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Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle

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Draft Guidance for Industry, Food and Drug Administration Staff, and Other Interested Parties

DRAFT GUIDANCE

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When final, this guidance will supersede "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," issued August 2016.

U.S. FOOD & DRUG ADMINISTRATION

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Preface

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Table of Contents

Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 or Office 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. The Agency understands that people who live with a disease or condition and utilize devices in their care (hereafter "patients") may have developed their own insights into and perspectives on the benefits and risks of devices regulated by FDA. 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.

Patients provide valuable input to FDA in a variety of forms. Section 569C(c)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended (including by section 3001(3) of the 21st Century Cures Act, Pub. L. No. 114-255), states that, for purposes of section 569C, "the term 'patient experience data' includes data" that are "intended to provide information about patients' experiences with a disease or condition." FDA encourages industry to consider patient experience data in device development and evaluation. This includes patient preferences for outcomes and treatments. This guidance focuses on "**patient preference information**" (PPI) as one specific type of patient experience data.

Patient perspective on benefit and tolerance for risk may be considered in FDA's assessment of the benefit-risk profile of certain devices. The policy described in this document is

consistent with FDA's Benefit-Risk Guidance Documents.[1]

This guidance document provides recommendations on how voluntary PPI may be considered by FDA staff in decision-making. The objectives of this guidance are:

1) to encourage submission of PPI, if available, by sponsors or other interested parties 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,[2]
3) to provide practical 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 hypothetical examples that illustrate how PPI may inform FDA's decision-making.

The knowledge gleaned from the use of Patient Preference Information could be used across the total product lifecycle, including for review in investigational device exemption (IDE) applications, premarket approval applications (PMAs), humanitarian device exemption (HDE) applications, De Novo classification requests, or 510(k)s.

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

II. Background

In 2016, FDA issued the guidance document, "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

[1] For more information, see FDA's guidances titled "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics" (referred to as "Substantial Equivalence in Premarket Notifications (510(k))"); "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions" (referred to as "Benefit-Risk Determinations for Investigational Device Exemptions"); "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions" (referred to as "Medical Device Product Availability, Compliance, and Enforcement Decisions"); "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions"; and "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" (referred to as "Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications").

[2] "Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective." 21 CFR 860.7(c)(1); *see* FD&C Act section 513(a)(3)(B), (D), (e). This guidance provides recommendations on how to produce high quality, reliable evidence, including valid scientific evidence where required.

Labeling," in which we provided 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 was part of FDA's response to section 1137 of the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, which 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).

Since that time there have been many developments in the use of PPI, including a growing volume of industry-sponsored PPI studies provided to FDA for consideration as part of a benefit-risk assessment, and numerous collaborations between FDA scientists and a variety of interested parties to conduct PPI studies to inform clinical trial design and FDA decision-making across a wide range of diseases, conditions and device areas. In addition, FDA has co-hosted or participated in numerous convenings and international collaborations to advance scientific methods and practical applications of PPI. Meanwhile, FDA has expanded its benefit-risk guidance framework to apply to the total product life cycle, including the submission and review of IDE applications, 510(k)s, PMAs, De Novo requests, and HDEs applications, and FDA decisions involving administrative, enforcement, and other actions.

FDA is issuing this draft guidance to propose revisions to the 2016 guidance to reflect the current scope of FDA's benefit-risk paradigm, which may under appropriate circumstances include PPI, and to provide additional considerations and practical recommendations based on additional experience evaluating patient preferences regarding devices. This draft guidance also fulfills a commitment in Section V.E. of the Medical Device User Fee Amendments Performance Goals and Procedures, Fiscal Years 2023 Through 2027 (MDUFA V).[3] This guidance, when finalized, is intended to provide updated recommendations to industry and FDA staff for designing, collecting, and evaluating PPI in the context of benefit-risk assessments of devices. This includes practical recommendations intended to address common questions for those interested in the voluntary inclusion of PPI for FDA consideration.

III. Scope

This guidance is applicable to voluntary PPI for consideration by FDA staff in decision-making relating to devices. Voluntary PPI can, if it meets applicable legal standards, be considered by FDA during all stages of the total product life cycle.[4]

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

[3] For more information, see MDUFA Performance Goals and Procedures, FY 2023-2027.

[4] For more information, see, e.g., FDA's guidance titled "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics"; "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions."

1) multiple options exist and there is no option that is clearly superior for all patients, that is, there may be a plurality of options for treatment none of which is superior
2) the evidence supporting one option over others is considerably uncertain or variable, that is, there may be a clearly superior treatment but not for every patient population, and/or
3) patients' views about the most important benefits and acceptable risks of a technology vary considerably within or among populations or differ from those of healthcare professionals.

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 meaningful benefit), 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 any standards for marketing authorization or premarket reviews, nor does it create any burden on sponsors of devices. Rather, it provides recommendations relating to the voluntary collection of PPI that may be submitted for consideration. FDA may consider certain submitted PPI, along with the totality of evidence from clinical and nonclinical testing and real-world performance, throughout the total product life cycle. 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 be informative to sponsors during the design, nonclinical testing, investigational, and pre-submission phases of their device development.

Additionally, this guidance may be informative to other interested parties such as patient groups and those in academia who may wish to consider conducting patient preference studies. The Agency encourages sponsors and other interested parties 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.

The following sections describe considerations for including voluntary PPI in submissions to FDA and for FDA evaluating PPI in its benefit-risk decisions over the total product life cycle.

