and how to collect and report voluntary patient preference information for certain devices to aid in FDA's assessment of the overall benefit-risk profile as well as added information for labeling of these devices.

Who does it impact & how?
This guidance applies to Sponsors and other stakeholders of diagnostic and therapeutic devices submitting PMAs, HDE Exemption Applications and de novo requests by providing recommendations for obtaining quality patient preference information, providing that information to FDA and how to incorporate patient preference information in device labeling.

What did ACRP RAC have to say about it?
ACRP's RAC requested that the Agency remove the possibility of a caregiver providing patient-centric information on a patient's behalf. In one instance, the FDA made comment about requiring special informed consent. The Review Team requested that this be clarified and supported by regulatory citations. Additional comments included minor suggestions for improved clarity and removal of inapplicable text and new terms to be defined. The committee also requested clarification on whether this guidance applies to In Vitro Diagnostics as well as IDEs.

When were the RAC's comments sent to the agency?
August 17th, 2015

Where can I access this document?
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf

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August 17, 2015

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In reference to docket number: **FDA-2015-D-1580-0001**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

In light of the growing movement for the "Right to Try" unapproved medical products, which concern our constituents on many levels, we are pleased to support the efforts on the part of the Agency to encourage to measure risk-tolerance and incorporate that into the decision making process for approvals. These concepts fit well with the device development lifecycle, quality system management and design control processes already in place in the US. ACRP appreciates the opportunity to provide the FDA with our comments on the *Patient Preference Information – Submission, Review in PMAs, HDE Applications, and* De Novo *Requests, and Inclusion in Device Labeling* draft guidance as this issue has a significant impact on our membership. The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

We applaud the FDA's efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Terri Hinkley, RN, BScN, MBA, CCRC
Interim Executive Director

FDA-2015-D-1580-0001 :Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling			
Page Number	**Text Line**	**Reference** *(if applicable)*	**Comments**
2	66-67	Overview and Scope	Please clarify if In Vitro Diagnostics are also within the scope of this guidance document.
4	104	IDE	This text indicates the guidance is applicable to IDEs, so please add IDE to the title of and throughout the document.
10	337-339	Patient Innovator	Please define what a "Patient Innovator" is.
10	342-343	Computer Modeling	We are unclear why this bullet is included. What does computer modeling have to do with Patient Preference Information?
10	347-349	Visit Schedules	Since most study visit follow-up schedules are medically defined, we would like to request that you add "in so far as medically acceptable" to the sentence indicating that patient preference may be taken into account regarding visit schedules.
10	352-355	CDRH Study cited	We request that FDA add information confirming that the study used in the example was designed and statistically powered to support these conclusions and if it was not, we would request removal of this section of text from the guidance.
10-11	NA	Figure 1	Figure 1 identifies one of the "Patient Sparing Testing Methods" as "natural clinical trials". The text describing Figure 1 does not mention this, but does state "non-clinical trials". Should Figure 1 state non-clinical rather than natural? If not, please provide details about what a "natural clinical trial" is.
13	427-430	Patient Centeredness	"Patient preference studies should ensure that the patient, not the health care professional, is the central part of the study. The study should aim to measure inherent attitudes and values of well-informed patients. This could also include evaluating caregiver, parent, or guardians' preferences in situations when the patient may not be able to provide the patient preference perspective."

			We are not in favor of permitting care givers to provide patient centric information any more than we would be of having healthcare providers provide such information on their patient's behalf. We would request removal of caregiver from last sentence.
18	610-612	MDDTs	If any of the current MDDTs are PPI tools, please specify in this document as examples.
19	647-648	Last sentence	We request that FDA expand on this section regarding how to add PPI information to labeling by clarifying what section of the label to include this and what prominence means to a reviewer.
19	650-653	Special Informed Consent	Is the Agency proposing a new type of informed consent? What Regulatory Citation is applicable to this requirement? Informed Consent requirements currently in place do not appear to address this type of need. Clarification is requested.
22	773	'sizeable group'	Please provide specifics rather than generalities here. Please provide further guidance on how industry can determine what constitutes a sizeable group.
23	804	'majority'	Please provide specific numbers or percentages rather than generalities.

Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling

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Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on May 18, 2015.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov) or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1500006 to identify the guidance you are requesting.

Additional copies are available from the Center for Biologics Evaluation and Research (CBER) by written request from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., WO71, Room 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-7800, by email, ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

The U.S. Food and Drug Administration (FDA or the Agency) values the experience and perspectives of patients with devices. The Agency understands that patients and caregivers who live with a disease or condition on a daily basis and utilize devices in their care may have developed their own insights and perspectives on the benefits and risks of devices under PMA, HDE, or *de novo* review. FDA believes that patients can and should bring their own experiences to bear in helping the Agency evaluate the benefit-risk profile of certain devices. This kind of input can be important to consider during regulatory decision-making for certain devices.

For this reason, FDA's guidance document "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications"[1]

[1] See FDA's *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* issued on March 28, 2012

(hereafter referred to as the Benefit-Risk Guidance) explains that reviewers may consider certain data measuring patient perspectives during the premarket review process for premarket approval applications (PMAs) and *de novo* classification requests, when such information is available. That guidance specifies that patient tolerance for risk and perspective on benefit, in addition to several other factors, may be considered in FDA's assessment of the benefit-risk profile of certain devices when the information meets FDA's standards for valid scientific evidence.[2]

This draft guidance document takes the next step and provides guidance on patient preference information that may be used by FDA staff in decision-making relating to PMAs, Humanitarian Device Exemption (HDE) applications, and *de novo* requests. The objectives of this draft guidance are: 1) to encourage voluntary submission of patient preference information by sponsors or other stakeholders, in certain circumstances; 2) to outline recommended qualities of patient preference studies, which may result in valid scientific evidence; 3) to provide recommendations for collecting patient preference information to FDA; and 4) to provide recommendations for including patient preference information in labeling for patients and health care professionals. This draft guidance also includes several hypothetical examples that illustrate how patient preference information may inform FDA's regulatory decision-making.

This draft guidance is proposing edits to the Benefit-Risk Guidance that are shown in Appendix A.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Overview and Scope

This draft guidance document explains the principal concepts that sponsors and other stakeholders should consider when choosing to collect patient preference information, which may inform FDA's benefit-risk determinations in the premarket review of PMAs, HDE applications, and *de novo* requests. This draft guidance also provides recommendations on how patient preference information should be incorporated into device labeling for patients and health care professionals. This draft guidance is applicable to both diagnostic and therapeutic devices that are subject to these review processes.

(http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandguidance/guidanceDocuments/UCM296379.pdf).

[2] See 21 CFR 860.7 for a further discussion of valid scientific evidence.

This draft guidance addresses only patient tolerance for risk and perspective on benefit, and does not address other factors in FDA's assessment of the benefit-risk profile of a device, as described in the Benefit-Risk Guidance. FDA may consider certain submitted patient preference information, along with the totality of evidence from clinical and nonclinical testing, during the premarket review process and FDA's benefit-risk determination for devices. Notably, this draft guidance does not change any review standards for safety or effectiveness (refer to Section 3.6), or create any extra burden on sponsors of premarket submissions. Rather, it provides recommendations relating to the *voluntary* collection of patient preference information that may be submitted for consideration as valid scientific evidence as part of FDA's benefit-risk assessment during its review of PMAs, HDE applications, and *de novo* requests.

Submission of patient preference information to FDA is voluntary. Patient preference information can be useful during FDA's benefit-risk assessment for devices in several major ways: 1) to help identify the most important benefits and risks of a technology from a patient's perspective; 2) to assess the relative importance to patients of different attributes of benefit and risk, and clarify how patients think about the tradeoffs of these benefits and risks for a given technology; and 3) to help understand the heterogeneity or distribution of patient preferences regarding benefits and risks of various treatment or diagnostic options. Because the mechanism of action for devices is often well-characterized and fairly localized, patient preference information may be more practical to obtain for devices than for pharmaceutical or biologic treatments, where more systemic effects occur and off-target adverse effects may not always be comprehensively anticipated.

Patient preference information may not be relevant or appropriate for all device types. Furthermore, not all benefit-risk scenarios are "preference-sensitive." Preference-sensitive benefit-risk scenarios may occur when multiple treatment options exist and there is no option that is clearly superior for all preferences, when the evidence supporting one option over others is considerably uncertain or variable, and/or when patients' views about the most important benefits and acceptable risks of a technology differ considerably from those of health care professionals.

Certain concepts discussed in this draft guidance are applicable to the device development process from design to market. As such, the patient preference considerations set out herein also may be informative to sponsors during the design, non-clinical testing, pre-submissions, and Investigational Device Exemption (IDE) phases of their device development. Additionally, this draft guidance may be informative to other stakeholders such as patient groups and academia who may wish to consider conducting patient preference studies. The Agency encourages sponsors and other stakeholders considering conducting patient preference studies for regulatory purposes to FDA to have early interactions with the relevant FDA review division.

