Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

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

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For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov)..

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Preface

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I. Introduction

The U.S. Food and Drug Administration (FDA or the Agency) values the experience and perspectives of patients. The Agency understands that patients and care-partners who live with a disease or condition on a daily basis and utilize devices in their care may have developed their own insights into and perspectives on the benefits and risks of devices reviewed under the premarket approval, humanitarian device exemption (HDE), or *de novo* classification pathway. 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 FDA's decision making for these 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] (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 qualifies as valid scientific evidence.[2]

This guidance document takes the next step and provides guidance on patient preference information (PPI) that may be used by FDA staff in decision making related to PMAs, HDE applications, and *de novo* requests. The objectives of this guidance are:

1) to encourage submission of PPI, if available, by sponsors or other stakeholders to FDA and to aid in FDA decision making;
2) to outline recommended qualities of patient preference studies, which may result in valid scientific evidence;
3) to provide recommendations for collecting and submitting PPI to FDA; and
4) to discuss FDA's inclusion of PPI in its decision summaries and provide recommendations for the inclusion of such information in device labeling.

This guidance also includes several hypothetical examples that illustrate how PPI may inform FDA's decision making.

The policy described in this guidance document is consistent with FDA's Benefit-Risk Guidance. In particular, the Worksheet for Benefit-Risk Determinations from the Benefit-Risk Guidance has been updated to reflect the Agency's current thinking on patient preference information.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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.

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

[2] See section 513(a)(3)(B), (a)(3)(D), and (e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360c(a)(3)(B), (a)(3)(D), and (e)); see also 21 CFR 860.7 for a further discussion of valid scientific evidence.

II. Overview and Scope

This guidance document explains the principal concepts that sponsors and other stakeholders should consider when choosing to collect PPI, which may inform FDA's benefit-risk determinations in the premarket review of PMAs, HDE applications, and *de novo* requests. This guidance is applicable to both diagnostic and therapeutic devices that are subject to these review processes. This guidance also discusses FDA's inclusion of PPI in its decision summaries and provides recommendations for the inclusion of such information in device labeling for certain devices.

Patients provide valuable input to the FDA in a variety of forms. "**Patient input**" includes a wide range of information and perspectives 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, and quantitative measurements of patient-reported outcomes.

"**Patient perspectives**" refer to a type of patient input, and includes information relating to patients' experiences with a disease or condition and its management. This may be useful for better understanding the disease or condition and its impact on patients, identifying outcomes most important to patients, and understanding benefit-risk tradeoffs for treatment. This guidance focuses on "**patient preference information**" as one specific type of patient perspective.

PPI may be particularly useful in evaluating a device's benefit-risk profile when patient decisions are "*preference sensitive*." Patient decisions regarding treatment options are preference sensitive when:

1) multiple treatment options exist and there is no option that is clearly superior for all patients;
2) when the evidence supporting one option over others is considerably uncertain or variable; and/or
3) patients' views about the most important benefits and acceptable risks of a technology vary considerably within a population, or differ from those of healthcare professionals.

PPI may not be relevant or appropriate for all device types. Submission of PPI to FDA is voluntary. PPI can be useful during FDA's benefit-risk assessment for certain devices in several major ways, including:

1) to help identify the most important benefits and risks of a technology from a patient's perspective (including to inform selection of primary or secondary endpoints);
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 (including to inform minimum clinically important benefit and effect size); and

3) to help understand the heterogeneity or distribution of patient preferences regarding benefits and risks of various treatment or diagnostic options (including to inform patient subgroup considerations as part of benefit-risk assessments).

Notably, this guidance does not change the review standards for PMAs, HDE applications or *de novo* requests (refer to Section 3.7), nor does it create any extra burden on sponsors of premarket submissions. Rather, it provides recommendations relating to the *voluntary* collection of PPI 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.

This guidance focuses on 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, which are described in the Benefit-Risk Guidance. FDA may consider certain submitted PPI, along with the totality of evidence from clinical and nonclinical testing, during the premarket review process and FDA's benefit-risk determination for devices subject to review in a PMA, HDE application, or *de novo* request.