IV. Including patient input in FDA decision-making

A. 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 regardless if it is a primary or co-occurring condition, and other patient preferences and perspectives for specific treatment options. Patient experience data 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).

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

B. What is patient preference information?

Patient preference information, 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.[5]

PPI captures the value patients place on features of devices. PPI includes different patient perspectives on the benefits and risks of using devices and treating medical conditions. PPI is different from a patient-reported outcome, which is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.[6]

PPI studies should elicit which attributes are important to patients, how important they are, and what tradeoffs patients may be willing to make amongst them. PPI is also referred to as health-preference assessment, stated-preference health survey, health-preference research, and patient-centered research in the scientific literature.[7,8]

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.

[5] For more information, see Medical Device Innovation Consortium (MDIC) Patient Centered Benefit-Risk Project Report: A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology. This will be referred to as MDIC Patient Centered Benefit-Risk Project Report.

[6] For more information, see FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools).

[7] For more information, see The PREFER Consortium. PREFER Recommendations - Why, when and how to assess and use patient preferences in medical product decision-making. This will be referred to as PREFER Recommendations.

[8] *See* MDIC Patient Centered Benefit-Risk Project Report.

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 benefit and risk. 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. 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. 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.

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.

C. 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 their 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 other interventions, such as medical procedures or medications). Some patients may be willing to accept higher risks to potentially achieve a certain benefit, whereas others may be more risk averse, requiring a greater 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 their 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 might inform FDA's benefit-risk assessment for a device subject to FDA review. For example, 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.

Furthermore, it may be appropriate to consider marketing authorization for a device for use in a subset of a population, 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 available. If FDA determines that the relevant statutory standard is not met for any definable sub-population, FDA will not approve or grant marketing authorization for such a device.

D. How is patient preference information different from patient-reported outcomes?

A ***patient-reported outcome (PRO)*** is a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.[9] For example, two widely used PRO measures are the Numeric Rating Scale (NRS) 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 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.[10,11,12]

E. 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 devices, particularly for those product types and diseases or conditions where usage decisions by patients and healthcare professionals are preference-sensitive.

F. When could it be useful to include patient preference information?

PPI might be useful for the following device characteristics:[13]

- Devices with a direct patient interface,
- Devices intended to yield significant health or 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,

[9] For more information, see FDA's guidance titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."

[10] *See* MDIC Patient Centered Benefit-Risk Project Report.

[11] 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).

[12] 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).

[13] *See* MDIC Patient Centered Benefit-Risk Project Report.

- Devices that offer alternative benefits to those already marketed,
- Devices with novel technology.

There may also be instances in which FDA staff may find preference information useful, such as[14]:

- FDA staff are looking to better understand the full impact of the disease or condition and treatment option on patients and/or caregivers.
- Patients may value the benefits and risks of a device differently from healthcare professionals and/or caregivers.
- Population-level differences in patient perspectives are not well understood because of differences in:
  - Demographic characteristics
  - Stages of a disease
  - Disease phenotype
- There is significant public health impact (such as high mortality or morbidity rates and high prevalence rates of the disease or few treatment options available such as in rare diseases).

G. What are some examples of patient preference information studies that helped support device review decisions?

Example of a PPI study to support benefit-risk decisions

CDRH sponsored a patient preferences study intended to inform the benefits versus risk tolerance related to weight-loss device treatments for obesity.[15] 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.

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 who would prefer receiving the device to the status quo.

Design, conduct, and analysis of the study followed good research practices endorsed by a

[14] For more information, see Patient Preference-Sensitive Areas: Using Patient Preference Information in Medical Device Evaluation.

[15] Ho, M.P., Gonzalez, J.M., Lerner, H.P. *et al.* Incorporating patient-preference evidence into regulatory decision-making. *Surg Endosc* **29**, 2984–2993 (2015). https://doi.org/10.1007/s00464-014-4044-2.

recognized professional organization such as the Professional Society for Health Economics and Outcomes Research (ISPOR). Research conducted at the study design stage and during the face-to-face interviews with patients was designed to ensure that the survey instrument was patient-centered, the communication of benefits, 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.

Example of PPI study to support indication expansion and updates to labeling

A PPI study was conducted to support the expansion of the indications for use of a hemodialysis device marketed under 510(k).[16] The device was previously cleared for home use with a care partner present. The manufacturer wished to modify the labeled indication to include home use without a care partner (solo home hemodialysis or solo HHD) based on the results of a PPI study conducted by the industry sponsor.[17,18] The PPI study used a threshold technique to assess patients' willingness to choose solo HHD over hemodialysis in a center given the increased risks of solo HHD. Based on the survey responses from 142 patients, the results demonstrated that patients were willing to accept the increased risks of death and needle dislodgement to receive the benefit of increased treatment accessibility through use of solo HHD. This contributed to FDA's decision to clear the device for solo HHD.

[16] "Under section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)), FDA may determine that a new device is [substantially equivalent] to a predicate device if, among other things, it has the same intended use. Differences in the indications for use . . . may not necessarily result in a new intended use. In other words, FDA may find a new device with indications for use . . . that are different from those of the predicate device [substantially equivalent] to a predicate device." Substantial Equivalence in Premarket Notifications (510(k)) at 8. "[T]his determination depends upon the safety and effectiveness of the new device for the new indications relative to the safety and effectiveness of the predicate device." The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)].

[17] For more information, see NxStage System One Summary Letter.

