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Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Interested Parties

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 6, 2024.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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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. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

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Preface

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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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

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35 consistent with FDA’s Benefit-Risk Guidance Documents.¹

36

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

- 39 1) to encourage submission of PPI, if available, by sponsors or other interested parties to
40 FDA and to aid in FDA decision-making,
41 2) to outline recommended qualities of patient preference studies, which may result in
42 valid scientific evidence,²
43 3) to provide practical recommendations for collecting and submitting PPI to FDA; and
44 4) to discuss FDA’s inclusion of PPI in its decision summaries and provide
45 recommendations for the inclusion of such information in device labeling.

46

47 This guidance also includes hypothetical examples that illustrate how PPI may inform FDA’s
48 decision-making.

49

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

54

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

60 **II. Background**

61 In 2016, FDA issued the guidance document, [“Patient Preference Information –Voluntary
62 Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption
63 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.

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64 [Labeling](#),” in which we provided recommendations relating to the *voluntary* collection of PPI
65 that may be submitted for consideration as valid scientific evidence as part of FDA’s benefit-
66 risk assessment during its review of PMAs, HDE applications, and De Novo requests. This
67 guidance was part of FDA’s response to section 1137 of the Food and Drug Administration
68 Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, which directs the Agency to
69 “develop and implement strategies to solicit the views of patients during the medical product
70 development process and consider the perspectives of patients during regulatory discussions”
71 (section 569C of the FD&C Act).

72
73 Since that time there have been many developments in the use of PPI, including a growing
74 volume of industry-sponsored PPI studies provided to FDA for consideration as part of a
75 benefit-risk assessment, and numerous collaborations between FDA scientists and a variety
76 of interested parties to conduct PPI studies to inform clinical trial design and FDA decision-
77 making across a wide range of diseases, conditions and device areas. In addition, FDA has
78 co-hosted or participated in numerous convenings and international collaborations to advance
79 scientific methods and practical applications of PPI. Meanwhile, FDA has expanded its
80 benefit-risk guidance framework to apply to the total product life cycle, including the
81 submission and review of IDE applications, 510(k)s, PMAs, De Novo requests, and HDEs
82 applications, and FDA decisions involving administrative, enforcement, and other actions.
83

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

95 **III. Scope**

96 This guidance is applicable to voluntary PPI for consideration by FDA staff in decision-
97 making relating to devices. Voluntary PPI can, if it meets applicable legal standards, be
98 considered by FDA during all stages of the total product life cycle.⁴
99

100 PPI may be particularly useful in evaluating a device’s benefit-risk profile when patient
101 decisions are *preference sensitive*. Patient decisions regarding diagnostic or treatment
102 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](#).”

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

111

112 PPI can be useful during FDA's benefit-risk assessment for certain devices in several major
113 ways, including:

- 114 1) to help identify the most important benefits and risks of a technology from a patient's
115 perspective (including to inform selection of primary or secondary endpoints),
116 2) to assess the relative importance to patients of different attributes of benefit and risk,
117 and clarify how patients think about the tradeoffs of these benefits and risks for a
118 given technology (including to inform meaningful benefit), and
119 3) to help understand the heterogeneity or distribution of patient preferences regarding
120 benefits and risks of various treatment or diagnostic options (including to inform
121 patient subgroup considerations as part of benefit-risk assessments).

122

123 Notably, this guidance does not change any standards for marketing authorization or
124 premarket reviews, nor does it create any burden on sponsors of devices. Rather, it provides
125 recommendations relating to the voluntary collection of PPI that may be submitted for
126 consideration. FDA may consider certain submitted PPI, along with the totality of evidence
127 from clinical and nonclinical testing and real-world performance, throughout the total
128 product life cycle. Certain concepts discussed in this guidance are applicable to the device
129 development process from design to market. As such, the patient preference considerations
130 set out herein may be informative to sponsors during the design, nonclinical testing,
131 investigational, and pre-submission phases of their device development.

132

133 Additionally, this guidance may be informative to other interested parties such as patient
134 groups and those in academia who may wish to consider conducting patient preference
135 studies. The Agency encourages sponsors and other interested parties considering conducting
136 patient preference studies and submitting PPI to FDA to have early interactions with FDA
137 during the design phase of such studies and obtain feedback from the relevant FDA review
138 division.

139

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

143 **IV. Including patient input in FDA decision-making**

144 **A. How can patient input impact decision-making?**

145 Patients can provide useful information on a range of topics, including (but not limited to) an

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146 individual patient’s overall view of his or her condition, the natural history of the condition,
147 the impact of the condition on the patient’s life, the patient’s own experience with treatments
148 or perspective on unmet needs, outcomes and endpoints important to the patient, priorities for
149 disease management regardless if it is a primary or co-occurring condition, and other patient
150 preferences and perspectives for specific treatment options. Patient experience data can be
151 obtained in a variety of ways and can often be supplemented with other sources of
152 information (e.g., literature review, care-partner or healthcare professional input).

153

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

159 **B. What is patient preference information?**

160 *Patient preference information*, for the purposes of this guidance, is defined as qualitative or
161 quantitative assessments of the relative desirability or acceptability to patients of specified
162 alternatives or choices among outcomes or other attributes that differ among alternative
163 health interventions.⁵

164

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

171

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

176

177 FDA may also consider the preferences of care-partners (e.g., parents) and healthcare
178 professionals to the extent they are relevant in the benefit-risk assessments for a particular
179 device.

180

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.

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181 In the context of benefit-risk assessments, qualitative PPI may be useful in identifying which
182 outcomes, endpoints, or other attributes are valued most by patients and which factors affect
183 patients' perspectives on benefit and risk. Quantitative PPI can provide estimates of how
184 much different outcomes, endpoints or other attributes are valued by patients, and the
185 tradeoffs that patients state or demonstrate they are willing to make among them. Such
186 outcomes or other attributes of a device include demonstrated or posited measures of
187 effectiveness, safety, and other device characteristics that may impact benefit-risk
188 considerations, including (but not limited to) means of implantation, duration of effect,
189 duration and frequency of use, and utility of the device. Patients may be queried about their
190 risk tolerance and benefit-risk preferences in the context of a specified therapy *a priori* (to
191 prospectively report their preferences without prior experience with a particular device) or
192 after receiving treatment.