Certain concepts discussed in this guidance are applicable to the device development process from design to market. As such, the patient preference considerations set out herein may also be informative to sponsors during the design, nonclinical testing, pre-submissions, and Investigational Device Exemption (IDE) phases of their device development.

Additionally, this 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 and submitting PPI to FDA to have early interactions with FDA during the design phase of such studies and obtain feedback from 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 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 FD&C Act (21 U.S.C. 360bbb-8c(a))).

[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, May 10, 2016).
[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).

To solicit stakeholders' views, better understand the barriers patients have experienced in trying to participate in the regulatory process for devices, and evaluate the state of the science of measuring patient preferences, FDA held a public workshop on September 18 and 19, 2013.[5] 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 patient groups, and has considered their comments and suggestions on using PPI in the review of PMAs, HDE applications, and *de novo* requests.

FDA aims to provide a systematic way to ensure that patients are represented and patient perspectives are considered in the decision making process. Patient representatives have long served as non-voting members on panels of FDA's Medical Devices Advisory Committee. In 2015, FDA announced the establishment of the Patient Engagement Advisory Committee (PEAC), to advise FDA on complex issues relating to medical devices, the regulation of devices, and their use by patients.[6] The PEAC was established to help ensure the needs and experiences of patients are incorporated into FDA's work in areas such as:

1) advising FDA on ways to include and foster participation of patients, where appropriate, throughout the total product lifecycle;
2) advising FDA on patient perspectives about current and new approaches or policies for integrating patient input in decision making; and
3) serving as a resource to FDA as a body of experts in patient experience, needs, and the activities of the patient community.

3.1 How can patient input impact decision making?

Patients can provide useful information on a range of topics, including (but not limited to) an individual patient's overall view of his or her condition, the natural history of the condition, the impact of the condition on the patient's life, the patient's own experience with treatments or perspective on unmet needs, outcomes and endpoints important to the patient, priorities for disease management, and other patient preferences and perspectives. Patient input can be obtained in a variety of ways and can often be supplemented with other sources of information (e.g., literature review, care-partner or healthcare professional input).

[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).

[6] Patient Engagement Advisory Committee, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PatientEngagementAdvisoryCommittee/default.htm (last visited, September 18, 2015); see also Establishment of the Patient Engagement Advisory Committee; Establishment of a Public Docket; Request for Comments, 80 FR 57007 (September 21, 2015).

Patients' input regarding their experiences and perspectives on their disease or condition and its management may be useful throughout the total product lifecycle for certain devices, by improving understanding of the disease or condition, defining design inputs to meet needs of the patient end user, assessing outcomes most important to patients, and more. See Appendix A for more information.

3.2 What is patient preference information?

This guidance focuses on the specific type of patient input referred to as ***patient preference information***, which, for the purposes of this guidance, is defined as: qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.[7]

FDA may also consider the preferences of care-partners (e.g., parents) and healthcare professionals to the extent they are relevant in the benefit-risk assessments for a particular device subject to review in a PMA, HDE application, or *de novo* request.

The specific role of quantitative PPI is to provide estimates of how much different outcomes, endpoints or other attributes are valued by patients, and the tradeoffs that patients state or demonstrate they are willing to make among them. Such outcomes or other attributes of a device include demonstrated or posited measures of effectiveness, safety, and other device characteristics that may impact benefit-risk considerations, including (but not limited to) means of implantation, duration of effect, duration and frequency of use, and utility of the device.

Patient preference assessments should take into account both the patient's willingness and unwillingness to accept the identified 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 subject to review in a PMA, HDE application, or *de novo* request.[8]

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

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[7] Adapted from: *Medical Device Innovation Consortium*. A framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology. 2015. (http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Proof5_Web.pdf).

[8] See Footnote 1.

3.3 Why include patient preference information in 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 benefits as his/her healthcare professional, a family member, regulator, or another individual. Furthermore, patient preferences may vary both regarding perspective on benefits and risks, as well as 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). Some patients may be willing to accept higher risks to potentially achieve a small benefit, whereas others may be more risk averse, requiring more benefit to be willing to accept certain risks.