[18] Tarver ME, Neuland C. Integrating Patient Perspectives into Medical Device Regulatory Decision Making to Advance Innovation in Kidney Disease. *Clin J Am Soc Nephrol*. Apr 7 2021;16(4):636-638. doi:10.2215/cjn.11510720.

Example of PPI study to establish performance threshold

The primary effectiveness endpoint of a clinical study to support a PMA for a novel pediatric ear tube system was based on the results of a PPI study. The PPI study results were used to establish the performance goal.[19] Four hundred subjects were enrolled and were administered a web-based survey instrument that described the in-office and operating room (OR) -based procedure options for the insertion of ear tubes along with related treatment features. Choice questions were then presented using an icon graphic with 100 figures representing a percentage point and respondents were presented with a binary choice. They could choose the OR procedure with a fixed success rate of more than 99% or the in-office procedure with a lower success rate. The procedural success threshold was found to be 68%, the level at which the respondents were indifferent to having the procedure in the office or in the OR. These results indicated that parents would prefer the in-office procedure over the alternative (OR-based tube placement under general anesthesia) if the procedure had a success rate that exceeded 68%.

For more information, sponsors can also refer to the FDA website on "Patient Preference Information (PPI) in Medical Device Decision-Making" for a list of published studies and ongoing projects and past PPI-related FDA workshops conducted.[20]

H. When and how does FDA consider patient preference information?

As noted previously, voluntary PPI could be considered by FDA during all stages of the total product life cycle for devices. Consistent with FDA's benefit-risk guidances pertaining to various decisions over the device total product life cycle, FDA recognizes that patient perspective on benefit and tolerance for risk can vary among patients. Patient preference studies can be informative by providing patient perspectives on benefits, including whether results are significant from a patient perspective, and risks, including whether patients would consider the risks to be acceptable or unacceptable.

In addition, for IDEs, FDA's benefit-risk assessment includes consideration of the risks and anticipated benefits to study subjects and societal benefits in terms of knowledge to be gained from the study. In the context of a clinical study, patient preferences may vary in which outcomes matter most to a particular patient, the amount of risk they would be willing to accept in exchange for a certain amount of benefit, their preferred modality of treatment/diagnostic procedure (often devices are one option to be considered in a clinical care path which may include medication or surgical procedures), as well as the value they assign to the potential societal benefits of the research itself, in advancing potential medical options for patients in the future.[21]

[19] For more information, see Summary of Safety and Effectiveness Data.
[20] For more information, see Patient Preference Information (PPI) in Medical Device Decision Making.
[21] *See* Benefit-Risk Determinations for Investigational Device Exemptions.

For 510(k)s, patient preferences about benefit and risk may be an informative and helpful factor when FDA considers the risk profile (relative to a predicate) of the new device.[22]

There may be situations in which some patients and caregivers would prefer to have access to the device despite that the device is not in compliance with FDA requirements. When making decisions involving administrative, enforcement, and other actions, FDA intends to consider, among other things, patient impact, whether patients and caregivers adequately understand related benefits and risks, and information that may be available regarding patient preferences for availability of nonconforming or non-compliant devices.[23]

I. What important factors should sponsors consider when designing a patient preference study to address an FDA decision-making question?

There are several key aspects that sponsors should consider when planning a fit-for-purpose study that is designed to collect PPI for an FDA device-related decision-making purpose:

- the scientific question,
- the study objective,
- the study parameters,
- the type of study design, qualitative or quantitative, and method(s),
- the study population, including the enrollment criteria and recruitment method(s), and
- if a survey method is used, the specific survey design.

Depending on the phase within the total product life cycle, the scientific question can be different. For example, early in the total product life cycle, the key question may be how patients prioritize clinical endpoints, whereas, later in the total product life cycle, the key question may be how patients weigh the benefits and risks of a specific device.

Depending on the research question, the study objective(s) will differ, and different patient preference parameters of interest may be appropriate. If the objective prior to the clinical stage is to determine how important specific endpoints are to patients, the patient preference parameter of interest may be the relative importance preference weights of endpoints. If the objective is to determine the performance goal of a device, a Minimal Acceptable Benefit (MAB) estimation may be a useful parameter. Further along in the total product life cycle, if the objective is to support benefit-risk assessment of a specific device, a combination of several parameters, such as preferences weights, Maximum Acceptable Risk (MAR) and MAB may be needed.

The types of patient preference parameters selected may influence the type of study design (qualitative or quantitative), the choice of method(s), and other key aspects of a study.

[22] *See* Substantial Equivalence in Premarket Notifications (510(k)); FDA's guidance titled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]."

[23] *See* Medical Device Product Availability, Compliance, and Enforcement Decisions.

V. Recommendations and Practical Considerations for Patient Preference Studies

The Agency relies upon only valid scientific evidence, whether PPI or not, to determine whether there is reasonable assurance that a device is safe and effective. For quantitative patient preference studies in particular, the Agency considers the study qualities outlined in this section,[24] among other things, when reviewing a given quantitative dataset of PPI.[25,26]

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 approach could also include evaluating care-partner or healthcare professional preferences in appropriate situations.

B. Relevance to Patients

Critical aspects of benefit, risk, 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, 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 importance of key clinical parameters to clinical outcomes should be clearly communicated to patients to properly elicit their preferences. 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.