193

194 Patient preference assessments should take into account both the patient's willingness and
195 unwillingness to accept the identified risks associated with device use. Both willingness and
196 unwillingness are helpful in determining patient tolerance for risk and perspective on benefit
197 and may be informative in FDA's assessment of the benefit-risk profile of a device.

198

C. Why include patient preference information in 199 decision-making?

200

201 It is important to acknowledge that individual patient preferences may vary and that a patient
202 may not assign the same values to various risks and benefits as their healthcare professional,
203 a family member, regulator, or another individual. Furthermore, patient preferences may vary
204 both regarding perspective on benefits and risks, as well as in preferred modality of
205 treatment/diagnostic procedure (e.g., often devices are one option to be considered in a
206 treatment care path, which may include other interventions, such as medical procedures or
207 medications). Some patients may be willing to accept higher risks to potentially achieve a
208 certain benefit, whereas others may be more risk averse, requiring a greater benefit to be
209 willing to accept certain risks.

209

210 An individual's personal values, disease stage, family circumstances, age and other
211 demographic characteristics may also influence their benefit-risk preferences. Evaluations of
212 patient-centered variations in tolerance to risks and perspective on benefits may, in the
213 aggregate, reveal a population-level assessment of patient benefit-risk preference for that
214 device, which might inform FDA's benefit-risk assessment for a device subject to FDA
215 review. For example, if this assessment reveals that a significant number of reasonable and
216 well-informed patients would accept the probable benefits despite the probable risks, this
217 may help support a favorable benefit-risk profile.

218

219 Furthermore, it may be appropriate to consider marketing authorization for a device for use
220 in a subset of a population, when valid scientific evidence shows that the requisite statutory
221 standard is met for use of the device in that subset. In making such a determination, FDA
222 may consider PPI along with the totality of evidence available. If FDA determines that the
223 relevant statutory standard is not met for any definable sub-population, FDA will not approve
224 or grant marketing authorization for such a device.

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

227 A *patient-reported outcome (PRO)* is a measurement based on a report that comes directly
228 from the patient (i.e., study subject) about the status of a patient’s health condition without
229 amendment or interpretation of the patient’s response by a clinician or anyone else.⁹ For
230 example, two widely used PRO measures are the Numeric Rating Scale (NRS) for pain and
231 the Health Assessment Questionnaire (HAQ) and Disability Index (DI) score for physical
232 function. PRO instruments are designed to measure a patient’s perceptions of health status
233 before, during, and after therapy, while patient preference studies are designed to measure
234 what specified type of therapy or attributes of a given therapeutic or diagnostic strategy a
235 patient might prefer. While PRO measures may provide a snapshot of a patient’s own
236 assessment of various outcomes at a given point in time, they do not convey how much the
237 patient values one specified outcome or therapy when compared to other potential outcomes
238 and therapies. Assessing this type of comparison or tradeoff is what patient preference
239 studies are designed to do. These studies may address, for example, whether a patient would
240 be willing to choose a treatment that causes a specified level of reduction (i.e., loss) in
241 physical function in exchange for a specified improvement (i.e., gain) in pain relief.
242 Quantitative methods have been developed to answer this type of question by eliciting patient
243 preferences for attributes that differ among alternative options.^{10,11,12}

244 **E. Is the submission of patient preference information**
245 **required for sponsors?**

246 Submission of PPI to FDA is voluntary. PPI may not be relevant or appropriate for all device
247 types. However, it may be useful for sponsors to collect and submit such information for
248 certain devices, particularly for those product types and diseases or conditions where usage
249 decisions by patients and healthcare professionals are preference-sensitive.

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

252 PPI might be useful for the following device characteristics:¹³

- 253 • Devices with a direct patient interface,
- 254 • Devices intended to yield significant health or appearance benefits,
- 255 • Devices intended to directly affect health-related quality of life,
- 256 • Certain life-saving but high-risk devices,
- 257 • 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.

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

260

261 There may also be instances in which FDA staff may find preference information useful,
262 such as¹⁴:

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

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

278

279 **Example of a PPI study to support benefit-risk decisions**

280 CDRH sponsored a patient preferences study intended to inform the benefits versus risk
281 tolerance related to weight-loss device treatments for obesity.¹⁵ The sample included more
282 than 500 patients drawn from an online panel that was designed to represent a cross section
283 of the U.S. population. The study sample had similar demographic characteristics to those of
284 obese patients in the U.S. population. The sample size was planned to capture a wide
285 spectrum of patient preferences and provided better representativeness of the U.S. obese
286 population than anecdotal remarks or small focus group studies. The study was designed to
287 measure quantitative patient preference heterogeneity and conduct preference segmentation.

288

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

294

295 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>.

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296 recognized professional organization such as the Professional Society for Health Economics
297 and Outcomes Research (ISPOR). Research conducted at the study design stage and during
298 the face-to-face interviews with patients was designed to ensure that the survey instrument
299 was patient-centered, the communication of benefits, risks and uncertainty was clear, and the
300 format of the questions would keep potential cognitive bias to a minimum. Rigorous internal
301 validation tests were conducted to make sure the data quality was sufficiently high. The
302 benefits (weight loss amount and duration, improvement in comorbidities), risks (mortality,
303 adverse events, and hospitalization), and key attributes (type of surgery, diet restrictions) of
304 the device were carefully defined so that the tradeoff among the benefits and risks would be
305 comprehensible to patients, healthcare professionals, and the Agency.

306
307 The study showed that a substantial portion of obese patients would accept the risks
308 associated with a surgically implanted device if they lost a sufficient number of pounds. The
309 data generated from this study could also be used to inform clinical trial design, to estimate
310 the tradeoffs in risks that obese patients are willing to accept in exchange for a certain
311 amount of weight loss, or the minimum number of pounds they would have to lose to tolerate
312 the risks of a weight loss device.