An individual's personal values, disease stage, family circumstances, age and other demographic characteristics may also influence his/her benefit-risk preferences. Evaluations of patient-centered 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 subject to review in a PMA, HDE application, or *de novo* request. 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.[9]

Furthermore, it may be appropriate to approve a PMA, approve an HDE application, or grant a *de novo* request for a device for use in a subset of the population for which an indication is requested, when valid scientific evidence shows that the requisite statutory standard is met for use of the device in that subset. In making such a determination, FDA may consider PPI along with the totality of evidence from clinical and nonclinical testing. If FDA determines that the relevant statutory standard is not met for any definable sub-population, FDA would not approve or grant marketing authorization for such a device.

3.4 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 a spectrum of patient preferences 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

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

direct comparison.[10,11] Many of these studies have used a class of methods called *stated preference*, in which preferences are elicited by offering choices or posing contingent valuation questions to study participants. These stated-preference methods involve some simplification of the decision problem to a manageable subset of decision variables or to some simple valuation questions compared to what individual patients are likely to face.

Other studies have used *revealed-preference* methods in which patient preferences are obtained from the actual observed choices made by patients. These studies can avoid the hypothetical bias associated with the stated-preference studies. However, the revealed-preference methods often cannot be applied when a device profile of interest is not yet available for patients to choose because a device is still under regulatory review. Therefore, use of revealed-preference methods is typically limited when the benefit-risk profile of a device is not comparable to any other devices on the market. Moreover, these methods are also subject to potential biases such as financial considerations of individual patients.

Both stated-preference and revealed-preference methods may be informative for understanding patient preferences. Selection of appropriate methods will depend on the primary use of PPI.

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

3.5 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 PRO measures are the Visual Analogue Score (VAS) for pain and the Health Assessment Questionnaire (HAQ) and Disability Index (DI) score for physical function.

PRO instruments are designed to measure a patient's perceptions of health status before, during, and after therapy, while patient preference studies are designed to measure what specified type of therapy or attributes of a given therapeutic or diagnostic strategy a patient might prefer. While PRO measures may provide a snapshot of a patient's own assessment of

[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 visualization techniques to be used in the assessment of benefit and risk of medicines* (2013).
[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).

various outcomes at a given point in time, they do not convey how much the patient values one specified outcome or therapy when compared to other potential outcomes and therapies. Assessing this type of comparison or tradeoff is what patient preference studies are designed to do. These studies may address, for example, whether a patient would be willing to choose a treatment that causes a specified level of reduction (i.e., loss) in physical function in exchange for a specified improvement (i.e., gain) in pain relief. 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]

3.6 Is the submission of patient preference information required for sponsors?

Submission of PPI to FDA is voluntary. PPI may not be relevant or appropriate for all device types. However, it may be useful for sponsors to collect and submit such information for certain PMAs, HDE applications, and *de novo* requests, particularly for those product types and diseases or conditions where usage decisions by patients and healthcare professionals are preference-sensitive (as described in Section II).

PPI might be useful for the following device characteristics[16]:

- Devices with a direct patient interface.
- Devices intended to yield significant health and appearance benefits.
- Devices intended to directly affect health-related 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 that offer alternative benefits to those already marketed.
- Devices with novel technology.

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

Well-designed and conducted patient preference studies can provide valid scientific evidence regarding patients' risk tolerance and perspective on benefit. This may inform FDA's evaluation of a device's benefit-risk profile during the PMA, HDE application, and *de novo* request review processes.

Patient preference studies can be informative for devices under PMA and *de novo* review by providing patient perspectives on benefits, including whether results are significant from a

[13] See Footnote 7.
[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.
[16] Refer to the MDIC Framework (see Footnote 7) for examples of types of preference sensitive decisions where patient preference information could be useful.

patient perspective, and risks, including whether patients would consider the risks to be unreasonable. Furthermore, patient preference studies can also be informative for devices under HDE application review by providing patient perspectives on whether "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))).

The following sections provide a brief overview of the focus of FDA's review during these processes. Hypothetical examples of how FDA might consider PPI when making benefit-risk assessments are described in Section VIII.