III. Background

Historically, some patients have brought their views to FDA regarding the approval or clearance of FDA-regulated medical products. Their views have influenced regulatory decisions by providing additional insight and helped to provide the public with faster access to safe and effective medical products, such as those for patients with HIV[3] and multiple sclerosis.[4]

Section 1137 of the Food and Drug Administration Safety and Innovation Act (FDASIA) directs the Agency to "develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions" (section 569C of the Federal Food, Drug & Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-8c(a))).

In recent years, patient representatives have served as non-voting members on panels of FDA's Medical Devices Advisory Committee. FDA intends to provide a systematic way to help to ensure that patients are represented and patient perspectives are considered in the regulatory decision-making process.

To solicit stakeholders' views and better understand the barriers patients have expressed in trying to participate in the regulatory process for devices and the state of the science of measuring patient preferences, FDA opened a public docket and announced a public workshop,[5] which was held on September 18 and 19, 2013. This workshop served as the public launch of CDRH's Patient Preference Initiative for devices, announced in 2012 as a strategy to better understand and assess patient perspectives to help inform the development and FDA review of devices. The Agency heard from a range of researchers, industry representatives, and numerous patient groups and has considered their comments and suggestions on using patient preference information in the review of PMAs, HDE applications, and *de novo* requests.

3.1 What is patient preference information?

[3] Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS, http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm134331.htm (last visited, October 1, 2014).
[4] See FDA's *Guidance for Industry; Expedited Programs for Serious Conditions—Drugs and Biologics*, issued May 2014 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf).
[5] See Public Workshop - The Patient Preference Initiative: Incorporating Patient Preference Information into the Medical Device Regulatory Processes, September 18-19, 2013, http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm361864.htm (last visited January 15, 2015); see also The Patient Preference Initiative: Incorporating Patient Preference Information Into Medical Device Regulatory Processes: Public Workshop; Request for Comments (78 FR 45538) (July 29, 2013) (https://www.federalregister.gov/articles/2013/07/29/2013-18080/the-patient-preference-initiative-incorporating-patient-preference-information-into-the-medical).

Patient perspectives include a wide range of information including anecdotal comments in correspondence to the FDA or testimony at Advisory Committee Panel meetings, patient opinions expressed publicly including through social media, patient responses to qualitative *ad hoc* surveys, quantitative measurements of patient-reported outcomes, and more.

This draft guidance focuses on ***patient preference information***, which for the purposes of this draft guidance, is defined as qualitative or quantitative assessments of the relative desirability or acceptability of attributes that differ among alternative diagnostic or therapeutic strategies.[6]

Attributes of a device are features such as effectiveness, safety, means of implantation, duration of effect, duration of use, and other device characteristics that may affect benefit-risk considerations.

In the context of benefit-risk assessments, qualitative information may be useful in identifying which outcomes, endpoints or attributes matter most to patients and which factors affect patients' risk tolerance and perspective on benefit. Quantitative information can provide estimates of *how much* different outcomes of features matter to patients and the tradeoffs that patients state they are willing to make among them. Patients may be queried about their risk tolerance and benefit-risk preferences *a priori* (to prospectively report their preferences without prior experience with a particular device) or after receiving treatment.

Patient-centric assessments should take into account both the patient's willingness and unwillingness to tolerate risks associated with device use. Both willingness and unwillingness are helpful in determining patient tolerance for risk and perspective on benefit and may be informative in FDA's assessment of the benefit-risk profile of a device.[7]

3.2 Why include patient preference information in regulatory decision-making?

It is important to acknowledge that individual patient preferences may vary, and that a patient may not assign the same values to various risks and anticipated benefits as his/her health care professional, a family member, regulator, or another individual. Furthermore, patient preferences may vary both in preferred modality of treatment/diagnostic procedure (e.g., often devices are one option to be considered in a treatment care path, which may include surgery or medication) as well as in risk tolerance. Some patients may be willing to take on higher risks to potentially achieve a small benefit, whereas others may be more risk-averse, requiring more benefit to be willing to take on certain risks.

[6] See definition set forth in the Patient-Centered Benefit-Risk (PCBR) Assessment presentation at the Medical Device Innovation Consortium (MDIC) Annual Meeting, June 25, 2014 Washington, DC, available at http://mdic.org/wp-content/uploads/2014/06/Patient-Centered-Benefit-Risk-PCBR-Project-update.pdf ("Qualitative or quantitative assessments of the relative desirability or acceptability of features that differ among alternative diagnostic or therapeutic strategies.").

[7] See Footnote 1.

An individual's personal values, disease stage, family circumstances, age and demographic characteristics may also influence his/her benefit-risk preferences. Evaluations of patient-centric variations in tolerance to risks and perspective on benefits may, in the aggregate, reveal a population-level assessment of patient benefit-risk preference for that device, which may be considered valid scientific evidence (see 21 CFR 860.7) and may inform FDA's benefit-risk assessment for a device. If this assessment reveals that a significant number of reasonable and well-informed patients would accept the probable benefits despite the probable risks, this may help support a favorable benefit-risk profile.[8]

Furthermore, it may be appropriate to approve a PMA, approve an HDE application, or grant a *de novo* request for use of a device by a subset of the population for which an indication is requested when valid scientific evidence shows that the probable benefit of a device outweighs probable risks of the device for that subset. In making such a determination, FDA would consider patient preference information along with the totality of evidence from clinical and nonclinical testing. If FDA determines the device would expose patients to an unreasonable or significant risk of illness or injury, or the benefits do not outweigh the risks for some definable target population, FDA would not approve such a device.

3.3 Are there established quantitative methods to elicit patient preferences?

There are a variety of quantitative approaches to eliciting patient preferences. Such approaches attempt to quantify the whole patient-preferences spectrum from individual patients, which requires careful study design, conduct, and analysis. For straightforward decisions regarding risk tolerance and patient preference, qualitative input may be sufficient. Complex questions regarding such issues, however, may require quantitative evidence to ensure that different outcomes are properly weighed in the same scale and therefore can be compared.

Multiple studies have identified and compared a variety of methods to measure patient preferences on benefits and risks and derive preference weights in a scale that allows for direct comparison.[9,10,11] The majority of these studies have used a class of methods called stated preference , in which preferences are elicited by offering choices to participants. Other studies have used revealed-preference methods, in which patient preferences are obtained from the actual clinical choices made by patients. Both stated-preference and revealed-preference methods may be informative for understanding patient preferences. Some stated-preference and revealed-preference methods are outlined in Appendix B to this draft guidance.

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[8] See Footnote 1 for guidance on other principal factors that FDA considers when making benefit-risk determinations in the premarket review of certain devices.

[9] "Catalog of methods for assessing patient preferences for benefits and harms of medical technologies," MDIC deliverable for the FDA Board Agency Announcement Contract, April 22, 2015.

[10] A.B. Hauber, *et al.,* "Quantifying Benefit–Risk Preferences for Medical Interventions: An Overview of a Growing Empirical Literature," *App. Health Econ. Health Policy*, 319-329 (2013).

[11] D. Hughes, *et al., IMI-PROTECT Benefit-Risk Group: Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines* (2013).

Many of the standard stated-preference methods require some simplification of the decision problem to a manageable subset of decision variables compared to what individual patients are likely to face. For an assessment of actual patient choices and behavior it may be feasible to obtain information via revealed-preference methods. However, revealed-preference methods often cannot be applied because a device profile of interest may not yet be available for patients to choose when a device is under regulatory review. Selection of appropriate testing methods will depend on the primary use of patient preference information.

FDA acknowledges that quantitative patient preference assessment is an active and evolving research area. We hope this draft guidance serves as a catalyst for advancement of the science, through continual development and refinement of quantitative methods for eliciting patient preferences regarding benefits and risks associated with use of devices.

3.4 How is patient preference information different from patient-reported outcomes?

A ***patient-reported outcome (PRO)*** is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.[12] PROs are patient-reported information that otherwise might not be clinically observable or reported. For example, two widely used PROs are the Visual Analogue Score (VAS) for pain and the Health Assessment Questionnaire (HAQ) and Disability Index (DI) score for physical function.

While PROs may provide a snapshot of a patient's own assessment of various outcomes at a given point in time, they do not convey how much the patient values one outcome when facing a trade-off with other potential therapies. Assessing this type of tradeoff is what patient preference studies are designed to measure. These studies may address, for example, whether a patient would be willing to choose a treatment that causes a certain level of reduction in physical function (in HAQ and DI) in exchange for an improvement in pain relief (in VAS). Quantitative methods have been developed to answer this type of question by eliciting patient preferences for attributes that differ among alternative options.[13, 14, 15] PROs are designed to measure a patient's perceptions of health status before and after therapy, while patient preference studies are designed to measure what type of therapy or attributes of a given therapeutic or diagnostic strategy a patient might prefer.

3.5 Is the submission of patient preference information required?

[12] See FDA's *Guidance for Industry; Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, issued December 2009 (http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf).
[13] See Footnote 9.
[14] M Agapova, *et al.*, "Applying Quantitative Benefit–Risk Analysis to Aid Regulatory Decision Making in Diagnostic Imaging: Methods, Challenges, and Opportunities," *Academic Radiology*, 1138-1143 (2014).
[15] See Footnote 10.