C. Appropriate methods for eliciting patient preferences

There are several methods that are available for collecting PPI and they can be broadly categorized as qualitative and quantitative methods. Considering the point along the total product life cycle at which the PPI will be used, the research question, objective, and type of patient preference parameters needed, the approach to address the research question might be more oriented towards the use of a qualitative or quantitative methodology.

A sponsor's investigational plan must include a "written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound." 21 CFR 812.25(b); see 21 CFR 812.20(b)(2). If a quantitative preference survey is planned, relevant details on the survey design should be included in the

[24] *See* MDIC Patient Centered Benefit-Risk Project Report.
[25] *See* MDIC Patient Centered Benefit-Risk Project Report.
[26] See also 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); See also 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); *See* also F. Mussen, *et al., Benefit-Risk Appraisal of Medicines*, John Wiley & Sons Ltd (2009).

protocol. For example, if a discrete choice experiment or best-worst scaling is planned, sponsors are encouraged to include information on the experimental design. For a more detailed discussion of different quantitative methods, please see the Appendix B. A PPI study plan is not necessarily limited to one study or method and can include both quantitative and qualitative approaches.

In general, qualitative methods produce descriptive data that may be useful for understanding the subjective experiences of patients.[27] Early in the total product life cycle, if the intent is to identify attributes or device features that are important to patients to inform device design, a qualitative study may be sufficient. Qualitative patient input on preferences can also be useful to inform the design of clinical trials by identifying endpoints that are important and relevant from the patient's perspective. There are different methods to conduct qualitative research to obtain PPI, including but not limited to one-on-one interviews, focus groups, and Delphi panels. Sponsors are encouraged to refer to available resources[28] for more information on each method and the potential strengths and limitations associated with each method. Qualitative preference studies that follow recommended good research practices laid out by relevant health preference research professional organizations may be more likely to produce valid scientific evidence.[29]

D. Representative Study Population that Supports Generalizability Results

In general, the study should sample a population that is reflective of the full spectrum of the intended population for the indication for use of the device. This should be reflected in the enrollment criteria and patient recruitment and enrollment methods of the patient preference study.

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.

An 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 be 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.

Careful consideration should be given to the characteristics that are most likely to affect preferences in the specific study. Sponsors should encourage enrollment of relevant

[27] *See* PREFER Recommendations.

[28] *See also* https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[29] *See* PREFER Recommendations.

subgroups in numbers that are sufficient for the scientific question being addressed and the intended use of the device. In addition, if preferences are expected to vary considerably among subgroups, these should be considered and examined in the study. If the sponsor intends to identify a clinically relevant subgroup(s) in the PPI study to support a specific performance outcome, the subgroup(s) should be distinct and identifiable. For example, a Stage III oncology patient may have different preferences from a Stage I oncology patient. Further, the overall sample should be large enough to ensure that a diverse patient population will be included that is sufficiently representative of the intended use population.

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. If subgroups' sizes are not adequate, insignificant statistical results of hypothesis testing may not necessarily be a reflection of preference similarity between subgroups.

E. Reflects 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 status, cultural background, and other life circumstances, a patient's own experience of their disease may influence the patient's personal tolerance for risk. As mentioned in the FDA guidance, Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,[30] 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 generally reflect the preferences of patients from the full spectrum of disease for which the device is intended to be used.

While some study analysis methods can account for preference heterogeneity with sufficient sample size, not all analysis 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.

F. Appropriate selection of attributes and attribute levels

In general, attributes included should be relevant for the FDA decision and salient to the patients. To ensure that all critical attributes important to making a decision are included, sponsors are strongly encouraged to engage with FDA to obtain feedback on proposed

[30] For more information, see FDA's guidance titled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."

attributes during the protocol development stage. Omitting an important benefit or risk in a PPI study may render the study of limited value for decision-making. If the PPI study is conducted to support the benefit-risk assessment of a device, it is often important for the key attributes to reflect the endpoints in the clinical studies. Sponsors should also note that discussions with FDA on attribute selection do not preclude seeking patients' input in the selection process. When engaging with FDA on attribute selection, it may be useful to submit results of prior qualitative research conducted with patients, if any, so that FDA feedback can account for the patients' input. If a PPI study is designed to support FDA decision-making, inclusion of attributes that are not relevant to FDA decisions may skew the relative importance of other attributes (e.g., cost).

Besides patient and FDA decision-making relevance, other considerations for attribute selection include mutual exclusivity where the final set of attributes should be non-overlapping in terms of outcomes measured. The framing and presentation of the benefit and risk attributes should not unfairly bias the respondents' perception of those attributes either positively or negatively. If risk attributes are included, efforts should be made to ensure that the attribute descriptions appropriately convey the severity and impact of the risks to the patients. It may be useful to refer to published literature when developing attribute descriptions; nevertheless, these should be pre-tested with the targeted patient population to ensure that they are fit-for-purpose.

In most quantitative preference studies, attributes can have different levels (i.e., values). These levels can be presented on a probability scale (e.g., 5% risk), ordinal scale (e.g., mild, moderate, and severe risk), or as categorical values (e.g., pill, injection, infusion). The number of attributes or treatment features that can be included in a PPI study is limited by what is cognitively feasible for a patient to consider simultaneously, and this is especially true for attributes measured on a probability scale (e.g., 5% risk of an event). Having too many attributes on a probability scale in a preference study can be cognitively challenging for patients; however, certain attribute levels need to adopt a numerical value to allow for the estimation of relevant MAR or MAB values. Therefore, the presentation of attribute levels can be dependent on the parameters that need to be estimated from the study.