FDA's Evaluation of PMAs. In the PMA 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))).[17] 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 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 application 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 there is no legally marketed predicate device for their new device, they may submit a *de novo* request for FDA to make a risk-based classification. FDA also will review

[17] See Footnote 1.

devices under the *de novo* pathway if it has determined the device is not substantially equivalent due to a (1) 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 patients 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."[18]

IV. Recommended Qualities of Patient Preference Studies

The Agency considers valid scientific evidence, whether it be PPI or any clinical/nonclinical information, in support of a regulatory submission. For quantitative patient preference studies in particular, the Agency considers the study qualities outlined in this section[19], among other things, when deciding whether a given quantitative dataset of PPI constitutes valid scientific evidence.[20,21,22,23]

a) ***Patient Centeredness***: Patient preference studies should ensure that the patient, not the healthcare professional, is the central focus of the study. The study should aim to measure preferences and perspectives on benefits and risks of well-informed patients. This could also include evaluating care-partner or healthcare professional preferences in appropriate situations.

b) ***Representativeness of the Sample and Generalizability of Results***: A study should measure the preferences of a representative sample of adequate size so that the study results can be reasonably generalized to the population of interest.

[18] See Footnote 1.
[19] These study qualities are based on the literature on good research practices in patient preference studies, and are informed by the Medical Device Innovation Consortium Patient-Centered Benefit-Risk Assessment Framework Report and Catalog of Methods. See Footnote 7.
[20] See Footnote 7.
[21] 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).
[22] F. Mussen, *et al., Benefit-Risk Appraisal of Medicines*, John Wiley & Sons Ltd (2009).
[23] See Footnote 11.

In cases in which detecting differences in preferences between pre-specified subgroups may be important, the sample should include sufficient numbers in each subgroup and the subgroups should be clinically well-defined.

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 subject variability in the population of interest is large but a study sample size is small, 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.

c) ***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 sex, age, race, ethnicity, socioeconomic, cultural background, and other life circumstances, a patient's own experience of his/her disease may influence the patient's personal tolerance for risk. 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 alternative options. It is important to account for these variations when considering PPI. This variability may be population-, condition-, treatment-, and study- specific. Therefore, patient preference studies should reflect the preferences of patients from the full 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, not all methods can effectively identify and quantify preference heterogeneity. PPI may help identify a subgroup of patients (e.g., patients with higher pain and functional limitation) who may 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.

d) ***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 (ISPOR) published a set of good research practices for preference-based methods.[24, 25, 26]

[24] 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).
[25] 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).

Newer methods may also be acceptable, and FDA intends to consider these on a case-by-case basis.

e) ***Effective Communication of Benefit, Harm[27], Risk, and Uncertainty***: Health numeracy means the ability to understand and use numbers in making health-related decisions. Given the varying levels 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.[28, 29] Examples of formats used to communicate numerical values include:

- 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 (if 1000 people have this test every year, 20 people will be saved from dying from this illness every 5 years); and
- numbers needed to treat (e.g., 15 patients need to receive this treatment to avoid 1 additional death in 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.[30] For example, we recommend the following:

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[26] A.B. Huber, J. González, C.G.M. Groothuis-Oudshoorn, T. Prior, D.A. Marshall, C. Cunningham, M.J. IJzerman, J.F.P. Bridges, "Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force," Value in Health, available online: http://dx.doi.org/10.1016/j.jval.2016.04.004, (2016).

[27] ISO 14971: 2007 – Medical Devices – Application of Risk Management to Medical Devices defines "harm" as physical injury or damage to health of people, or damage to property or the environment. "Risk" is defined as the combination of the probability of occurrence of harm and the severity of that harm.

[28] B. Fischhoff, *et al*, "Communicating Risks and Benefits: An Evidence Based User's Guide," U.S. Food and Drug Administration (2011).

[29] 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).

[30] See Footnote 28.