Submission of patient preference information to FDA is voluntary. Patient preference information may not be relevant or appropriate for all device types. However, it may be useful for sponsors to collect and submit such information for PMAs, HDE applications, and *de novo* requests, particularly for those product types and diseases or conditions where usage decisions by patients and health care professionals are "preference-sensitive." Preference-sensitive decision scenarios may occur when a patient has multiple treatment options and there is no option that is clearly superior for all preferences, when the evidence supporting one option over others is considerably uncertain or variable, and/or when patients' views about the most important benefits and acceptable risks of a technology vary considerably within a population.

Such circumstances may exist for devices with the following attributes:

- Devices with a direct patient interface.
- Devices intended to yield significant health and appearance benefits.
- Devices intended to directly affect quality of life.
- Certain life-saving but high-risk devices.
- Devices developed to fill an unmet medical need or treat a rare disease or condition.
- Devices with novel technology.

3.6 When and how might FDA consider patient preference information during the review of PMAs, HDE applications, and *de novo* requests?

As discussed further below, patient preference studies can provide valid scientific evidence regarding patients' risk tolerance and perspective on benefit may inform FDA's evaluation of a device's benefit-risk profile. This draft guidance discusses the Agency's evaluation of a device's benefit-risk profile during the PMA, HDE, and *de novo* review processes below. Moreover, hypothetical examples of how FDA might consider patient preference information when making benefit-risk assessments are described in Section VIII.

FDA's Evaluation of PMAs. In the PMA approval review, FDA determines whether a device provides a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors (section 513(a)(2)(C) of the FD&C Act (21 U.S.C. 360c(a)(2)(C))).[16] A reasonable assurance of safety occurs when "it can be determined, based upon valid scientific evidence, that the probable benefits … outweigh any probable risks," and the valid scientific evidence adequately demonstrates "the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use" (21 CFR 860.7(d)(1)). Moreover, a reasonable assurance of effectiveness occurs when "it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses … will provide clinically significant results" (21 CFR 860.7(e)(1)). The evidence used to

[16] See Footnote 1.

determine the effectiveness of a device is demonstrated principally through "well-controlled investigations" (see 21 CFR 860.7(e)(2), as defined in 21 CFR 860.7(f)).

FDA's Evaluation of HDE Applications. An HDE application is similar to a PMA, but is exempt from the effectiveness requirements of sections 514 and 515 of the FD&C Act (21 U.S.C. 360d and 360e). FDA approval of an HDE authorizes an applicant to market a Humanitarian Use Device (HUD), a device intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals, subject to certain profit and use restrictions set forth in section 520(m) of the FD&C Act (21 U.S.C. 360j(m)). To approve a HUD under the HDE pathway, FDA must determine, among other things, that "the device will not expose patients to an unreasonable or significant risk of illness or injury" and "the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment" (section 520(m) of the FD&C Act (21 U.S.C. 360j(m)).

FDA's Evaluation of* De Novo *Requests. Section 513(f)(2)(A)(ii) of the FD&C Act (21 U.S.C. 360c(f)(2)(A)(ii)), modified by section 607 of FDASIA, provides a regulatory pathway whereby if sponsors believe their devices are appropriate for classification into class I or class II and that there is no legally marketed predicate device, they may submit a *de novo* request for FDA to make a risk-based classification. FDA also will review devices under the *de novo* pathway if it has determined the device to be not substantially equivalent due to (1) the lack of an identifiable predicate device, (2) new intended use or (3) different technological characteristics that raise different questions of safety and effectiveness (see section 513(f)(2)(A)(i) of the FD&C Act (21 U.S.C. 360c(f)(2)(A)(i))).

As noted in the Benefit-Risk Guidance, "because devices classified under this pathway (*de novo* devices) are low to moderate risk devices, they may not need to confer as substantial benefit to patient in order to have a favorable benefit-risk profile." As such, FDA has said that "[d]evices granted marketing authority under *de novo* petitions should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general and/or special controls to provide reasonable assurance of safety and effectiveness. Further, devices classified under *de novo* petitions may serve as predicates for future devices which can be appropriately regulated through the 510(k) program; therefore, FDA carefully considers the benefit-risk profile of these devices in the determination that there is reasonable assurance of safety and effectiveness.[17]

3.7 Can FDA or sponsors use or consider patient preference information be used at times other than during the submission and review of PMAs, HDE applications, and *de novo* requests?

[17] See Footnote 1.

In addition to FDA's consideration of patient preference information during the review of PMAs, HDE applications, and *de novo* requests, FDA and sponsors may use patient preference information throughout the total product lifecycle as shown in Figure 1. For example:

- During the discovery and ideation phase, patient preferences may inform device design and/or features. Additionally, patient innovators may influence which devices are developed.
- During invention and prototyping, patient-sensitive design inputs may help developers refine device design, such as through human factors testing.
- During nonclinical testing, patient-sparing test methods, such as computer modeling, may reduce the risk to patients of early stage devices.
- Qualitative patient preference information may inform the design of clinical trials by helping to identify what endpoints are important to patients. For example, qualitative patient preference information could inform which PROs should be part of the data obtained. Moreover, qualitative patient preferences can inform aspects of design and conduct of clinical trial which may affect subject participation, such as visit schedules and follow-up procedures.
- Quantitative patient preference information may inform the design of clinical trials by providing prior evidence regarding the level of benefit patients require in order to accept a certain level of risk of medical device treatments. Moreover, as exemplified in the CDRH Patient Preferences of Weight Loss Devices Study (see Section IV), quantitative patient preferences can be used to inform the establishment of the "minimum clinically meaningful benefit" to be used in the design of a clinical trial.
- After the product is launched, patient responsive device labeling and shared clinical decision-making tools may be employed to make sure that the benefit-risk determinations are appropriately communicated to patient and health care professionals.
- Once a device is widely available, benefit-risk determinations may become an important part of postmarket data collection and monitoring.
- As postmarket patient-centered data accumulates, it may be used by developers to inform redesign and improve devices for future patients or lead to new innovations or to support expanded indications.

In a product development program that is patient-centered, patient preference information may be considered at various decision points throughout the total product lifecycle. In many cases, this information is best considered not as discrete and disconnected, but rather may be informative to future development stages. For example, qualitative patient preference information which informs device design or clinical trial design may shape future quantitative studies of patient preference which may inform FDA benefit-risk assessments during premarket review.

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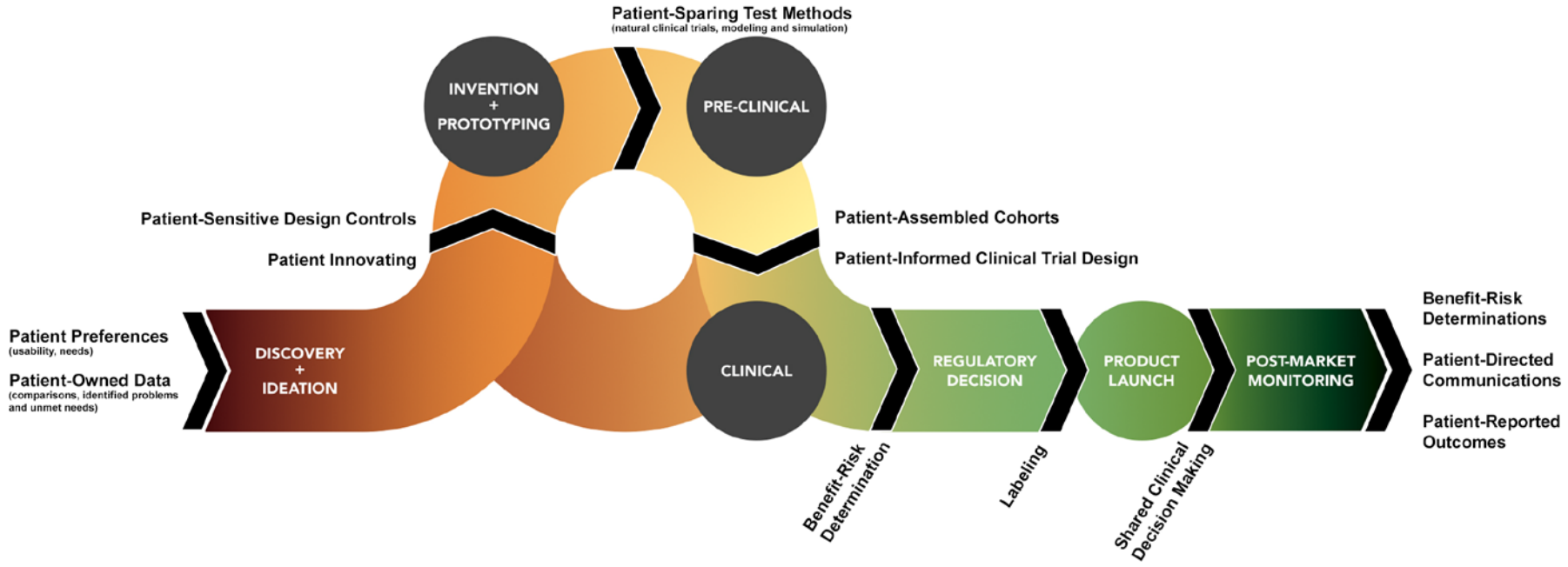

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375 Figure 1. Patient Preference Information in the Total Product Lifecycle

IV. Recommended Qualities of Patient Preference Studies

Based on the literature on standard practices in patient preference studies, the Agency intends to consider the following study qualities, among other things, when deciding whether patient preference information constitutes valid scientific evidence:[18,19,20,21]

a) ***Representativeness of the Sample and Generalizability of Results***: A study should measure the preferences of a representative sample of adequate size to ensure that the study results can be generalized to the population of interest. In those cases in which detecting differences in preferences between pre-specified subgroups may be important, the sample should include sufficient numbers in each subgroup.