In general, the attribute levels included in a PPI study should encompass clinically and FDA decision-making relevant ranges or values. If the PPI study is designed to support the benefit-risk assessment of a device, the attribute levels included should align with the range of values observed or expected from the clinical studies. Data from real-world observational studies may be relevant to characterize existing treatment alternatives. If the range of attribute levels included in a PPI study do not include all relevant values observed in clinical studies, this could skew the study results and make the study difficult to interpret, diminishing the overall usefulness of the study to inform FDA decision-making. Extrapolation of patient preference data beyond the levels included in the study is generally not considered a valid practice because the specific and relative weights patients assign to preferences must be elicited and cannot be inferred.

Selected attribute levels should be clearly defined levels (e.g., 5% to 10% risk of event).

Sponsors should ensure that attribute levels are spaced sufficiently apart such that patients can distinguish between them. When defining numeric attribute levels, sponsors should also consider whether patients are likely to recode the levels, for example, to "low-medium-high," and how potential recoding will be addressed. Recommendations from health preference research professional organizations on other considerations related to attributes and levels selection are available.[31,32] When engaging with the FDA, it may be useful to include an attribute table for reference.

An example of an attribute table for a PPI study using the discrete choice experiment (DCE) method is included below:

Table 1. Example of an attribute table for PPI study using the DCE method

Attribute	Patient-facing label	Patient-facing attribute level	Reference
Weight loss	Average amount of weight loss in the next year	• 30 lbs • 20 lbs • 15 lbs	reference a, reference b
Risk of myocardial infarction	Additional risk of heart attack in the next year	• X out 100 people (X%) • Y out 100 people (Y%) • Z out 100 people (Z%)	reference a
Mode of administration	How you take the medicine	• Pump • Infusion every 4 weeks (about once a month)	reference c

The table above has four columns. The headers from left to right are:

- Attribute
- Patient-facing label
- Patient-facing attribute level
- Reference

The first column contains example attributes: weight loss, risk of myocardial infarction, and mode of administration. The patient-facing label column indicates what the survey respondent would see; in one case, weight loss would be defined as "average amount of weight loss in the next year." For the attribute risk of myocardial infarction, the label would read "additional risk of heart attack in the next year," and for mode of administration the patient facing label would read "how you take the medicine." The patient-facing attribute levels indicate what specific amount of weight loss a patient might expect to lose in the next year, in this instance 30, 20 or 15 lbs. The reference would indicate the source(s) from which the attribute levels are derived. As an example, we have included "reference a, reference b." These principles would then apply for risk of myocardial infarction and mode of administration for the remaining cells.

[31] *See* PREFER Recommendations.

[32] Bridges JF, Hauber AB, Marshall D, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health. Jun 2011;14(4):403-13. doi:10.1016/j.jval.2010.11.013.

G. Effective Communication of Benefit, 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 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, risks, and uncertainties associated with them. Communicating the quantitative aspects of health information has been widely recognized as a challenge.[33,34] 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 variation.[35] For example, we recommend the following:

- 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. Absolute scales 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,

[33] B. Fischhoff, *et al*, "Communicating Risks and Benefits: An Evidence Based User's Guide," U.S. Food and Drug Administration (2011).
[34] 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).
[35] B. Fischhoff, *et al*, "Communicating Risks and Benefits: An Evidence Based User's Guide," U.S. Food and Drug Administration (2011).

- 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.

We recommend pre-testing 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.

H. Study Comprehension with Minimal Cognitive Bias

Efforts should be made to ensure that study participants fully understand the benefit, risk, 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. Comprehension assessments could be added to assess if respondents are interpreting the presented benefit and risk information as intended. It is possible that respondents may oversimplify the information and provide responses based on such oversimplification, thereby producing invalid measurements.

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.[36]

I. Logical Soundness

The data should include internal-validity tests of logic and consistency and should be verified for conformity with logic and consistency.

Sponsors are encouraged to include data quality checks of the survey responses, and the protocol should describe how the data quality checks will be used in the analysis and interpretation of study results. There are several ways to assess data quality, including but not limited to:

- comprehension assessments,
- internal validity assessments of dominance,
- consistency, recoding effects assessments, and
- anchoring effects assessments.

[36] 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).

Sponsors can refer to published literature on the common types of internal validity tests used in preference elicitation studies.[37,38]

J. 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.[39] 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.

K. Study Conduct

The validity and reliability of study results depend 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, risks, and uncertainty presented in the study questions, and of comprehension by study participants.

L. Follows Established Good Research Practices by Recognized Health Preference Research 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, ISPOR published a set of good research practices for preference-based methods.[40,41,42]

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[37] Janssen EM, Marshall DA, Hauber AB, Bridges JFP. Improving the quality of discrete-choice experiments in health: how can we assess validity and reliability? *Expert Rev Pharmacoecon Outcomes Res.* Dec 2017;17(6):531-542. doi:10.1080/14737167.2017.1389648.

[38] Johnson FR, Yang JC, Reed SD. The Internal Validity of Discrete Choice Experiment Data: A Testing Tool for Quantitative Assessments. *Value Health*. Feb 2019;22(2):157-160. doi:10.1016/j.jval.2018.07.876.

[39] 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).

[40] Bridges JF, Hauber AB, Marshall D, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. *Value Health*. Jun 2011;14(4):403-13. doi:10.1016/j.jval.2010.11.013.

[41] 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).