- Avoid solely verbal descriptions 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, describe the benefits and risks in absolute scales instead of relative terms, which better inform the actual benefits and risks.
- 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, 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.[31]

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 harm, risk, benefit, and uncertainty should be included in the elicitation of preferences, and omission of any should be well justified. Often it is most useful to ensure some consistency among the benefits, harms, risks and other attributes evaluated in a preference study, and the endpoints and other outcome data collected in the clinical study. Preferences should be measured over relevant clinical domains to be useful in evaluating available evidence. The relevance of specific endpoints to potential clinical outcomes should be clearly communicated to patients to properly elicit preference. For example, if clinical endpoints take the form of surrogate biomarkers (e.g., Hemoglobin A1c for diabetic patients) the study should help patients understand how changes in the biomarkers may correspond with the likelihood of more serious outcomes.

[31] McNeil BJ, Pauker SG, Sox HC, Jr., Tversky A. "On the elicitation of preferences for alternative therapies," *New England Journal of Medicine*. 1259-1262 (1982).

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.[32] 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 adequate comprehension and compliance with the study protocol. The quiz results should be documented as supportive evidence of patients being properly informed of the benefits, harms, and uncertainty presented in the study questions, and of comprehension by study participants.

k) ***Comprehension by Study Participants***: Efforts should be made to ensure that study participants fully understand the harm, risk, benefit, uncertainty and other medical information being communicated to them. For example, if a survey instrument's presumed reading level of the target patient population is not appropriate, some respondents may not understand a question. In this case, the respondents may 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.[33] The sample included more than 500 patients drawn from an online panel that was designed to represent a cross section of the U.S. population. The study sample had similar demographic characteristics to those of obese patients in the U.S. population. The sample size was planned to capture a wide spectrum of patient preferences and provided better representativeness of the U.S. obese population than anecdotal remarks or small focus group studies. The study was designed to measure quantitative patient preference heterogeneity and conduct preference segmentation.

[32] 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).
[33] 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*, 29(10): 2984-2993 (2015).

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 a recognized professional organization (ISPOR). 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), risks (mortality, adverse events, and hospitalization), and key attributes (type of surgery, diet restrictions) of the device were carefully defined so that the tradeoff among the benefits and risks would be comprehensible to patients, healthcare 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 decision making and potentially informing the design and analysis of clinical trials.

V. Additional Regulatory Considerations

The discussion below addresses additional regulatory considerations regarding PPI.

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. Further, applicable regulations, including the IDE regulation in 21 CFR Part 812, must be followed. For patient preference studies conducted independent from a device clinical study, FDA generally considers the studies to be nonsignificant risk.[34] If PPI is collected as part of a device clinical investigation,

[34] See FDA's *Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed*, issued August 2013 (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf).

participating investigators of IDEs are responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device. See 21 CFR 812.140(a)(3). Such case histories may include patient diaries, assessments, electronic patient diaries, and other electronic patient-reported outcome tools (ePRO).[35]

The Agency also considers PPI from outside the U.S. if the data is valid scientific evidence, reliable, and applicable to the intended patient populations within the U.S.[36] and otherwise sufficient.

5.2 Conditions of Approval

FDA may impose conditions of approval in certain PMA approvals, including where the Agency takes PPI into account. These conditions of approval may help to mitigate risk and facilitate use in patients for whom benefits are expected to outweigh risks.

In some cases where FDA determines a product has reasonable assurances of safety and effectiveness in a subset of patients (e.g., based on disease severity) but the device may pose serious or life-threatening risks, FDA may determine that conditions of approval are warranted. Patient preference studies may help sponsors and FDA identify a subset of patients for whom the benefits outweigh the risks, and the approval would not be for the general population but instead would be limited to the population where FDA determines the benefits outweigh the risks. Certain conditions of approval[37], such as a shared decision making tool[38,39] or specialized patient labeling[40], may be appropriate to mitigate risk and facilitate use in patients for whom benefits are expected to outweigh risks.

As with other PMA approvals, HDE application approvals, or *de novo* classifications for certain devices, FDA may require the collection of postmarket evidence through a post-approval surveillance study or "522 study."[41]

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[35] 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 14.

[36] For the requirements relating to FDA acceptance of studies conducted outside the U.S. and submitted in support of a PMA, see 21 CFR 814.15.