   Another important factor to consider is how similar the sample of interest is to the population of interest. The representativeness of a sample may be influenced by its size, the between-subject variability, and how subjects were sampled from the population of interest. For example, if a sample size is small but subject variability in the population of interest is large, the study result may not be representative of the population of interest because it may not include the whole spectrum of patient preferences. Moreover, when a sample is very small, the estimates of patient preference parameters may not be sufficiently precise and the study conclusion may not be reliable.

b) ***Capturing Heterogeneity of Patients' Preferences***: Patients' benefit-risk tradeoff preferences may be heterogeneous even among those with the same disease or condition. Individual circumstances of patients vary. Besides gender, age, race, socioeconomic, and cultural background, a patient's own experience of his/her disease may influence the patient's personal risk tolerance attitude. As mentioned in the Benefit-Risk Guidance, patient views may be influenced by the severity of the disease or condition, disease chronicity, or availability or lack of alternatives. It is important to account for these variations when considering patient preference information. This variability may be population-, condition-, treatment-, and study-specific. Therefore, patient preference information should reflect the preferences of patients from the entire spectrum of disease for which the device is intended to be used.

   While some study methods can account for preference heterogeneity with sufficient sample size, only a few methods such as discrete choice experiments may effectively identify and quantify preference heterogeneity. Patient preference information may

[18] See Footnote 9.
[19] F.R. Johnson, *et al*., *Quantifying Patient Preferences to Inform Benefit-Risk Evaluations* in *Benefit-Risk Assessment in Pharmaceutical Research and Development*, CRC Press (2013).
[20] F. Mussen, *et al., Benefit-Risk Appraisal of Medicines*, John Wiley & Sons Ltd (2009).
[21] See Footnote 11.

help identify a subgroup of patients (e.g. patients with higher pain and functional limitation) who consider the benefit-risk profile of a medical intervention favorable, and FDA can take this information into account in its benefit-risk determinations. These quantitative methods may help the Agency identify this subgroup and estimate its relative size with respect to the overall surveyed patient population.

c) ***Established Good Research Practices by Recognized Professional Organizations***: The quality of a study may be established if it follows guidelines for good research practices established by a recognized professional organization. For example, the International Society for Pharmacoeconomics and Outcomes Research published a set of good research practices for discrete-choice experiments.[22, 23] Newer methods may also be acceptable, and FDA intends to consider these on a case-by-case basis.

d) ***Patient Centeredness***: Patient preference studies should ensure that the patient, not the health care professional, is the central part of the study. The study should aim to measure inherent attitudes and values of well-informed patients. This could also include evaluating caregiver, parent, or guardians' preferences in situations when the patient may not be able to provide the patient preference perspective.

e) ***Effective communication of benefit, harm, uncertainty, and risk***: Health numeracy means the ability to understand and use numbers in making health-related decisions. Given the level of numeracy in the general population, it is important for patient preference studies to define the context of the benefit-risk tradeoffs, explain the level of effectiveness and the severity of treatment-related harms, and help patients conceptualize probabilities using appropriate numeric, verbal, and graphic representations of uncertainty.

In a typical patient preference study, a patient may be asked to consider various combinations of health outcomes and to indicate which combination is preferred and by how much. The patient should understand and cognitively process these health outcomes, and the benefits, harms, risks, and uncertainties associated with them. Communicating the quantitative aspects of health information has been widely recognized as a challenge.[24, 25] Examples of formats used to communicate numerical values include:

[22] J.F.P. Bridges, *et al.*, "Conjoint analysis applications in health—a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force," *Value in Health*, 403-13 (2011).
[23] F.R. Johnson, *et al.*, "Constructing experimental designs for discrete-choice experiments: Report of the ISPOR conjoint analysis experimental design good research practices task force," *Value in Health*, 3-13 (2013).
[24] B. Fischhoff, *et al*, "Communicating Risks and Benefits: An Evidence Based User's Guide," U.S. Food and Drug Administration (2011).
[25] L.M. Schwartz and S. Woloshin, "The Drug Facts Box: Improving the communication of prescription drug information," *Proceedings of the National Academy of Sciences*, 14069-14074 (2013).

- natural frequency (e.g., 20 in 1000), percent (e.g., 2%);
- solely verbal (e.g., high, low);
- verbal frequency (e.g., twenty out of one thousand);
- pictograph/graphical icon array (e.g., a 10 by 10 array of 100 small human-shaped icons, all in white with 2 in black);
- relative and absolute risk reduction; and
- numbers needed to treat (e.g., if 1000 people have this test every year, 20 people will be saved from dying from this illness every 5 years).

While no single format is universally superior to other formats, some general practices are supported by scientific evidence to reduce the uncertainty caused by health numeracy.[26] For example, we recommend the following:

- Avoid solely verbal description of uncertainty. Patients may interpret what "low" and "high" risks are differently.
- Avoid fractions, decimals, and different denominators when presenting risks of multiple treatments. These are relatively difficult for cognitive processing.
- If possible, use multiple formats simultaneously (e.g., verbal frequency, percent, and icon array/pictograph). Relative understanding of these formats varies from patient to patient. Moreover, one format may make the other formats easier to understand.
- If possible, describe uncertainty in both positive and negative frames (e.g., 20% chance of adverse events or 80% chance of no adverse events) to avoid cognitive bias.
- Pretest the communication format. Since patient populations vary, pre-testing the chosen format can improve the comprehension of the format by the study population of interest.

f) ***Minimal cognitive bias***: Study design should minimize potential cognitive biases such as framing (e.g., describing changes as gains or losses), anchoring (e.g., signaling a reference value), simplifying heuristics (e.g., recoding numerical values or percentages as low, medium, and high), or ordering effect (e.g., the response to a question depending on its relative position in the question sequence). For example, a group of study subjects were asked to imagine they were lung cancer patients and choose between different treatments, such as surgery and radiation, based on cumulative probabilities and life-expectancy data. More individuals chose surgery when they were told that it had a 90% survival rate than when they were told that the surgery had a 10% mortality rate.[27]

[26] See Footnote 24.

[27] McNeil BJ, Pauker SG, Sox HC, Jr., Tversky A. On the elicitation of preferences for alternative therapies. New England Journal of Medicine. 1982;306(21):1259-1262.

g) ***Logical soundness***: The data should include internal-validity tests of logic and consistency and should be verified for conformity with logic and consistency.

h) ***Relevance***: Critical aspects of risk, benefit, and uncertainty should be included in the elicitation of preferences, and omission of any should be well justified. Preferences should be measured over relevant clinical domains to be useful in evaluating available evidence. If clinical endpoints take the form of surrogate markers (e.g., liver enzymes) that may be asymptomatic, the study should help patients understand how such measures affect the likelihood of more serious outcomes.

i) ***Robustness of Analysis of Results:*** After measurements are made in a scientific study, an analysis of these results should ensure appropriate interpretation of the collected evidence. Quantitative analyses often involve development of statistical models, which in turn provide estimates of the parameters of interest. It is important that the sources of uncertainty are well understood because decisions may be made based on these estimates. The uncertainty of an estimate can be reported through a confidence interval and standard error. Sensitivity analysis is an effective method to determine the value of the parameter that would change the final decision.[28] For example, if the parameter does not affect the final decision regardless of its value, then its uncertainty may not be important to the overall analysis.

j) ***Study Conduct:*** The validity and reliability of study results depends in large part on compliance of research staff and study participants with the study protocol. A patient preference study should be administered by trained research staff. If the preference study is self-administered by patients, they should go through a tutorial and a quiz before answering questions, to help to ensure compliance with the study protocol.

k) ***Comprehension by Study Participants***: Efforts should be made to ensure that study participants fully understand the risk and other medical information being communicated to them. For example, if a survey instrument's presumed reading level of the target patient population is too high, some respondents may not understand a question. In this case, the respondents may use heuristics or mentally turn the question at hand into an easier but different question to answer, which would render an invalid measurement.