313
314 Studies like this may provide information on the relative importance of certain device
315 attributes to patients as well as how benefits and risks are weighted, enabling more patient-
316 centric decision-making and potentially informing the design and analysis of clinical trials.

317 318 Example of PPI study to support indication expansion and updates to labeling

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

329

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.

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330 **Example of PPI study to establish performance threshold**

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

344
345 For more information, sponsors can also refer to the FDA website on “Patient Preference
346 Information (PPI) in Medical Device Decision-Making” for a list of published studies and
347 ongoing projects and past PPI-related FDA workshops conducted.²⁰

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

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

357
358 In addition, for IDEs, FDA’s benefit-risk assessment includes consideration of the risks and
359 anticipated benefits to study subjects and societal benefits in terms of knowledge to be gained
360 from the study. In the context of a clinical study, patient preferences may vary in which
361 outcomes matter most to a particular patient, the amount of risk they would be willing to
362 accept in exchange for a certain amount of benefit, their preferred modality of
363 treatment/diagnostic procedure (often devices are one option to be considered in a clinical
364 care path which may include medication or surgical procedures), as well as the value they
365 assign to the potential societal benefits of the research itself, in advancing potential medical
366 options for patients in the future.²¹

367

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.

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

370

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

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

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

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

388

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

393

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

403

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

406

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.

407 **V. Recommendations and Practical Considerations for**
408 **Patient Preference Studies**

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

413 **A. Patient-Centeredness**

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

418 **B. Relevance to Patients**

419 Critical aspects of benefit, risk, and uncertainty should be included in the elicitation of
420 preferences, and omission of any should be well justified. Often it is most useful to ensure
421 some consistency among the benefits, risks and other attributes evaluated in a preference
422 study and the endpoints and other outcome data collected in the clinical study. Preferences
423 should be measured over relevant clinical domains to be useful in evaluating available
424 evidence. The importance of key clinical parameters to clinical outcomes should be clearly
425 communicated to patients to properly elicit their preferences. For example, if clinical
426 endpoints take the form of surrogate biomarkers (e.g., Hemoglobin A1c for diabetic patients),
427 the study should help patients understand how changes in the biomarkers may correspond
428 with the likelihood of more serious outcomes.

429 **C. Appropriate methods for eliciting patient preferences**

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

435
436 A sponsor's investigational plan must include a "written protocol describing the
437 methodology to be used and an analysis of the protocol demonstrating that the investigation
438 is scientifically sound." 21 CFR 812.25(b); see 21 CFR 812.20(b)(2). If a quantitative
439 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).

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

445
446 In general, qualitative methods produce descriptive data that may be useful for understanding
447 the subjective experiences of patients.²⁷ Early in the total product life cycle, if the intent is to
448 identify attributes or device features that are important to patients to inform device design, a
449 qualitative study may be sufficient. Qualitative patient input on preferences can also be
450 useful to inform the design of clinical trials by identifying endpoints that are important and
451 relevant from the patient’s perspective. There are different methods to conduct qualitative
452 research to obtain PPI, including but not limited to one-on-one interviews, focus groups, and
453 Delphi panels. Sponsors are encouraged to refer to available resources²⁸ for more information
454 on each method and the potential strengths and limitations associated with each method.
455 Qualitative preference studies that follow recommended good research practices laid out by
456 relevant health preference research professional organizations may be more likely to produce
457 valid scientific evidence.²⁹

458 **D. Representative Study Population that Supports** 459 **Generalizability Results**

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

464
465 A study should measure the preferences of a representative sample of adequate size so that
466 the study results can be reasonably generalized to the population of interest.

467
468 An important factor to consider is how similar the sample of interest is to the population of
469 interest. The representativeness of a sample may be influenced by its size, the between-
470 subject variability, and how subjects were sampled from the population of interest. For
471 example, if subject variability in the population of interest is large but a study sample size is
472 small, the study result may not be representative of the population of interest because it may
473 not be the whole spectrum of patient preferences. Moreover, when a sample is very small, the
474 estimates of patient preference parameters may not be sufficiently precise, and the study
475 conclusion may not be reliable.

476
477 Careful consideration should be given to the characteristics that are most likely to affect
478 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.

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

487

488 In cases in which detecting differences in preferences between pre-specified subgroups may
489 be important, the sample should include sufficient numbers in each subgroup and the
490 subgroups should be clinically well-defined. If subgroups' sizes are not adequate,
491 insignificant statistical results of hypothesis testing may not necessarily be a reflection of
492 preference similarity between subgroups.

493

E. Reflects Heterogeneity of Patients' Preferences

494 Patients' benefit-risk tradeoff preferences may be heterogeneous even among those with the
495 same disease or condition. Individual circumstances of patients vary. Besides sex, gender,
496 age, race, ethnicity, socioeconomic status, cultural background, and other life circumstances,
497 a patient's own experience of their disease may influence the patient's personal tolerance for
498 risk. As mentioned in the FDA guidance, [Factors to Consider when Making Benefit-Risk
499 Determinations in Medical Device Premarket Approval and De Novo Classifications](#),³⁰
500 patient views may be influenced by the severity of the disease or condition, disease
501 chronicity, or availability or lack of alternative options. It is important to account for these
502 variations when considering PPI. This variability may be population-, condition-, treatment-,
503 and study-specific. Therefore, patient preference studies should generally reflect the
504 preferences of patients from the full spectrum of disease for which the device is intended to
505 be used.

506

507 While some study analysis methods can account for preference heterogeneity with sufficient
508 sample size, not all analysis methods can effectively identify and quantify preference
509 heterogeneity. PPI may help identify a subgroup of patients (e.g., patients with higher pain
510 and functional limitation) who may consider the benefit-risk profile of a medical intervention
511 favorable, and FDA can take this information into account in its benefit-risk determinations.
512 These quantitative methods may help the Agency identify this subgroup and estimate its
513 relative size with respect to the overall surveyed patient population.