[37] See 21 CFR 814.82.

[38] Toward Minimum Standards for Certifying Patient Decision Aids: A Modified Delphi Consensus Process. Joseph-Williams N, Newcombe R, Politi M, Durand MA, Sivell S, Stacey D, O'Connor A, Volk RJ, Edwards A, Bennett C, Pignone M, Thomson R, Elwyn G. Med Decis Making. 2013 Aug 20;34(6):699-710 (2013).

[39] Assessing the quality of decision support technologies using the International Patient Decision Aid Standards instrument (IPDASi). Elwyn G, O'Connor AM, Bennett C, Newcombe RG, Politi M, Durand MA, Drake E, Joseph-Williams N, Khangura S, Saarimaki A, Sivell S, Stiel M, Bernstein SJ, Col N, Coulter A, Eden K, Härter M, Rovner MH, Moumjid N, Stacey D, Thomson R, Whelan T, van der Weijden T, Edwards A. PLoS One. 2009;4(3):e4705.

[40] For example, in a previous PMA approval, specialized patient labeling was required. See the FDA PMA database for more information on this device: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P050034.

[41] 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 that meets certain criteria. For more information, see FDA's *Guidance for Industry and Food and Drug*

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 and submitting to FDA PPI.

PPI may be submitted to FDA through a variety of pathways. Sponsors and stakeholders interested in designing a patient preference study or submitting a patient preference study to the Agency may request an informational pre-submission meeting.[42] Sponsors may provide PPI as a part of their PMA, HDE application, or *de novo* request 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 PPI with FDA for informational purposes. The Agency may also consider obtaining its own PPI 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:

- premarket submission/device-specific study submitted to FDA,
- disease/condition or device type study submitted to FDA,
- premarket submission/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 PPI is through the Medical Device Development Tool (MDDT) qualification process.[43]

VII. Inclusion of Patient Preference Information in Decision Summaries and Device Labeling

FDA typically provides a public decision summary when it approves a PMA, approves an HDE application, or grants a *de novo* request.[44] These summaries generally include clinical

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Administration Staff; Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act issued on May 16, 2016 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268064.htm).

[42] See FDA's *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff,* issued on February 18, 2014 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf).

[43] 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 decision making. See FDA's MMDT website: http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm

study summaries and other evidence considered in FDA's regulatory evaluation. When FDA considers patient preference studies in its consideration of a premarket submission, such studies generally are included in the decision summary. Inclusion of PPI in FDA's public decision summaries can be helpful to healthcare professionals and patients in making healthcare decisions involving difficult benefit-risk tradeoffs or novel treatments.

Additionally, PPI that is reviewed by FDA and supports FDA's approval or marketing authorization should also be described in the device labeling. 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 product labeling, and particularly when there is a complex benefit-risk tradeoff, it is important to communicate the benefit-risk information to patients, care-partners, and healthcare professionals as they make treatment decisions. Labeling must be consistent with the applicable requirements in 21 CFR Parts 801 and 809.[45] For additional information on developing labeling, consult FDA Guidance: Labeling - Regulatory Requirements for Medical Devices (FDA 89-4203).

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.[46] 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 generally contain information that may assist patients in understanding:

- the potential benefits from use of the device, and the likelihoods of such benefits,
- the potential risks or complications from use of the device, and the likelihoods of such risks,
- any relevant contraindications, warnings, and precautions,
- any additional information about what is known and not known about patient outcomes (e.g., long-term outcomes, rare complications).

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[44] See, e.g., 21 CFR 814.44 and 814.116. FDA currently posts decision summaries for PMAs, HDE applications, and *de novo* classifications on its website. (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/default.htm).

[45] All labeling must comply with the FD&C Act and applicable FDA regulations. See 21 CFR Parts 801 and 809. The labeling recommendations in this guidance are consistent with the requirements of Parts 801 and 809.

[46] 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).

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%.[47,48]

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 PPI 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.

8.1 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, per pre-specified statistical analysis, 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 PPI submitted to FDA, the expected benefits among patients with the greatest pain and functional limitations exceed the minimum level of benefits that patients in the patient preference study find acceptable given expected risks.