Example: CDRH Patient Preferences of Weight Loss Devices Study

A patient preferences study sponsored by CDRH followed many of the recommendations listed in this section.[29] The sample included more than 500 patients drawn from an online panel that represented a cross section of the US population. The sample size was planned to

[28] A.H. Briggs, *et al*., "Model Parameter Estimation and Uncertainty Analysis A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group–6," *Medical Decision Making*, 722-732 (2012).
[29] M. Ho, M. Gonzalez, H. Lerner, C. Neuland, J. Whang, M. McMurry-Heath, A. Hauber, and T. Irony. "Incorporating patient-preference evidence into regulatory decision making." Surgical endoscopy (2015): 1-10.

capture a wide spectrum of patient preferences and provided better representativeness of the U.S. obese population than anecdotal remarks or focus group studies. The study was designed to measure quantitative patient preference heterogeneity and conduct preference segmentation.

The study's stratified sampling by Body Mass Index (BMI) ensured that estimates were precise across the whole BMI range of interest. Moreover, the study used a preference elicitation method that not only allowed investigators to identify and divide patients into different segments by patients' risk-tolerance level, but also provided the estimated percentage of patients that would prefer receiving the device to the status quo.

Design, conduct, and analysis of the study followed good research practices endorsed by an international professional society representing health outcome researchers across the world. Research conducted at the study design stage and during the face-to-face interviews with patients helped ensure that the survey instrument was patient-centered, the communication of benefits, harms, risks and uncertainty was clear, and the format of the questions would keep potential cognitive bias to a minimum. Rigorous internal validation tests were conducted to make sure the data quality was sufficiently high. The benefits (weight loss amount and duration, improvement in comorbidities), harms (type of surgery, diet restrictions) and risks (mortality, adverse events, and hospitalization) of the device were carefully defined so that the tradeoff among the benefits and risks would be comprehensible to patients, health care professionals, and the Agency.

The study showed that a substantial portion of obese patients would accept the risks associated with a surgically implanted device if they lost a sufficient number of pounds. The data generated from this study could also be used to inform clinical trial design, to estimate the tradeoffs in risks that obese patients are willing to accept in exchange for a certain amount of weight loss, or the minimum number of pounds they would have to lose to tolerate the risks of a weight loss device.

Studies like this may provide information on the relative importance of certain device attributes to patients as well as how benefits and risks are weighted, enabling more patient-centric regulatory decision-making and potentially informing the design and analysis of clinical trials.

V. Additional Considerations

The discussion below addresses additional considerations regarding patient preference information.

5.1 Maintaining the Integrity of Patient Preference Information

As with other data submitted for premarket review, efforts should be made to ensure that data integrity and validity are maintained. For example, participating investigators of IDEs are

570 responsible for maintaining accurate, complete, and current records of each subject's case
571 history and exposure to the device. See 21 CFR 812.140(a)(3). Such case histories may
572 include patient diaries, assessments, electronic patient diaries, and other electronic patient-
573 reported outcome tools (ePRO).[30]
574
575 **5.2 Conditions of Approval**
576 FDA may impose conditions of approval in certain situations, including for approvals where
577 it takes patient preference data into account. In some cases where FDA determines a product
578 has reasonable assurances of safety and effectiveness in a subset of patients (e.g., based on
579 disease severity) but the device poses potentially serious or life-threatening risks, FDA may
580 determine that conditions of approval are warranted. Patient preference studies may help
581 FDA identify a subset of patients in whom the benefits outweigh the risks, and the approval
582 would not be for the general population but instead would be limited to the population where
583 FDA determines the benefits outweigh the risks. In such cases, certain conditions of
584 approval[31] may be appropriate to mitigate risk and facilitate use in patients in whom benefits
585 are expected to outweigh risks. As with other PMA approvals, HDE application approvals or
586 *de novo* classifications for certain devices, FDA may require the collection of postmarket
587 evidence through a post-approval surveillance study or "522 study."[32]

[30] Further information on the use of ePROs and the role of both the sponsor and the clinical investigator in collecting and maintaining ePROs can be found in the document referenced in Footnote 12.

[31] See 21 CFR 814.82. Post-approval requirements may include as a condition to approval of the device:

- **(1)** Restriction of the sale, distribution, or use of the device as provided by section 515(d)(1)(B)(ii) or 520(e) of the act.
- **(2)** Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted.
- **(3)** Prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards, or precautions important for the device's safe and effective use, including patient information, e.g., information provided to the patient on alternative modes of therapy and on risks and benefits associated with the use of the device.
- **(4)** Inclusion of identification codes on the device or its labeling, or in the case of an implant, on cards given to patients if necessary to protect the public health.
- **(5)** Maintenance of records that will enable the applicant to submit to FDA information needed to trace patients if such information is necessary to protect the public health. Under section 519(a)(4) of the act, FDA will require that the identity of any patient be disclosed in records maintained under this paragraph only to the extent required for the medical welfare of the individual, to determine the safety or effectiveness of the device, or to verify a record, report, or information submitted to the agency.
- **(6)** Maintenance of records for specified periods of time and organization and indexing of records into identifiable files to enable FDA to determine whether there is reasonable assurance of the continued safety and effectiveness of the device.
- **(7)** Submission to FDA at intervals specified in the approval order of periodic reports containing the information required by § 814.84(b).
- **(8)** Batch testing of the device.
- **(9)** Such other requirements as FDA determines are necessary to provide reasonable assurance, or continued reasonable assurance, of the safety and effectiveness of the device.

[32] A "522 study" refers to a post-approval study authorized by section 522 of the FD&C Act (21 U.S.C. 360l), which gives FDA the authority to require a manufacturer to conduct postmarket study of a class II or III device

VI. Submission of Patient Preference Information

The Agency encourages sponsors and other stakeholders to have early interactions with the relevant review division if considering collecting patient preference information for regulatory purposes.

Patient preference information may be submitted through a variety of pathways. Sponsors may provide patient preference information as a part of their submission as supporting evidence, for example, that the probable benefits of a device outweigh probable risks. Other stakeholders (e.g., academia or patient groups) may consider sharing patient preference information with FDA for informational purposes. The Agency may also consider obtaining its own patient preference information to further understand the benefit-risk factors affecting patients with diseases or conditions who may be considering using a specific device type.

FDA expects the specificity of the data to differ based on the scope of the study conducted. For example, the studies may differ in the following ways:

- application/device-specific study submitted to FDA,
- disease/condition or device type study submitted to FDA,
- application/device-specific study published in literature, or
- disease/condition or device type study published in literature.

An additional pathway to get input from the Agency about the tools and instruments created to measure patient preference information is through the Medical Device Development Tool (MDDT) qualification process.[33]

VII. Communicating Patient Preference Information in Device Labeling

When FDA considers patient preference studies in its consideration of a premarket application, such studies generally should be described in the labeling. Such information can

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that meets certain criteria. For more information, see FDA's *Draft Guidance for Industry and Food and Drug Administration Staff; Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act* issued on August 16, 2011 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268064.htm). This draft guidance, when finalized, will represent FDA's current thinking on this topic.

[33] MDDTs are scientifically validated tools created to support device development and regulatory evaluation. Qualification reflects CDRH's expectation that within a specified context of use, the results of an assessment that uses an MDDT can be relied upon to support device development and regulatory decision-making. See FDA's *Medical Device Development Tools; Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff*, issued on November 14, 2013 (http://www.fda.gov/MedicalDevices/GuidanceRegulationandGuidance/GuidanceDocuments/ucm374427.htm). This draft guidance, when finalized, will represent FDA's current thinking on this topic.

be helpful to healthcare providers and patients in making healthcare decisions involving difficult benefit-risk tradeoffs or novel treatments. Therefore, it is important for the device product labeling to contain sufficient information about the benefits and risks of the treatment and diagnostic options under consideration. As with all required product labeling, and particularly when there is a complex benefit-risk tradeoff, it is important to communicate the benefit-risk information to patients, caregivers, and health care professionals as they make treatment decisions.

This section includes recommendations for incorporating patient preference information into device labeling and suggestions to help prepare such labeling consistent with the requirements of 21 CFR Part 801.[34] For additional information on developing labeling, please consult FDA Guidance: Labeling - Regulatory Requirements for Medical Devices (FDA 89-4203).

7.1 General Labeling Recommendations

Clear, accurate, and informative labeling helps patients and health care professionals understand the potential benefits and risks of devices and thus allows them to make informed choices.

When submitting draft labeling to FDA for a device for which patient preference information is submitted, sponsors should include a plan for how they intend to communicate that information to patients and health care professionals, if appropriate.

For a device for which FDA considers patient preference information in its benefit-risk determination, in addition to the standard elements of labeling (e.g., indications for use, contraindications, benefits, risks, warnings, and user instructions), the labeling should describe the patient preference study data, including the range of patient preferences and characteristics of patients who considered the device's probable benefits to outweigh its probable risks. It also may be appropriate to include such information in a prominent section of the labeling.

Under certain rare circumstances, a specialized informed consent section may be appropriate to facilitate use in patients who explicitly accept the probable risks in exchange for the probable benefits.[35] In such cases, FDA may include such an informed consent process as a condition of approval.

The health care professional labeling should include a summary of the patient preference study, which describes the population studied, the method used to elicit patient preferences, attributes and levels of benefit and risk included in the design, and results of the study.