514

F. Appropriate selection of attributes and attribute levels

515 In general, attributes included should be relevant for the FDA decision and salient to the
516 patients. To ensure that all critical attributes important to making a decision are included,
517 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](#)."

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

528
529 Besides patient and FDA decision-making relevance, other considerations for attribute
530 selection include mutual exclusivity where the final set of attributes should be non-
531 overlapping in terms of outcomes measured. The framing and presentation of the benefit and
532 risk attributes should not unfairly bias the respondents' perception of those attributes either
533 positively or negatively. If risk attributes are included, efforts should be made to ensure that
534 the attribute descriptions appropriately convey the severity and impact of the risks to the
535 patients. It may be useful to refer to published literature when developing attribute
536 descriptions; nevertheless, these should be pre-tested with the targeted patient population to
537 ensure that they are fit-for-purpose.

538
539 In most quantitative preference studies, attributes can have different levels (i.e., values).
540 These levels can be presented on a probability scale (e.g., 5% risk), ordinal scale (e.g., mild,
541 moderate, and severe risk), or as categorical values (e.g., pill, injection, infusion). The
542 number of attributes or treatment features that can be included in a PPI study is limited by
543 what is cognitively feasible for a patient to consider simultaneously, and this is especially
544 true for attributes measured on a probability scale (e.g., 5% risk of an event). Having too
545 many attributes on a probability scale in a preference study can be cognitively challenging
546 for patients; however, certain attribute levels need to adopt a numerical value to allow for the
547 estimation of relevant MAR or MAB values. Therefore, the presentation of attribute levels
548 can be dependent on the parameters that need to be estimated from the study.

549
550 In general, the attribute levels included in a PPI study should encompass clinically and FDA
551 decision-making relevant ranges or values. If the PPI study is designed to support the
552 benefit-risk assessment of a device, the attribute levels included should align with the range
553 of values observed or expected from the clinical studies. Data from real-world observational
554 studies may be relevant to characterize existing treatment alternatives. If the range of
555 attribute levels included in a PPI study do not include all relevant values observed in clinical
556 studies, this could skew the study results and make the study difficult to interpret,
557 diminishing the overall usefulness of the study to inform FDA decision-making.

558 Extrapolation of patient preference data beyond the levels included in the study is generally
559 not considered a valid practice because the specific and relative weights patients assign to
560 preferences must be elicited and cannot be inferred.

561

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

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

570

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

573

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	<ul style="list-style-type: none">• 30 lbs• 20 lbs• 15 lbs	reference a, reference b
Risk of myocardial infarction	Additional risk of heart attack in the next year	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Pump• Infusion every 4 weeks (about once a month)	reference c

574

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

575

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

576

577

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589

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.

590 **G. Effective Communication of Benefit, Risk, and**
591 **Uncertainty**

592 Health numeracy means the ability to understand and use numbers in making health-related
593 decisions. Given the varying levels of numeracy in the general population, it is important for
594 patient preference studies to define the context of the benefit-risk tradeoffs, explain the level
595 of effectiveness, and help patients conceptualize probabilities using appropriate numeric,
596 verbal, and graphic representations of uncertainty.
597

598 In a typical patient preference study, a patient may be asked to consider various combinations
599 of health outcomes and to indicate which combination is preferred and by how much. The
600 patient should understand and cognitively process these health outcomes, and the benefits,
601 risks, and uncertainties associated with them. Communicating the quantitative aspects of
602 health information has been widely recognized as a challenge.^{33,34} Examples of formats used
603 to communicate numerical values include:

- 604 • natural frequency (e.g., 20 in 1000), percent (e.g., 2%),
- 605 • solely verbal (e.g., high, low),
- 606 • verbal frequency (e.g., twenty out of one thousand),
- 607 • pictograph/graphical icon array (e.g., a 10 by 10 array of 100 small human-shaped
608 icons, all in white with 2 in black),
- 609 • relative and absolute risk reduction (if 1000 people have this test every year, 20
610 people will be saved from dying from this illness every 5 years), and
- 611 • numbers needed to treat (e.g., 15 patients need to receive this treatment to avoid 1
612 additional death in 5 years).

613
614 While no single format is universally superior to other formats, some general practices are
615 supported by scientific evidence to reduce the uncertainty caused by health numeracy
616 variation.³⁵ For example, we recommend the following:

- 617 • Avoid solely verbal descriptions of uncertainty. Patients may interpret what “low”
618 and “high” risks are differently,
- 619 • Avoid fractions, decimals, and different denominators when presenting risks of
620 multiple treatments. These are relatively difficult for cognitive processing,
- 621 • If possible, describe the benefits and risks in absolute scales instead of relative
622 terms. Absolute scales better inform the actual benefits and risks,
- 623 • If possible, use multiple formats simultaneously (e.g., verbal frequency, percent,
624 and icon array/pictograph). Relative understanding of these formats varies from
625 patient to patient. Moreover, one format may make the other formats easier to
626 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).

- 627 • If possible, describe uncertainty in both positive and negative frames (e.g., 20%
628 chance of adverse events or 80% chance of no adverse events) to avoid cognitive
629 bias.

630 We recommend pre-testing the communication format. Since patient populations vary, pre-
631 testing the chosen format can improve the comprehension of the format by the study
632 population of interest.

633 **H. Study Comprehension with Minimal Cognitive Bias**

634 Efforts should be made to ensure that study participants fully understand the benefit, risk,
635 uncertainty and other medical information being communicated to them. For example, if a
636 survey instrument’s presumed reading level of the target patient population is not
637 appropriate, some respondents may not understand a question. Comprehension assessments
638 could be added to assess if respondents are interpreting the presented benefit and risk
639 information as intended. It is possible that respondents may oversimplify the information and
640 provide responses based on such oversimplification, thereby producing invalid
641 measurements.