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. 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.

8.2 Patient preference information helps inform FDA reviewer considerations

An implanted, resorbable 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.

[47] E. Akl, *et al*., "Using alternative statistical formats for presenting risks and risk reductions," *Cochrane Database Syst. Rev.* (2011).
[48] A. Fagerlin, B.J. Zikmund-Fisher, and P.A. Udel, "Helping patients decide: ten steps to better risk communication," *Journal of the National Cancer Institute*, 103(19):1436-1443, (2011).

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 considered that the temporary nature of the benefit may not be sufficient to outweigh the risks, particularly given that additional adverse effects may occur from repeat procedures over time. However, PPI 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 as the patient ages.

FDA may take the patient preference into account in its determination that the probable benefits outweigh the probable risks for this device. FDA may approve the device with appropriate labeling information regarding the limited duration of effect.

8.3 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 need for reoperation may be attributable to lower device durability. PPI 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 PPI. 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.

8.4 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, 510(k) exempt, low risk). However, PPI 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 PPI 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.

8.5 Pediatric HDE Application 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 application 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 a 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 PPI from a study of parents of patients. The parents of these pediatric patients are typically the primary caretakers and healthcare 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. Depending on the circumstances, a specialized patient labeling may be a condition of approval to help parents understand these tradeoffs and help ensure fully informed decision making.

Appendix A: Incorporating Patient Preference Information and Other Patient Input into the Total Product Lifecycle

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

- Nonclinical (Discovery + Ideation, Invention + Prototyping):
    - During the discovery and ideation phase, qualitative patient input on the types of treatment benefits or device attributes patients might value most may inform device design and/or features. Additionally, patient input may influence which devices are developed, such as by defining areas of unmet need.
    - During invention and prototyping, patient-sensitive design inputs may help developers refine device design to better meet patient end-user needs, such as through human factors engineering.
- Clinical:
    - Patient-informed clinical study design may reduce barriers to participation and affect willingness of participants to enroll and complete a clinical study, such as by streamlining visit schedules and follow-up procedures.
    - Qualitative patient input may also inform the design of clinical trials by helping to identify what endpoints may be of highest importance to patients. Patient input may also inform the development or selection of PRO measures.
    - Quantitative PPI 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 associated with medical device treatments. As exemplified in the CDRH Patient Preferences of Weight Loss Devices Study (see Section IV), quantitative PPI can be used to help define the "minimum clinically meaningful benefit," which may have implications for sample size and other aspects of clinical trial design.
- Postmarket:
    - Once the device is marketed, device labeling and shared clinical decision-making tools may be employed to assure that benefit-risk information as well as PPI is appropriately communicated to patients and healthcare professionals.

- Once a device is used more widely, ongoing benefit-risk determinations and patient-directed communications may become an important part of postmarket monitoring.

- As postmarket patient-centered data accumulates, it may lead to new innovations or inform redesign and improvement of existing devices, or expanded indications.

In a patient-centered product development program, PPI 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 as a dataset which can be built upon and which may be informative to future development stages. For example, qualitative PPI could inform device design or clinical trial design, which could shape future quantitative studies of patient preference, which could inform FDA benefit-risk assessments during premarket review of PMAs, HDE applications, or *de novo* requests.