[34] All labeling must comply with the FD&C Act and applicable FDA regulations. See 21 CFR Part 801. The labeling recommendations in this draft guidance are consistent with the requirements of Part 801.

[35] See for approved example of specialized informed consent: http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050034c.pdf.

Sponsors should also include study protocols and results of any label comprehension or label usability studies that were conducted to demonstrate that the target audience understood the risks and benefits of the device. When appropriate, labeling should be pretested with representative user populations in order to ensure that it is usable, appropriate, comprehensible, unbiased, and complete. Testing should be designed following or comparable to the methods described in ANSI/AAMI HE75 Human Factors Engineering – Design of Medical Devices.[36]

7.2 Additional Recommendations for Patient Labeling

Generally, labeling should be written in plain language so that patients are able to understand the information presented and form realistic expectations of the treatment and its potential risks.[37] The patient labeling should use terminology and numerical data in a way that is easily recognized and understood by the average layperson. When appropriate, visual language, such as pictorials, graphics, or tables, should be included as an adjunct to the written word. In addition, the labeling should include a clear indication of the population for whom the device is appropriate.

The patient labeling should contain information that may assist patients in understanding:

- if they might benefit from use of the device,
- the potential benefits from use of the device,
- the potential risks or complications from use of the device, and the likelihoods of each,
- any relevant contraindications, warnings, and precautions,
- if they share characteristics with the group of patients who view the benefits as outweighing the risks, and
- any additional information about what is known and not known about patient outcomes (e.g., long-term outcomes, rare complications).

When possible, the likelihoods of risks and benefits should be expressed in absolute terms rather than relative terms that may be confusing. For example, doubling a risk means very different things if that entails an increase from 10% to 20% rather than an increase from 0.001% to 0.002%.[38]

[36] ANSI/AAMI HE75, 2009/(R)2013 Human factors engineering—Design of Medical Devices.

[37] Sponsors may refer to the general format and principles discussed in FDA's Guidance on Medical Device Patient Labeling when constructing patient labels. See FDA's *Guidance on Medical Device Patient Labeling; Guidance for Industry and FDA Reviewers*, issued on April 19, 2001 (http://www.fda.gov/downloads/MedicalDevices/MedicalDeviceRegulationandGuidance/GuidanceDocuments/ucm070801.pdf).

[38] E. Akl, *et al.*, "Using alternative statistical formats for presenting risks and risk reductions," *Cochrane Database Syst. Rev.* (2011).

VIII. Hypothetical Examples

The following examples are offered for illustrative purposes only. The decisions described in these examples are not predictive of future FDA decisions and are intended only to demonstrate how FDA might consider patient preference information when making benefit-risk assessments. Similar scenarios or devices may result in different outcomes depending on the individual performance characteristics of a particular device and the population for which it is indicated.

A. Probable benefit outweighs probable risk for a subset of patients

A permanently implanted device is intended to treat knee pain and improve knee function. The device is studied in a population of patients with knee pain and functional limitation who manifest a broad spectrum of disease severity and duration.

The data indicate a smaller than expected improvement in the study population as a whole. However, patients with the highest pain and functional limitation may experience more pain reduction and functional improvement than the overall study population without any increase in adverse events. According to patient preference information submitted to FDA, patients with the highest pain and functional limitation state they would accept the moderate risks for the probable benefits.

FDA may conclude that the probable benefits outweigh the probable risks for patients with the highest pain and functional limitation. Therefore, FDA may approve the device with the indication limited to patients with higher pain and functional limitation, with labeling that contains important information about the patient preference study. A post-approval study to confirm the device's long-term safety and effectiveness in the high pain and functional limitation patient population may also be required.

B. Patient preference data helps inform FDA reviewer considerations

An implanted, resorbable, relatively low-risk novel device is intended to lessen the depth of facial wrinkles and improve age-related facial appearance. The device is studied to evaluate the improvement in appearance over time.

After a single treatment, improvement is noticed by about 75% of patients. Satisfaction in age-related facial appearance drops to about 50% at two years after the initial treatment, with reappearance of facial wrinkles over time. FDA reviewers note that the procedure does not result in permanent improvement, and the data suggest that patients may undergo additional procedures over time to maintain the aesthetic effect. Reviewers initially concluded that the temporary nature of the benefit may not suffice to outweigh the risks, particularly given the potential for additional adverse effects from repeat procedures. However, patient preference information indicates that a significant subset of patients may prefer a device with temporary effects, rather than a permanent durable implant inserted during a single procedure that may become aesthetically undesirable over time with further aging.

FDA may take the patient preference into account in its determination that the probable benefits outweigh the probable risks for this relatively low-risk device

FDA may approve the device with appropriate labeling information regarding the limited duration of effect, as well as information from the patient preference study.

C. Expected effectiveness but significant risk; risk not outweighed by probable benefit

A permanently implanted aesthetic device is intended to improve body appearance. The device is studied in a healthy patient population.

Data from the clinical trial suggest similar body improvement benefit as marketed alternatives but faster recovery from the surgical procedure to implant the device. However, a higher rate of meaningful adverse events was observed, including need for reoperation to remove and/or replace the device, with typically lesser improvement in body appearance with subsequent procedures. This difference may be attributable to lower device durability. Patient preference information indicates that some patients place a high value on the appearance enhancement the device provides and that some patients would accept the higher level of risk observed in the study, in exchange for the benefits.

However, FDA may conclude that the device poses an unreasonable risk of illness or injury that can be addressed with design modifications and enhanced quality manufacturing process efforts. Therefore, FDA may decide not to approve the device despite the patient preference information. FDA may recommend that the sponsor explore design and manufacturing process changes to improve the durability of the device, thereby mitigating some of the additional risk and improving the benefit-risk profile.

D. Increased risk and similar effectiveness in comparison to alternatives but clear patient preference for certain device attributes

A permanent, fully implantable device is intended to improve hearing. The device is studied in a patient population with advanced hearing loss.

Data from the clinical trial demonstrate rare but observed surgical risks with the implantation, such as facial nerve injury, as well as subsequent device failures requiring revision/reimplantation. These risks are not present with conventional, non-implanted auditory aids. The effectiveness data demonstrate similar performance to a conventional air conduction hearing aid (which is class I exempt, low risk). However, patient preference information clearly indicates that there is a sizeable group of patients who, unhappy with the inconvenience and poor cosmesis of conventional hearing aids, are willing to accept the greater risks of the implanted device despite equivalent effectiveness as non-implanted aids.

FDA may determine, after considering patient preference information along with other evidence, that the probable benefits outweigh the probable risks for this implantable device. Therefore, FDA may determine there is a reasonable assurance of safety and effectiveness, and may approve the device. The patient and health care professional labeling may also

contain important information regarding the additional risks, along with information from the patient preference study.

E. Pediatric HDE and Patient/Parent Preferences

A permanently implanted device is intended to treat pediatric patients with heart valve dysfunction caused by congenital heart disease. The clinical impact of congenitally deformed valves is significant and often lifelong. Pediatric valve replacement is a high-risk procedure involving high operative mortality, high reoperation rate, and late morbidity compared to adult patients undergoing the same operation. There are no approved/cleared comparable devices available for these pediatric patients at the time of HDE consideration. Most often, the available prosthesis is too large for the child's anatomy, resulting in delay in referral for surgery.

The new pediatric device includes smaller prosthesis sizes and is inserted via a surgical procedure which has an initial risk of higher operative mortality, but with long term device-related benefits of improved durability and lower reoperation rate compared to current treatment options for these patients. As stated previously, due to unavailability of comparable devices for these pediatric patients, treatment strategy typically entails waiting until the child grows big enough for anatomy to accommodate larger, available prosthesis. This information along with evidence from nonclinical testing on the device is shared with FDA's Advisory Committee. Additionally, a patient group submits patient preference information from a study of parents of patients. The parents of these pediatric patients are typically the primary caretakers and health care decision makers. The study shows that a majority of parents surveyed prefer the benefit-risk tradeoff of this new device compared to the current treatment options, despite the operative safety concerns.

In considering the totality of evidence on the new device and taking into account the benefits and risks of current alternative treatment options available, the Advisory Committee and FDA may consider the probable benefits of this new device to outweigh the risks. Therefore, FDA may approve this HDE application for this pediatric population. The patient and health care professional labeling may include important information about the benefits and risks as well as information about the patient parent preference study. Depending on the circumstances, the labeling may include a specialized informed consent approach to help parents understand these tradeoffs and help assure fully informed decision-making.

Appendix A: Proposed Modifications to the Benefit-Risk Worksheet from Benefit-Risk Guidance to Incorporate Patient Preference Information

The modifications to Appendix B: Worksheet for Benefit-Risk Determinations of the Benefit-Risk Guidance are shown below. Edits in *italics* indicate additional text, and edits that are stricken through indicate deleted text.