[42] 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

VI. Seeking FDA Feedback on Study Plans and Providing Results for Consideration

PPI may be submitted to FDA through a variety of pathways. Sponsors and other interested parties interested in designing a patient preference study or submitting a patient preference study to the Agency may request FDA's feedback or a meeting with FDA through the Q-Submission Program.[43] Sponsors may provide PPI as a part of a submission as supporting evidence, for example, that the probable benefits of a device outweigh probable risks. Other interested parties (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.

A. When is it useful for sponsors to seek FDA feedback on study plans?

The Agency encourages sponsors and other interested parties to have early interactions with the relevant review division if considering collecting and submitting PPI to FDA. Engagement with FDA may be useful at key milestones during preference study planning and implementation. Sponsors are encouraged to engage and receive feedback from FDA during protocol and survey development. This engagement with FDA can provide clarification for the sponsor as well as FDA to make the process more efficient.

Sponsors are highly encouraged to engage in discussions early with FDA to seek alignment on the scientific research question(s) of interest, the parameters of interest for decision-making questions, and study objectives.

During the protocol development stage, sponsors may seek alignment with FDA on the study objective(s) and key question(s) of interest, the study population, and the proposed attributes and levels that will be included in the study, if applicable. It would be useful to submit a draft protocol when soliciting feedback from FDA.

When designing a quantitative PPI study, the primary, secondary, and exploratory endpoints, including targets, that are consistent with study objectives and based upon appropriate preference parameters should be specified in the protocol along with the statistical analysis plan.

If relevant, including an attribute table in the protocol can be useful for seeking FDA's feedback on attribute levels. References should be included, where applicable and available, to justify the selection of attribute levels. Any qualitative work that is planned or has been conducted to inform the selection of attributes and levels should also be described in 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).

[43] See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

protocol. Development of the attributes table can be an iterative process and sponsors are encouraged to seek FDA's review and feedback on the attributes and levels before data collection. This iterative feedback process can help ensure that the clinically and regulatorily relevant attributes and levels are represented in the survey instrument before the final instrument is implemented in a study.

It is recommended that sponsors seek feedback from FDA prior to fielding the questions used to elicit input from patients, including those in the survey instrument. Submitting the pre-field test survey instrument for review may be helpful to ensure that FDA agrees the survey is patient-centric or to identify portions of the survey that FDA would recommend be adequately evaluated for patient / respondent comprehension.

Before finalization of the survey instrument, sponsors are encouraged to engage with FDA to seek alignment on the final instrument before implementation. During this engagement, it would be useful to submit a report of findings from the pre-testing that include details on how the instrument has been revised and refined based on patients' input. If the study includes attributes and levels in the design, this engagement would be an opportunity for the sponsor to seek alignment with FDA on the final attributes and ranges of attribute levels.

It is recommended that sponsors discuss recruitment and sampling strategies, approaches to obtain confirmation of diagnosis, and identification of clinically relevant subgroups with FDA before study implementation. If screening questions are used to identify eligible patients, sponsors should describe them so that early feedback can be sought from FDA.

B. What information is useful to provide to FDA when considering PPI results?

FDA recommends including the following key information when submitting PPI: (1) the scientific question, (2) the study objectives, (3) the study design and methods, including the endpoints and targets and statistical analysis plan (SAP), if applicable, (4) the eligibility criteria, (5) the recruitment approach, (6) the survey instrument design, and (7) the results, including the demographics of the study population.

The study objectives, choice of preference elicitation method (including the rationale supporting the choice of method), and endpoints and targets, if applicable, should be described in the context of addressing the research question of interest. Details of the survey instrument, its development (e.g., leading to the selection of the attributes and attribute levels) and its administration, as well as the instrument itself (e.g., screen shots), should be included in the submission. The results of the study should be presented in accordance with the prespecified SAP, if applicable, including relevant subgroup analyses. Results of any specific testing/assessments performed to evaluate data quality should be submitted.

It is important to clearly specify the intended use population for the device, the intended target population of the study, including the eligibility criteria and the recruitment approach, the size and demographics of the study sample, and discuss why the study sample is adequately representative of the U.S. population or subpopulation for which the device is

intended. Sponsors should provide detailed information on such aspects of this information as the following:

- ascertainment of diagnosis or condition (e.g., clinician-confirmed, or self-reported),
- approaches to obtain clinician-confirmed diagnosis (e.g., clinician's note, photo of prescription), if applicable,
- recruitment sources (e.g., clinics, clinician referrals, patient groups, patient panels),
- screening approach, and
- sampling method, if any.

The SAP should specify all primary endpoints, secondary endpoints, exploratory analyses, the analytical models that will be used to estimate the preference parameters of interest, and the software package(s) that will be used to perform the analyses. If several analytical models are planned, the sponsor can consider outlining the steps or any diagnostics that will guide the selection of the final model.

It is important to prespecify any subgroup analyses of interest in the SAP. Sponsors should consider if they have adequate sample size for each pre-specified subgroup, as discussed in Section V.D. Any planned sensitivity analysis should also be described in the SAP.

VII. Additional Considerations

The discussion below addresses additional considerations regarding PPI.

A. 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. Patient preference studies are social science experiments, and must comply with 21 CFR parts 50, 56, and 812 to the extent applicable, including by obtaining IRB review and approval and informed consent where required. Sponsors are also encouraged to follow ethical practices and principles standard in the PPI research community.