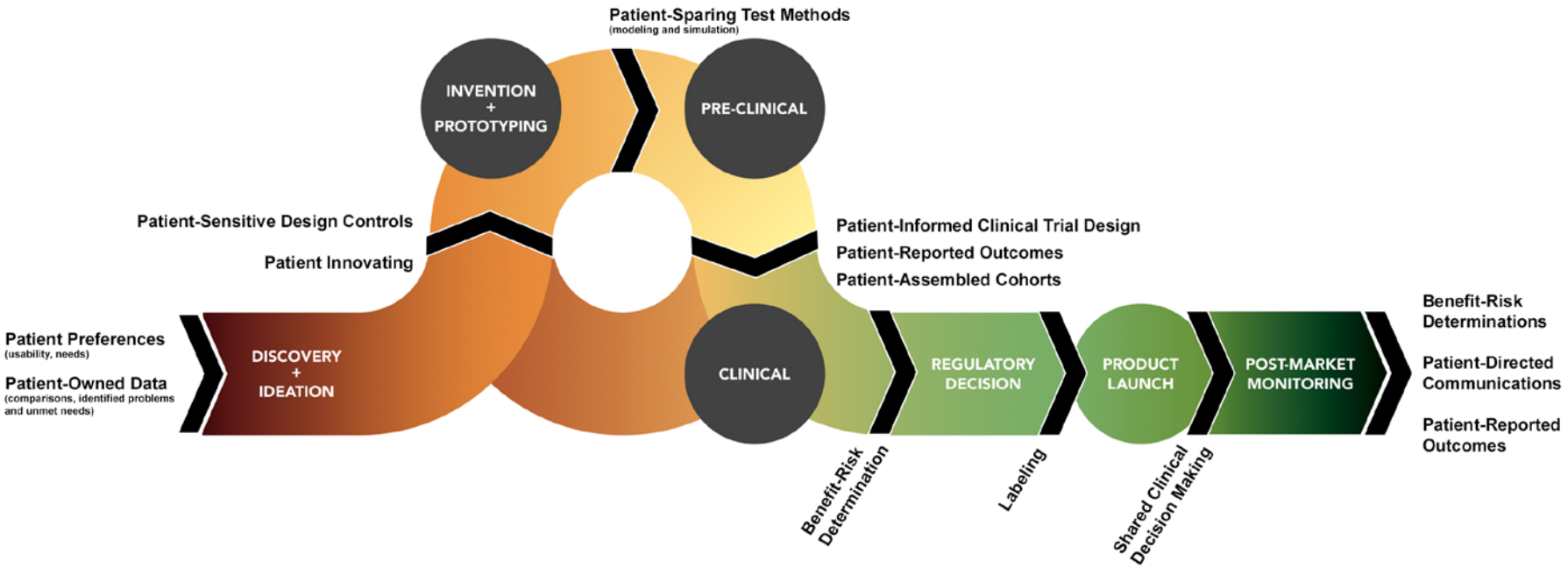

Figure 1. Patient Input in the Total Product Lifecycle

In the earliest stages of development—sometimes referred to as the discovery and ideation phase—it may be most useful to obtain patient input using open-ended questions and qualitative interactive discussion that may involve methods such as focus groups, social media, public meetings, workshops, or an FDA request for comments to the docket. At this early stage, for example, questions might be related to what disease impacts are most important to patients and their care-partners and healthcare professionals. The impacts explored may include discussion of burden of disease, burden of currently available treatment and other aspects of the disease experience (e.g., symptoms or functional impacts of the disease). This input also can provide useful information on the natural history of the condition, unmet needs, priorities for disease management, willingness to participate in clinical trials, and other broad questions of concern.

The open-ended qualitative patient input gathered early in the development process can help to frame the questions to be pursued in subsequent studies, which may be more focused and involve more structured methods and development of more specific quantitative or semi-quantitative measures. This can, for example, lead to development of data collection tools including Clinical Outcome Assessment (COA) tools such as PRO instruments. These tools can be incorporated into clinical trials to enable more direct measurement of the impact of the tested therapy on those aspects of disease and treatment identified as being most important to patients. The data obtained from these clinical studies can then be part of the study data set that a sponsor submits to FDA in support of their PMA, HDE application, or *de novo* request and can inform the FDA assessment of product benefit and risk in the decision phase.[49]

The open-ended qualitative patient input can also help to identify specific clinical outcomes that may represent changes in patient's symptoms, functioning, or survival. This information can be used to frame questions to be pursued in subsequent use of structured methods to elicit PPI. Surveys that elicit patient willingness to accept a specified type and level of expected risks, in exchange for a specified type and level of expected benefit, for a particular disease condition and sometimes a specified technology can also help to provide insight into the patient's perspective and thus inform the FDA assessment of product benefit versus risk in decision making.

[49] See Footnote 12.