642
643 Study design should minimize potential cognitive biases such as framing (e.g., describing
644 changes as gains or losses), anchoring (e.g., signaling a reference value), simplifying
645 heuristics (e.g., recoding numerical values or percentages as low, medium, and high), or
646 ordering effect (e.g., the response to a question depending on its relative position in the
647 question sequence). For example, study subjects were asked to imagine they were lung
648 cancer patients and choose between different treatments, such as surgery and radiation, based
649 on cumulative probabilities and life-expectancy data. More individuals chose surgery when
650 they were told that it had a 90% survival rate than when they were told that the surgery had a
651 10% mortality rate.³⁶

652 **I. Logical Soundness**

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

655
656 Sponsors are encouraged to include data quality checks of the survey responses, and the
657 protocol should describe how the data quality checks will be used in the analysis and
658 interpretation of study results. There are several ways to assess data quality, including but not
659 limited to:

- 660 • comprehension assessments,
661 • internal validity assessments of dominance,
662 • consistency, recoding effects assessments, and
663 • 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).

664 Sponsors can refer to published literature on the common types of internal validity tests used
665 in preference elicitation studies.^{37,38}

666 **J. Robustness of Analysis of Results**

667 After measurements are made in a scientific study, an analysis of these results should ensure
668 appropriate interpretation of the collected evidence. Quantitative analyses often involve
669 development of statistical models, which in turn provide estimates of the parameters of
670 interest. It is important that the sources of uncertainty are well understood because decisions
671 may be made based on these estimates. The uncertainty of an estimate can be reported
672 through a confidence interval and standard error. Sensitivity analysis is an effective method
673 to determine the value of the parameter that would change the final decision.³⁹ For example,
674 if the parameter does not affect the final decision regardless of its value, then its uncertainty
675 may not be important to the overall analysis.

676 **K. Study Conduct**

677 The validity and reliability of study results depend in large part on compliance of research
678 staff and study participants with the study protocol. A patient preference study should be
679 administered by trained research staff. If the preference study is self-administered by
680 patients, they should go through a tutorial and a quiz before answering questions, to help to
681 ensure adequate comprehension and compliance with the study protocol. The quiz results
682 should be documented as supportive evidence of patients being properly informed of the
683 benefits, risks, and uncertainty presented in the study questions, and of comprehension by
684 study participants.

685 **L. Follows Established Good Research Practices by 686 Recognized Health Preference Research Professional 687 Organizations**

688 The quality of a study may be established if it follows guidelines for good research practices
689 established by a recognized professional organization. For example, ISPOR published a set
690 of good research practices for preference-based methods.^{40,41,42}

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

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

693 PPI may be submitted to FDA through a variety of pathways. Sponsors and other interested
694 parties interested in designing a patient preference study or submitting a patient preference
695 study to the Agency may request FDA’s feedback or a meeting with FDA through the Q-
696 Submission Program.⁴³ Sponsors may provide PPI as a part of a submission as supporting
697 evidence, for example, that the probable benefits of a device outweigh probable risks. Other
698 interested parties (e.g., academia or patient groups) may consider sharing PPI with FDA for
699 informational purposes. The Agency may also consider obtaining its own PPI to further
700 understand the benefit-risk factors affecting patients with diseases or conditions who may be
701 considering using a specific device type.

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

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

710
711 Sponsors are highly encouraged to engage in discussions early with FDA to seek alignment
712 on the scientific research question(s) of interest, the parameters of interest for decision-
713 making questions, and study objectives.

714
715 During the protocol development stage, sponsors may seek alignment with FDA on the study
716 objective(s) and key question(s) of interest, the study population, and the proposed attributes
717 and levels that will be included in the study, if applicable. It would be useful to submit a draft
718 protocol when soliciting feedback from FDA.

719
720 When designing a quantitative PPI study, the primary, secondary, and exploratory endpoints,
721 including targets, that are consistent with study objectives and based upon appropriate
722 preference parameters should be specified in the protocol along with the statistical analysis
723 plan.

724
725 If relevant, including an attribute table in the protocol can be useful for seeking FDA’s
726 feedback on attribute levels. References should be included, where applicable and available,
727 to justify the selection of attribute levels. Any qualitative work that is planned or has been
728 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.](#)”

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

734

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

740

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

747

748 It is recommended that sponsors discuss recruitment and sampling strategies, approaches to
749 obtain confirmation of diagnosis, and identification of clinically relevant subgroups with
750 FDA before study implementation. If screening questions are used to identify eligible
751 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?

753

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

759

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

768

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

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

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

781

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

787

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

791 **VII. Additional Considerations**

792 The discussion below addresses additional considerations regarding PPI.

793 **A. Maintaining the Integrity of Patient Preference** 794 **Information**

795 As with other data submitted for premarket review, efforts should be made to ensure that data
796 integrity and validity are maintained. Patient preference studies are social science
797 experiments, and must comply with 21 CFR parts 50, 56, and 812 to the extent applicable,
798 including by obtaining IRB review and approval and informed consent where required.
799 Sponsors are also encouraged to follow ethical practices and principles standard in the PPI
800 research community.

801

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

⁴⁴ See 21 CFR 812.28, 814.15.

⁴⁵ 21 CFR 812.28(b)(6).

811 **B. Conditions of Approval**

812 FDA may impose conditions of approval in certain PMA⁴⁶ or HDE approvals,⁴⁷ including
813 where the Agency takes PPI into account. These conditions of approval may help to mitigate
814 risk and facilitate use in patients for whom probable benefits are expected to outweigh
815 probable risks.

816
817 Patient preference studies may help sponsors and FDA identify a subset of patients for whom
818 the probable benefits outweigh the probable risks, and the approval would not be for the
819 general population but instead would be limited to the population for which FDA determines
820 there is reasonable assurance that the device is safe and effective. Certain conditions of
821 approval, such as a shared decision-making tool^{48,49} or specialized patient labeling,⁵⁰ may be
822 appropriate to mitigate risk and facilitate use in patients for whom FDA determines there is
823 reasonable assurance that the device is safe and effective.