The Agency also considers PPI from outside the U.S. if the data is reliable, applicable to the intended patient populations within the U.S. and otherwise sufficient.[44] A "sponsor or applicant who submits data from a clinical investigation conducted outside the United States to support an IDE or a device marketing application or submission" must provide, among other things, a "discussion demonstrating that the data and information constitute valid scientific evidence within the meaning of" 21 CFR 860.7, if "the investigation is intended to support the safety and effectiveness of a device."[45] Considerations to ensure the data is relevant to FDA decision-making could include cultural considerations or health system differences, and how that impacts healthcare decisions.

[44] *See* 21 CFR 812.28, 814.15.
[45] 21 CFR 812.28(b)(6).

B. Conditions of Approval

FDA may impose conditions of approval in certain PMA[46] or HDE approvals,[47] including where the Agency takes PPI into account. These conditions of approval may help to mitigate risk and facilitate use in patients for whom probable benefits are expected to outweigh probable risks.

Patient preference studies may help sponsors and FDA identify a subset of patients for whom the probable benefits outweigh the probable risks, and the approval would not be for the general population but instead would be limited to the population for which FDA determines there is reasonable assurance that the device is safe and effective. Certain conditions of approval, such as a shared decision-making tool[48,49] or specialized patient labeling,[50] may be appropriate to mitigate risk and facilitate use in patients for whom FDA determines there is reasonable assurance that the device is safe and effective.

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

FDA typically provides a public decision summary when it approves a PMA,[51] approves an HDE application, or grants a De Novo classification request. These summaries generally include clinical study summaries and other evidence considered in FDA's evaluation. When FDA considers patient preference studies in its consideration of a premarket submission, such studies generally are included in the decision summary. This approach could also be used for sponsor 510(k) summaries. Inclusion of PPI in FDA's and industry'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 device options under consideration.

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[46] *See* 21 CFR 814.44(e).

[47] *See* 21 CFR 814.116(c).

[48] 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).

[49] 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.

[50] 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.

[51] *See*, e.g., 21 CFR 814.44 and 814.116. FDA currently posts decision summaries for PMAs, HDE applications, and De Novo requests on its website.

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. [52]

Generally, patient 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.[53] 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 statement about the population for whom the device is intended.

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).

When possible, the likelihoods of benefits and risks 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%.[54,55]

IX. Hypothetical Examples

The following examples are offered for illustrative purposes only. The decisions described in these examples 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.

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.

[52] 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.
[53] For more information, see FDA's Guidance titled "Medical Device Patient Labeling."
[54] E. Akl, *et al*., "Using alternative statistical formats for presenting risks and risk reductions," *Cochrane Database Syst. Rev.* (2011).
[55] 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).

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.

B. 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.

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.

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 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.

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 increased risks with the implantation, such as with facial nerve injury during surgical implantation. These risks are greater than with the available alternative devices with similar effectiveness. However, PPI clearly indicates that there is a sizeable group of patients who are willing to accept the greater risks of the new implanted device (despite similar effectiveness of the alternatives) due to additional benefits, such as being more discrete.

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.

E. Pediatric 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 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 would consider the quality of the PPI evidence and may favorably weigh the PPI when assessing whether the probable benefits of this new device outweigh the risks.

X. Appendix A: Incorporating Patient Preference Information and Other Patient Input into the Total Product Life Cycle

In addition to the specific examples described in the main body of the guidance, FDA and sponsors may use PPI and other types of patient input throughout the total product life cycle 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 user-centered design.

- 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 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 ensure 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 life cycle. 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 IDE applications, PMAs, 510(k)s, HDE applications, or De Novo classification requests.

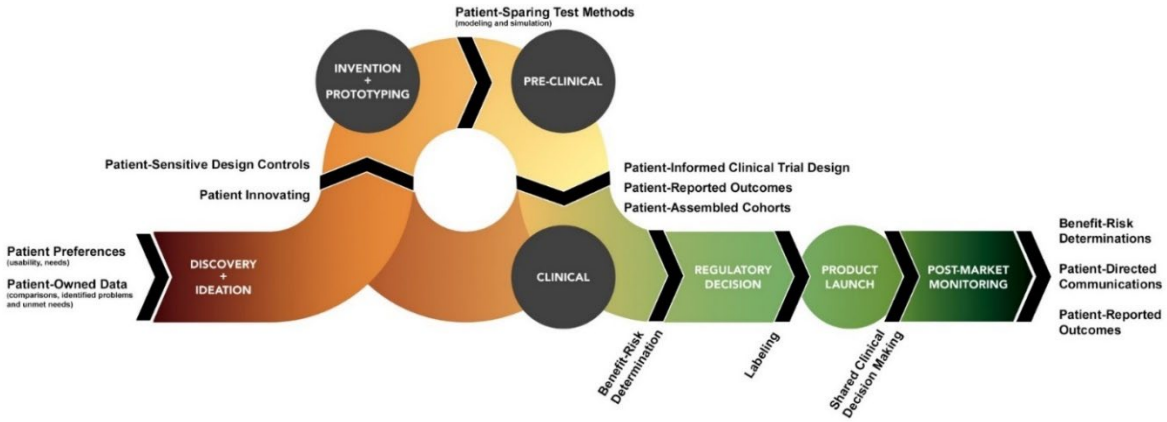

Figure 1. Patient Input in the Total Product Life Cycle

XI. Appendix B: Methods

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 direct comparison.[56,57] 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. One caution with stated preference studies is the issue of hypothetical bias. This bias come into play when a study does not have adequate relevance to the targeted sample population. This concern can be mitigated by use of various design techniques.[58]

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[59] 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 in development or under FDA 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.