From pages 27-28 of the Benefit-Risk Guidance:

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Patient tolerance for risk and perspective on benefit	~~Did the sponsor present data regarding how patients tolerate the risks posed by the device?~~ - *Are data available regarding how patients tolerate the risks posed by the device?* - Are the risks identifiable and definable? - *Do patients understand the type of risk(s) and the likelihood of the risk(s)?* - *Do patients understand the type of benefit(s) and the likelihood of the benefit(s)?*	
• Disease severity	- Is the disease so severe that patients may tolerate a higher amount of risk for a smaller benefit? - *Does the patient preference information (PPI) include patients across the spectrum of disease severity?* o *If yes, how does the PPI vary (if at all) across the spectrum?* o *If no, for what level of disease severity is PPI available?*	
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies? - *If chronic, does the patient preference information (PPI) include patients across the spectrum of disease chronicity?* o *If yes, how does the PPI vary (if at all) across the spectrum?* o *If no, for what level of disease chronicity is PPI available?*	

From page 28 of the Benefit-Risk Guidance:

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	~~How much do patients value this treatment?~~ - *What benefit(s) from this device is (are) of most value to patients?* o *Does the treatment improve overall quality of life?* ~~Are patients willing to take the risk of this treatment to achieve the benefit?~~ - *What risk(s) from this device is (are) of most concern to patients?* ~~Does the treatment improve overall quality of life?~~ - How well are patients able to understand the benefits and risks of the treatment? - *Are patients willing to take the risk(s) of this device to achieve the benefit(s)?* - *Do any of these issues vary according to the stage of disease severity or chronicity, and if so, how?*	
Risk mitigation *and indication targeting*	- Could you identify ways to mitigate the risks such as using product labeling *(including restricting the indication for use to a subset of the requested population derived from patient preference information in whom probable benefit outweighs probably risk),* establishing education programs, providing add-on therapy, *obtaining informed consent, etc.?* - What is the type of intervention proposed?	

Appendix B: Methodology

FDA recommends the use of both direct and indirect patient preference studies. The direct approach entails the involvement of individual patient representatives in the regulatory process, while the indirect approach uses established scientific methods to elicit benefit-risk tradeoff preferences of the patient population for which the treatment is indicated.[39]

The following issues should be considered when adopting the direct approach:

- the characteristics of patients who should be selected for the study;
- the representation of the whole intended patient population versus the individual selected patients for the study; and
- the generalizability of the selected patient views' to the entire population for which the device is indicated.

Quantitative patient preference assessment is an active and evolving research area. Various methods have been created and used to measure patient preferences for different purposes in the past two decades. However, no systematic analysis of these methods' relative strengths and weaknesses or their applications at various stages of medical device total product life cycle has been written, as of the time of publication of this draft guidance. This Appendix intends to provide a brief description of selected methods for reference purposes. Since patient preference assessment is an active and evolving research area, the Appendix should not be interpreted as a comprehensive account of existing methods or as an exclusive endorsement of the selected methods.

One can measure a patient's benefit-risk tradeoffs among alternative treatment options by considering two concepts: minimum acceptable benefit (MinB) and maximum acceptable risk (MaxR). Given a device's effectiveness, MaxR is defined as the treatment-related harms a decision maker is willing to accept in exchange for the treatment benefit. Alternatively, for the observed or expected level of risk of harms of a device, MinB is defined as the minimum level of effectiveness required for a decision maker to receive/use the device.

Multiple studies have identified and compared a variety of methods to measure patient preferences to be used to quantify patients' benefit-risk trade-off preferences. While the majority of these studies have used a class of methods called stated-preference (SP) methods by eliciting preferences obtained in experimental studies offering choices, some have used revealed preference (RP) methods by obtaining patient preferences through the actual clinical choices made by patients. Both SP and RP methods are informative for understanding patient preferences. We consider SP and RP methods below.

[39] M. Oude Egbrink & M. IJzerman, "The value of quantitative patient preferences in regulatory benefit-risk assessment," *Journal of Market Access & Health Policy*, 2 (2014).

i. Stated-Preference Methods

Stated-preference (SP) methods measure quantitative preferences by analyzing how decision makers respond when offered with various hypothetical choices in experimental studies. These SP methods differ from the revealed preference (RP) method, which explores the decision makers' preferences based on the actual decisions they made in their daily life. While RP methods sound ideal, it is impossible to use RP methods to infer patient preferences when the benefit-risk profile of a device is not comparable to any other devices on the market. For example, FDA could not use RP data for the gastric-banding device when it was the only approved weight-loss device in the US to infer patient preferences for other weight-loss devices that may be less effective but safer. However, SP study results may be translated into the profile of a new device under review and consequently may be useful to regulatory decision makers. Furthermore, SP methods are a relatively cost-effective way to elicit the preferences of large number of respondents, which is crucial to having a representative sample (as discussed in Section VI). While SP methods may be subject to hypothetical bias-preference because data is elicited using hypothetical devices and therefore may not truly reflect the decision makers' real-life preferences, this bias may be minimized and mitigated by adherence to good research practices. Therefore, SP methods may play an important role in informing FDA about patient preferences in its benefit-risk determinations of devices under review.

The SP methods can be divided into the following two categories: indirect-elicitation methods and direct-elicitation methods. Examples of indirect-elicitation methods are conjoint analysis (CA), discrete-choice experiment (DCE), contingent valuation (CV)/willingness to Pay (WTP), and best-worst scaling (BWS) methods.

Unlike indirect-elicitation methods, direct-elicitation methods require decision makers to explicitly identify their MaxR or MinB at a single point on the benefit–risk threshold. These methods present respondents with a hypothetical medical intervention and ask respondents to indicate their MaxR or their MinB. Each direct-elicitation task yields a single point on the benefit–risk threshold, because each direct-elicitation task involves eliciting either MaxR or MinB for one medical intervention. Direct-elicitation methods include health-state utility methods such as standard gamble (SG) and time tradeoff (TTO) methods.

ii. Conjoint Analysis (CA) Methods

Conjoint analysis (CA) methods present decision makers with multiple hypothetical scenarios or treatment options in parallel and elicit their preferences from their choices among these options. In these methods, the most salient outcomes and features of the treatment options, such as device-specific benefits and probabilities of treatment-related harms, are first identified as attributes. Next, the magnitude or category of each attribute is prospectively defined as levels. Then, decision makers will be presented with two or more hypothetical treatment options. Each option is characterized by a profile of multiple attributes, each of which represents a salient feature of the option. The levels of these attributes vary across the treatment alternatives. Decision makers are asked to rate or rank the alternatives or to choose the most preferred alternative among the presented alternatives, which are determined by an

experimental design. The pattern of their responses reveals trade-off preferences among the attributes and attribute levels. The tradeoff results can be used to estimate the benefit-risk threshold, which in turn define MaxR and MinB. Because the levels of each benefit and risk attribute vary over a range, the results of a CA study can be used to estimate the benefit–risk threshold over that range. There are several possible question formats for the survey instrument in CA studies, including ranking, graded pairs, and discrete-choice experiments.

iii. Discrete-Choice Experiments (DC)

According to Hauber *et al* (2013), the most commonly used SP format is discrete-choice experiments (DCE), which was identified by the European Medicines Agency (EMA) as a method that could help regulators in judging trade-offs between favorable and unfavorable effects.[40]

In a discrete-choice experiment (DCE), respondents are asked to choose the most-preferred alternative from a set of hypothetical profiles, assuming that these are the only alternatives available. While most common DCEs present decision makers with a forced choice in which decision makers are asked to choose from among a set of treatment alternatives, some studies allow decision makers to opt out; that is, to indicate that they prefer no medical intervention to the treatment alternatives presented in the choice task.[41]

DCE studies should allow decision makers to opt out of any treatment because doing so reflects the reality that patients may choose not to receive any treatment options presented to them. In addition, the design, conduct of research staff and study participants, and analysis of DCE studies should also follow good research practices.[42]

iv. Health-State Utility Methods: Standard Gamble (SG) and Time Tradeoff (TTO)

Health-state utility indicates the quality of a given health state. Utilities can be measured at the population or individual levels. Changes in health states can be expressed as incremental utility elicited by either standard gamble (SG) or time tradeoff (TTO) question formats. Utilities can be converted to quality-adjusted life years (QALYs). QALYs facilitate health-outcome comparisons across groups of people, health outcomes, and durations by expressing the value of a condition as the sum of the utility of each health state weighted by the duration of that state.