824

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

827 FDA typically provides a public decision summary when it approves a PMA,⁵¹ approves an
828 HDE application, or grants a De Novo classification request. These summaries generally
829 include clinical study summaries and other evidence considered in FDA's evaluation. When
830 FDA considers patient preference studies in its consideration of a premarket submission,
831 such studies generally are included in the decision summary. This approach could also be
832 used for sponsor 510(k) summaries. Inclusion of PPI in FDA's and industry's public decision
833 summaries can be helpful to healthcare professionals and patients in making healthcare
834 decisions involving difficult benefit-risk tradeoffs or novel treatments.

835

836 Additionally, PPI that is reviewed by FDA and supports FDA's approval or marketing
837 authorization should also be described in the device labeling. It is important for the device
838 product labeling to contain sufficient information about the benefits and risks of the device
839 options under consideration.

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, Mousmjid 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.

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841 As with all product labeling, and particularly when there is a complex benefit-risk tradeoff, it
842 is important to communicate the benefit-risk information to patients, care-partners, and
843 healthcare professionals as they make treatment decisions.⁵²

844

845 Generally, patient labeling should be written in plain language so that patients are able to
846 understand the information presented and form realistic expectations of the treatment and its
847 potential risks.⁵³ The patient labeling should use terminology and numerical data in a way
848 that is easily recognized and understood by the average layperson. When appropriate, visual
849 language, such as pictorials, graphics, or tables, should be included as an adjunct to the
850 written word. In addition, the labeling should include a clear statement about the population
851 for whom the device is intended.

852

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

855

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

861

862 When possible, the likelihoods of benefits and risks should be expressed in absolute terms
863 rather than relative terms that may be confusing. For example, doubling a risk means very
864 different things if that entails an increase from 10% to 20% rather than an increase from
865 0.001% to 0.002%.^{54,55}

866 **IX. Hypothetical Examples**

867 The following examples are offered for illustrative purposes only. The decisions described in
868 these examples are intended only to demonstrate how FDA might consider PPI when making
869 benefit-risk assessments. Similar scenarios or devices may result in different outcomes
870 depending on the individual performance characteristics of a particular device and the
871 population for which it is indicated.

872

A. Probable benefit outweighs probable risk for a subset 873 of patients

874

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).

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875 The device is studied in a population of patients with knee pain and functional limitation who
876 manifest a broad spectrum of disease severity and duration.

877

878 The data indicate a smaller than expected improvement in the study population as a whole.
879 However, per pre-specified statistical analysis, patients with the highest pain and functional
880 limitation may experience more pain reduction and functional improvement than the overall
881 study population without any increase in adverse events. According to PPI submitted to
882 FDA, the expected benefits among patients with the greatest pain and functional limitations
883 exceed the minimum level of benefits that patients in the patient preference study find
884 acceptable given expected risks.

885

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

891 **B. Patient preference information helps inform FDA**
892 **reviewer considerations**

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

896

897 After a single treatment, improvement is noticed by about 75% of patients. Satisfaction in
898 age-related facial appearance drops to about 50% at two years after the initial treatment, with
899 reappearance of facial wrinkles over time. FDA reviewers note that the procedure does not
900 result in permanent improvement, and the data suggest that patients may undergo additional
901 procedures over time to maintain the aesthetic effect. Reviewers initially considered that the
902 temporary nature of the benefit may not be sufficient to outweigh the risks, particularly given
903 that additional adverse effects may occur from repeat procedures over time. However, PPI
904 indicates that a significant subset of patients may prefer a device with temporary effects,
905 rather than a permanent durable implant inserted during a single procedure that may become
906 aesthetically undesirable over time as the patient ages.

907

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

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

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

915

916 Data from the clinical trial suggest similar body improvement benefit as marketed

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917 alternatives but faster recovery from the surgical procedure to implant the device. However, a
918 higher rate of meaningful adverse events was observed, including need for reoperation to
919 remove and/or replace the device, with typically lesser improvement in body appearance with
920 subsequent procedures. This need for reoperation may be attributable to lower device
921 durability. PPI indicates that some patients place a high value on the appearance
922 enhancement the device provides and that some patients would accept the higher level of risk
923 observed in the study, in exchange for the benefits.

924

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

931 **D. Increased risk and similar effectiveness in comparison** 932 **to alternatives but clear patient preference for certain device** 933 **attributes**

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

936

937 Data from the clinical trial demonstrate rare but observed increased risks with the
938 implantation, such as with facial nerve injury during surgical implantation. These risks are
939 greater than with the available alternative devices with similar effectiveness. However, PPI
940 clearly indicates that there is a sizeable group of patients who are willing to accept the greater
941 risks of the new implanted device (despite similar effectiveness of the alternatives) due to
942 additional benefits, such as being more discrete.

943

944 FDA may determine, after considering PPI along with other evidence, that the probable
945 benefits outweigh the probable risks for this implantable device. Therefore, FDA may
946 determine there is a reasonable assurance of safety and effectiveness and may approve the
947 device.

948 **E. Pediatric Application and Patient/Parent Preferences**

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

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958 The new pediatric device includes smaller prosthesis sizes and is inserted via a surgical
959 procedure which has an initial risk of higher operative mortality, but with long term device-
960 related benefits of improved durability and lower reoperation rate compared to current
961 treatment options for these patients. As stated previously, due to unavailability of comparable
962 devices for these pediatric patients, treatment strategy typically entails waiting until the child
963 grows big enough for anatomy to accommodate a larger, available prosthesis. This
964 information, along with evidence from nonclinical testing on the device, is shared with
965 FDA’s Advisory Committee.

966
967 Additionally, a patient group submits PPI from a study of parents of patients. The parents of
968 these pediatric patients are typically the primary caretakers and healthcare decision makers.
969 The study shows that a majority of parents surveyed prefer the benefit-risk tradeoff of this
970 new device compared to the current treatment options, despite the operative safety concerns.

971
972 In considering the totality of evidence on the new device and taking into account the benefits
973 and risks of current alternative treatment options available, the Advisory Committee and
974 FDA would consider the quality of the PPI evidence and may favorably weigh the PPI when
975 assessing whether the probable benefits of this new device outweigh the risks.