Qualitative research is important for supporting the design of a quantitative PPI study. When selecting the attributes to include in a quantitative PPI study, sponsors are encouraged to engage patients in the selection process, and this can be done using qualitative methods. For example, semi-structured one-on-one interviews or focus groups can be conducted among a sample of patients where a list of attributes and their respective descriptions are presented to

[56] 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).
[57] 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).
[58] Ozdemir S, Johnson FR, Hauber AB. Hypothetical bias, cheap talk, and stated willingness to pay for health care. J Health Econ. 2009 Jul;28(4):894-901. doi: 10.1016/j.jhealeco.2009.04.004. Epub 2009 Apr 18. PMID: 19464743. This will be referred to as Hypothetical bias, cheap talk, and stated willingness to pay for health care.
[59] *See* Hypothetical bias, cheap talk, and stated willingness to pay for health care.

the participants to solicit feedback. Typically, probes are used to assess if the proposed attributes are relevant to the patients and if the attribute descriptions are comprehensible to them. The survey instrument used in a quantitative PPI study should also be pre-tested using qualitative methods. Pre-testing is commonly conducted via one-on-one, "think-aloud" interviews, where respondents verbalize their thought process as they complete the survey instrument and the interviewer uses probes to assess if the patients understood the survey instrument as intended, and if patients are able to make tradeoffs in the preference elicitation questions. Additionally, if the aims of the PPI study include measuring MAR or MAB, the pre-test interviews should also evaluate whether the attribute levels encompass the range over which patients are able to make tradeoffs, and that patients are able to distinguish between the levels of the attribute. It should be noted that if substantial changes to the instrument are made after a round of pre-testing, it may be appropriate to conduct additional pre-testing on the revised instrument before final implementation.

In general, quantitative methods are useful when the intent is to quantify the value that patients place on certain attributes. The choice of methods can depend on several factors, including but not limited to, the research question, the type of preference parameters needed, and the number of attributes to be assessed.[60] If the intent is to quantify the tradeoffs that patients are willing to make between attributes, commonly used methods for eliciting tradeoff information include discrete choice experiment (DCE), best-worst scaling (BWS) case 3, threshold technique, and swing weighting (SW).[61] In general, if a MAR or MAB is needed for a single attribute, the threshold technique (TT) may be satisfactory; for example, in a preference study conducted to determine the performance goal (i.e., MAB) of a clinical study used the threshold technique.[62] The threshold technique increases or decreases the target attribute rate to estimate at what point a respondent would switch from what is generally the standard of care option to the new presented treatment option. If the relative tradeoffs among several treatment attributes are needed, the DCE methodology may be optimal. For example, in a study where the aim was to quantify the relative importance of several attributes related to the effectiveness, safety, and administration of obesity devices, the DCE technique was used.[63] This was done because the DCE allows for multiple attributes to vary independently which then allows for the creation of a data set where it is feasible to estimate the preferences of each attribute relative to the other attributes included. If the main research question is to prioritize endpoints, BWS Case 1 may be sufficient to provide a rank ordering, since BWS case one asks the respondent what is most important or least important or what is best or least important and then provides the ordinal ranking. Typically, TT and SW are more accommodating of small sample sizes (<100) compared to DCEs.[64]

[60] Tervonen T, Veldwijk J, Payne K, et al. Quantitative Benefit-Risk Assessment in Medical Product Decision Making: A Good Practices Report of an ISPOR Task Force. *Value Health*. Apr 2023;26(4):449-460. doi:10.1016/j.jval.2022.12.006.

[61] *See* PREFER Recommendations.

[62] For more information, see "Summary of Safety and Effectiveness Data."

[63] Ho MP, Gonzalez JM, Lerner HP, et al. Incorporating patient-preference evidence into regulatory decision making. *Surg Endosc*. Oct 2015;29(10):2984-93. doi:10.1007/s00464-014-4044-2.

[64] *See* PREFER Recommendations.

Sponsors are encouraged to refer to published literature for more information on the methods available, points to consider for method selection, and the respective strengths and limitations of various methods.[65,66,67,68,69] When multiple methods are available to estimate the parameters of interest, sponsors are encouraged to seek input from FDA on the proposed method selection.

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 FDA assessment of product benefit and risk in the decision phase.[70]

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

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[65] *See* PREFER Recommendations.

[66] Whichello C, Levitan B, Juhaeri J, et al. Appraising patient preference methods for decision-making in the medical product life cycle: an empirical comparison. *BMC Med Inform Decis Mak*. Jun 19 2020;20(1):114. doi:10.1186/s12911-020-01142-w.

[67] *See* MDIC Patient Centered Benefit-Risk Project Report.

[68] Hauber B, Coulter J. Using the Threshold Technique to Elicit Patient Preferences: An Introduction to the Method and an Overview of Existing Empirical Applications. *Appl Health Econ Health Policy*. Feb 2020;18(1):31-46. doi:10.1007/s40258-019-00521-3.

[69] Tervonen T, Gelhorn H, Sri Bhashyam S, et al. MCDA swing weighting and discrete choice experiments for elicitation of patient benefit-risk preferences: a critical assessment. *Pharmacoepidemiol Drug Saf*. Dec 2017;26(12):1483-1491. doi:10.1002/pds.4255.

[70] For more information, see FDA's guidance titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."

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 FDA assessment of product benefit versus risk in decision-making.