In SG studies, respondents are presented with a choice between a certain health state and a series of gambles with two possible outcomes—one better (often perfect health) and one worse (often death) than the certain health state. Each respondent begins with a gamble with a high probability of the better health state, which reasonably would be preferred over the certain health state. In subsequent gambles, the probability of the better health state systematically becomes lower (and the probability of the worse health state becomes higher)

[40] See Footnote 10.
[41] See Footnote 39.
[42] See Footnote 22.

until respondents are indifferent between the certain health state and the gamble. The SG technique typically is used to estimate health-state utilities, and 1 minus the probability at which the respondent is indifferent between the certain health state and the gamble is equal to the utility of the particular health state.[43]

In TTO studies, respondents evaluate specific treatment outcomes and are asked how much of a reduction in expected life years they would accept for living in perfect health instead of living the rest of their expected lifetime in the compromised health state. Health-state utility is measured as the ratio of equivalent years in perfect health to years in compromised health.

v. Threshold Techniques

The threshold technique (also referred to as the probability tradeoff technique and the probability threshold technique) presents respondents with a pair of medical interventions, each of which is defined by its salient characteristics. One intervention is the target intervention or intervention of interest. The other intervention is referred to as the reference intervention. Respondents then are asked to indicate which medical intervention they prefer. Depending on the objectives of the study, one characteristic is then varied until the preferred alternative becomes unambiguously less attractive or the alternative that was not chosen becomes more attractive and the question is repeated. The probability of benefit or harm is changed systematically until a respondent changes his or her choice. The probability of benefit or harm that induces the respondent to switch provides a point estimate of the MinB or MaxR of the target intervention, respectively.[44,45,46,47]

vi. Multiple-Criteria Decision Analysis[48,49,50]

Multi-Criteria Decision Analysis (MCDA) is a step-wise process that facilitates consensus building among decision makers to quantify the overall importance of multiple alternatives.

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[43] B. O'Brien & J. Viramontes, "Willingness to Pay A Valid and Reliable Measure of Health State Preference?" *Medical Decision Making*, 289-297 (1994).

[44] P.J. Devereaux, *et al.*, "Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study Commentary: Varied preferences reflect the reality of clinical practice." *BMJ* 323.7323 (2001): 1218.

[45] J. Kopec *et al.*, "Probabilistic threshold technique showed that patients' preferences for specific trade-offs between pain relief and each side effect of treatment in osteoarthritis varied." *Journal of Clinical Epidemiology* 60.9 (2007): 929-938.

[46] C. Richardson *et al.*, "Pain relief in osteoarthritis: patients' willingness to risk medication-induced gastrointestinal, cardiovascular, and cerebrovascular complications." *The Journal of Rheumatology* 34.7 (2007): 1569-1575.

[47] H.A. Llewellyn-Thomas, *et al*,. "In the queue for total joint replacement: patients' perspectives on waiting times." *Journal of Evaluation in Clinical Practice* 4.1 (1998): 63-74.

[48] R. Keeney and H. Raiffa, *Decisions with Multiple Objectives: Preferences and Value Tradeoffs*, Cambridge University Press (1993)

[49] F. Mussen, *et al.*, *Front Matter, in Benefit-Risk Appraisal of Medicines: A Systematic Approach to Decision-Making*, John Wiley & Sons, Ltd. (2008).

[50] Department for Communities and Local Government: London, *Multi-criteria analysis: a manual* (2009).[51] T. Tervonen & J. Figueira, "A survey on stochastic multicriteria acceptability analysis methods," *J. Multi-Criteria Decision Analysis*, 1-14. (2008).

In the context of weighing benefits and harms of multiple treatment alternatives, relative importance of the alternatives on the benefits and harms are judged for their clinical relevance, and all effects are weighted in the same unit of preference value or utility. Summing those common units of benefit and risk provides an overall benefit-risk preference value or utility for each alternative, enabling calculation of the difference of a treatment utility against the other treatment utilities.

In general, MCDA is a class of methods that consist of two steps: scoring and weighting. First, scoring is the process of measuring the decision makers' consensus value of options, one criterion at a time, using scaling techniques. Next, weighting ensures that the units of value on all the criteria are comparable to facilitate combining the scales of different criteria into one scale. By providing a common scale to benefits and harms, MCDA facilitates direct comparison of the gain in value of benefits to the loss in value of harms.

New MCDA approaches have been developed to tackle multi-criteria decision problems, including Analytical Hierarchy Process (AHP) and Stochastic Multi-criteria Acceptability Analysis (SMAA). The standard MCDA approach for medical product benefit-risk decision making lacks the ability to account for the uncertainty of the criteria measurements and its validity can be adversely affected when consensus is not reached. SMAA was introduced as a way to overcome these limitations by modelling them through simulations.[51,52].

AHP has been used to elicit patients' weights for the criteria considered.[53,54] The AHP has been used to demonstrate that patient relevant endpoints can be prioritized and weighted by decomposing a decision problem into multiple criteria and by then applying pair wise comparisons of the alternatives on the criteria.[55,56] Since MCDA methods are consensus building processes, the resultant weights of various treatment options may be sensitive to the way and the order of questions and given instructions throughout the process because decision makers can be subject to various cognitive biases, such as framing effect and anchoring effect. Therefore, an independent third party to conduct a MCDA study is recommended to avoid possible bias introduced to the process.

vii. Contingent Valuation (CV) or Willingness to Pay (WTP) Methods

[51] T. Tervonen & J. Figueira, "A survey on stochastic multicriteria acceptability analysis methods," *J. Multi-Criteria Decision Analysis*, 1-14. (2008).
[52] P. Salminen, *et al*., "Comparing multicriteria methods in the context of environmental problems," *Eur. J. Operational Research*, 485-496 (1998).
[53] M. Hummel, *et al*., "Using the Analytic Hierarchy Process to Elicit Patient Preferences," *The Patient*, 225-237 (2012).
[54] T. Sullivan, "Using MCDA (Multi-Criteria Decision Analysis) to prioritise publicly-funded health care," Doctoral Dissertation, University of Otago (2012).
[55] M. Danner, *et al*, "Integrating patients' views into health technology assessment: Analytic hierarchy process (AHP) as a method to elicit patient preferences," *Intl. J. Tech. Assessment Health Care*, 369-375 (2011).
[56] M. Ijzerman, et al., "A comparison of analytic hierarchy process and conjoint analysis methods in assessing treatment alternatives for stroke rehabilitation," *The Patient*, 45-56 (2012).

Contingent valuation (CV) or willingness to pay (WTP) method measures the monetary value decision makers place on hypothetical scenarios. In a CV survey, decision makers were presented with some hypothetical scenarios, such as outcomes of treatment options. The decision makers is then asked directly how much they are willing to pay for an option that is deemed to be more favorable than their status quo, and how much compensation they require to accept an option that is deemed to be inferior to their status quo. Due to the methods' known bias and different monetary valuations between people, CV and WTP methods are not considered to be valid evidence for regulatory consideration.

viii. Best-Worse Scaling (BWS)

In best-worst scaling (BWS) studies,[57,58] patients are presented with a set of options and ask them to choose the best (or most important or most desirable) option and the worst (or least important or least desirable) option. There are three types of BWS studies, or "cases": object case, single-profile case, and multiple-profile case. These cases are defined by the nature of the options presented to the patients. In each set of options, patients can indicate which of the attributes (object case), the attribute levels (single-profile case), or the profiles of attribute level combinations (multiple-profile case) is best and which is worst. The response pattern of patients reveals the relative importance of each attribute or attribute levels. The BWS multiple-profile cases are similar to a discrete choice experiment and each set typically consists of three or more profiles.

ix. Quality-adjusted Life Year (QALY)

Besides MaxR and MinB, utility and attitude are two other conventional indices that measure subjective value of an outcome or a health state to patients. The value of utility for a chronic condition ranges from 0 (being dead) to 1(living with perfect health). As a patient goes through a series of health states with varying quality of life, the quality-adjusted life-year (QALY) of the patient is defined as the weighted duration of the health state by their respective utility values. Therefore, QALY reflects both the morbidity and mortality of the patient.[59] Commonly used utilities elicitation methods include standard gamble (SG), time trade-off (TTO), visual analog scale (VAS), and rating scales. QALY is widely used in cost-effectiveness studies and health technology assessment. Since QALY is already a measure combining both benefits and harms of a health state or treatment option, it can be used to facilitate direct comparison between different treatment options in the benefit-risk assessment context. Attitude measures a patient's psychological tendency toward an entity expressed in some degree of favor or disfavor, and is usually measured through ratings or rankings such as importance ratings and best worst scaling. While QALY and other utility-related indices are used in cost-benefit analysis of treatment options as well as risk-benefit analysis of

[57] Louviere, Jordan J., and G. G. Woodworth. "Best-worst scaling: A model for the largest difference judgments." *University of Alberta* (1991).

[58] Peay, Holly L., Ilene Hollin, Ryan Fischer, and John FP Bridges. "A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy." *Clinical therapeutics* 36, no. 5 (2014): 624-637.

[59] M.C. Weinstein, *et al*. "QALYs: The Basics," *Value in Health*, S5-S9 (2009).

oncological treatment, QALY results may be sensitive to the elicitation method. Moreover, QALY estimates may not be available for the rare events observed in clinical trials of novel technologies. In such cases, sponsors may need to conduct a separate study to elicit QALY for these events.

x. Revealed-Preference Methods (RP)

Revealed-preference methods are used to analyze patients' choices and behavior in the real world. These methods can provide information on the number of patients for whom the benefits of a medical technology outweigh the risks and potentially the reasons why patients believe that benefits outweigh risks. However, unlike stated preference methods, revealed preference methods often cannot be used to derive weights for or the relative importance of individual features or changes in feature levels. Some examples of revealed-preference methods include patient-preference trials and direct questions in clinical trials.[60]

[60] See Footnote 9.