976 **Appendix A: Incorporating Patient Preference**
977 **Information and Other Patient Input into the Total**
978 **Product Life Cycle**

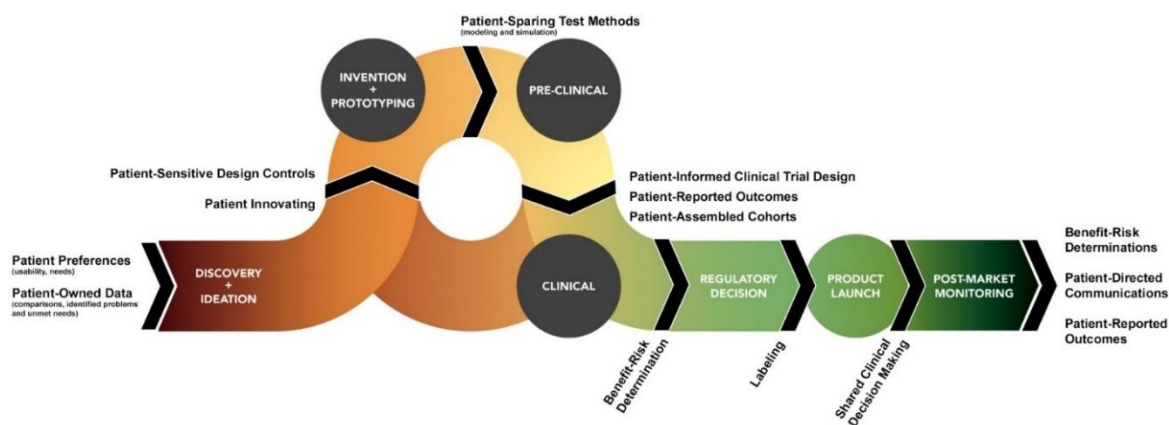
979 In addition to the specific examples described in the main body of the guidance, FDA and
980 sponsors may use PPI and other types of patient input throughout the total product life cycle
981 as shown in Figure 1. For example:

- 982 • Nonclinical (Discovery + Ideation, Invention + Prototyping):
 - 983 • During the discovery and ideation phase, qualitative patient input on the types
984 of treatment benefits or device attributes patients might value most may
985 inform device design and/or features. Additionally, patient input may
986 influence which devices are developed, such as by defining areas of unmet
987 need.
 - 988 • During invention and prototyping, patient-sensitive design inputs may help
989 developers refine device design to better meet patient end-user needs, such as
990 through user-centered design.
- 991 • Clinical:
 - 992 • Patient-informed clinical study design may reduce barriers to participation and
993 affect willingness of participants to enroll and complete a clinical study, such
994 as by streamlining visit schedules and follow-up procedures.
 - 995 • Qualitative patient input may also inform the design of clinical trials by
996 helping to identify what endpoints may be of highest importance to patients.
997 Patient input may also inform the development or selection of PRO measures.
 - 998 • Quantitative PPI may inform the design of clinical trials by providing prior
999 evidence regarding the level of benefit patients require in order to accept a
1000 certain level of risk associated with device treatments. As exemplified in the
1001 CDRH Patient Preferences of Weight Loss Devices Study (see Section IV),
1002 quantitative PPI can be used to help define the “minimum clinically
1003 meaningful benefit,” which may have implications for sample size and other
1004 aspects of clinical trial design.
- 1005 • Postmarket:
 - 1006 • Once the device is marketed, device labeling and shared clinical decision-
1007 making tools may be employed to ensure that benefit-risk information as well
1008 as PPI is appropriately communicated to patients and healthcare professionals.
 - 1009 • Once a device is used more widely, ongoing benefit-risk determinations and
1010 patient-directed communications may become an important part of postmarket
1011 monitoring.
1012 As postmarket patient-centered data accumulates, it may lead to new
1013 innovations or inform redesign and improvement of existing devices, or
1014 expanded indications.
1015
1016
1017

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1018 In a patient-centered product development program, PPI may be considered at various
1019 decision points throughout the total product life cycle. In many cases, this information is best
1020 considered not as discrete and disconnected, but as a dataset which can be built upon and
1021 which may be informative to future development stages. For example, qualitative PPI could
1022 inform device design or clinical trial design, which could shape future quantitative studies of
1023 patient preference, which could inform FDA benefit-risk assessments during premarket
1024 review of IDE applications, PMAs, 510(k)s, HDE applications, or De Novo classification
1025 requests.
1026



1027
1028 Figure 1. Patient Input in the Total Product Life Cycle
1029

1030 Appendix B: Methods

1031 There are a variety of quantitative approaches to eliciting patient preferences. Such
1032 approaches attempt to quantify a spectrum of patient preferences from individual patients,
1033 which requires careful study design, conduct, and analysis. For straightforward decisions
1034 regarding risk tolerance and patient preference, qualitative input may be sufficient. Complex
1035 questions regarding such issues, however, may require quantitative evidence to ensure that
1036 different outcomes are properly weighed in the same scale and therefore can be compared.

1037
1038 Multiple studies have identified and compared a variety of methods to measure patient
1039 preferences on benefits and risks and derive preference weights in a scale that allows for
1040 direct comparison.^{56,57} Many of these studies have used a class of methods called *stated*
1041 *preference*, in which preferences are elicited by offering choices or posing contingent
1042 valuation questions to study participants. These stated-preference methods involve some
1043 simplification of the decision problem to a manageable subset of decision variables or to
1044 some simple valuation questions compared to what individual patients are likely to face. One
1045 caution with stated preference studies is the issue of hypothetical bias. This bias come into
1046 play when a study does not have adequate relevance to the targeted sample population. This
1047 concern can be mitigated by use of various design techniques.⁵⁸

1048
1049 Other studies have used *revealed-preference* methods in which patient preferences are
1050 obtained from the actual observed choices made by patients. These studies can avoid the
1051 hypothetical bias⁵⁹ associated with the stated-preference studies. However, the revealed-
1052 preference methods often cannot be applied when a device profile of interest is not yet
1053 available for patients to choose because a device is still in development or under FDA
1054 review. Therefore, use of revealed-preference methods is typically limited when the benefit-
1055 risk profile of a device is not comparable to any other devices on the market. Moreover, these
1056 methods are also subject to potential biases such as financial considerations of individual
1057 patients. Both stated-preference and revealed-preference methods may be informative for
1058 understanding patient preferences. Selection of appropriate methods will depend on the
1059 primary use of PPI.

1060
1061 Qualitative research is important for supporting the design of a quantitative PPI study. When
1062 selecting the attributes to include in a quantitative PPI study, sponsors are encouraged to
1063 engage patients in the selection process, and this can be done using qualitative methods. For
1064 example, semi-structured one-on-one interviews or focus groups can be conducted among a
1065 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.

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1066 the participants to solicit feedback. Typically, probes are used to assess if the proposed
1067 attributes are relevant to the patients and if the attribute descriptions are comprehensible to
1068 them. The survey instrument used in a quantitative PPI study should also be pre-tested using
1069 qualitative methods. Pre-testing is commonly conducted via one-on-one, “think-aloud”
1070 interviews, where respondents verbalize their thought process as they complete the survey
1071 instrument and the interviewer uses probes to assess if the patients understood the survey
1072 instrument as intended, and if patients are able to make tradeoffs in the preference elicitation
1073 questions. Additionally, if the aims of the PPI study include measuring MAR or MAB, the
1074 pre-test interviews should also evaluate whether the attribute levels encompass the range over
1075 which patients are able to make tradeoffs, and that patients are able to distinguish between
1076 the levels of the attribute. It should be noted that if substantial changes to the instrument are
1077 made after a round of pre-testing, it may be appropriate to conduct additional pre-testing on
1078 the revised instrument before final implementation.

1079
1080 In general, quantitative methods are useful when the intent is to quantify the value that
1081 patients place on certain attributes. The choice of methods can depend on several factors,
1082 including but not limited to, the research question, the type of preference parameters needed,
1083 and the number of attributes to be assessed.⁶⁰ If the intent is to quantify the tradeoffs that
1084 patients are willing to make between attributes, commonly used methods for eliciting
1085 tradeoff information include discrete choice experiment (DCE), best-worst scaling (BWS)
1086 case 3, threshold technique, and swing weighting (SW).⁶¹ In general, if a MAR or MAB is
1087 needed for a single attribute, the threshold technique (TT) may be satisfactory; for example,
1088 in a preference study conducted to determine the performance goal (i.e., MAB) of a clinical
1089 study used the threshold technique.⁶² The threshold technique increases or decreases the
1090 target attribute rate to estimate at what point a respondent would switch from what is
1091 generally the standard of care option to the new presented treatment option. If the relative
1092 tradeoffs among several treatment attributes are needed, the DCE methodology may be
1093 optimal. For example, in a study where the aim was to quantify the relative importance of
1094 several attributes related to the effectiveness, safety, and administration of obesity devices,
1095 the DCE technique was used.⁶³ This was done because the DCE allows for multiple attributes
1096 to vary independently which then allows for the creation of a data set where it is feasible to
1097 estimate the preferences of each attribute relative to the other attributes included. If the main
1098 research question is to prioritize endpoints, BWS Case 1 may be sufficient to provide a rank
1099 ordering, since BWS case one asks the respondent what is most important or least important
1100 or what is best or least important and then provides the ordinal ranking. Typically, TT and
1101 SW are more accommodating of small sample sizes (<100) compared to DCEs.⁶⁴
1102

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.

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1103 Sponsors are encouraged to refer to published literature for more information on the methods
1104 available, points to consider for method selection, and the respective strengths and limitations
1105 of various methods.^{65,66,67,68,69} When multiple methods are available to estimate the parameters
1106 of interest, sponsors are encouraged to seek input from FDA on the proposed method
1107 selection.

1108
1109 In the earliest stages of development—sometimes referred to as the discovery and ideation
1110 phase—it may be most useful to obtain patient input using open-ended questions and
1111 qualitative interactive discussion that may involve methods such as focus groups, social
1112 media, public meetings, workshops, or an FDA request for comments to the docket. At this
1113 early stage, for example, questions might be related to what disease impacts are most
1114 important to patients and their care-partners and healthcare professionals. The impacts
1115 explored may include discussion of burden of disease, burden of currently available
1116 treatment and other aspects of the disease experience (e.g., symptoms or functional impacts
1117 of the disease). This input also can provide useful information on the natural history of the
1118 condition, unmet needs, priorities for disease management, willingness to participate in
1119 clinical trials, and other broad questions of concern.

1120
1121 The open-ended qualitative patient input gathered early in the development process can help
1122 to frame the questions to be pursued in subsequent studies, which may be more focused and
1123 involve more structured methods and development of more specific quantitative or semi-
1124 quantitative measures. This can, for example, lead to development of data collection tools
1125 including Clinical Outcome Assessment (COA) tools such as PRO instruments. These tools
1126 can be incorporated into clinical trials to enable more direct measurement of the impact of
1127 the tested therapy on those aspects of disease and treatment identified as being most
1128 important to patients. The data obtained from these clinical studies can then be part of the
1129 study data set that a sponsor submits to FDA in support of their PMA, HDE application, or
1130 De Novo request and can inform FDA assessment of product benefit and risk in the decision
1131 phase.⁷⁰

1132
1133 The open-ended qualitative patient input can also help to identify specific clinical outcomes
1134 that may represent changes in patient’s symptoms, functioning, or survival. This information
1135 can be used to frame questions to be pursued in subsequent use of structured methods to elicit

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.”](#)

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1136 PPI. Surveys that elicit patient willingness to accept a specified type and level of expected
1137 risks, in exchange for a specified type and level of expected benefit, for a particular disease
1138 condition and sometimes a specified technology can also help to provide insight into the
1139 patient’s perspective and thus inform FDA assessment of product benefit versus risk in
1140 decision-making.

DRAFT