

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

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

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

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

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1 **Patient Preference Information –**
2 **Submission, Review in PMAs, HDE**
3 **Applications, and *De Novo* Requests,**
4 **and Inclusion in Device Labeling**
5 **Draft Guidance for Industry, Food**
6 **and Drug Administration Staff, and**
7 **Other Stakeholders**

8
9
10 *This draft guidance, when finalized, will represent the current thinking of the Food and*
11 *Drug Administration (FDA or Agency) on this topic. It does not establish any rights for*
12 *any person and is not binding on FDA or the public. You can use an alternative approach*
13 *if it satisfies the requirements of the applicable statutes and regulations. To discuss an*
14 *alternative approach, contact the FDA staff responsible for this guidance as listed on the*
15 *title page.*

16
17 **I. Introduction**

18
19 The U.S. Food and Drug Administration (FDA or the Agency) values the experience and
20 perspectives of patients with devices. The Agency understands that patients and caregivers
21 who live with a disease or condition on a daily basis and utilize devices in their care may
22 have developed their own insights and perspectives on the benefits and risks of devices under
23 PMA, HDE, or *de novo* review. FDA believes that patients can and should bring their own
24 experiences to bear in helping the Agency evaluate the benefit-risk profile of certain devices.
25 This kind of input can be important to consider during regulatory decision-making for certain
26 devices.

27
28 For this reason, FDA’s guidance document “Factors to Consider When Making Benefit-Risk
29 Determinations in Medical Device Premarket Approval and *De Novo* Classifications”¹

¹ See FDA’s *Guidance for Industry and Food and Drug Administration Staff; Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* issued on March 28, 2012

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

37
38 This draft guidance document takes the next step and provides guidance on patient preference
39 information that may be used by FDA staff in decision-making relating to PMAs,
40 Humanitarian Device Exemption (HDE) applications, and *de novo* requests. The objectives
41 of this draft guidance are: 1) to encourage voluntary submission of patient preference
42 information by sponsors or other stakeholders, in certain circumstances; 2) to outline
43 recommended qualities of patient preference studies, which may result in valid scientific
44 evidence; 3) to provide recommendations for collecting patient preference information to
45 FDA; and 4) to provide recommendations for including patient preference information in
46 labeling for patients and health care professionals. This draft guidance also includes several
47 hypothetical examples that illustrate how patient preference information may inform FDA's
48 regulatory decision-making.

49
50 This draft guidance is proposing edits to the Benefit-Risk Guidance that are shown in
51 Appendix A.

52
53 FDA's guidance documents, including this draft guidance, do not establish legally
54 enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a
55 topic and should be viewed only as recommendations, unless specific regulatory or statutory
56 requirements are cited. The use of the word *should* in Agency guidance means that
57 something is suggested or recommended, but not required.

58 59 **II. Overview and Scope**

60
61 This draft guidance document explains the principal concepts that sponsors and other
62 stakeholders should consider when choosing to collect patient preference information, which
63 may inform FDA's benefit-risk determinations in the premarket review of PMAs, HDE
64 applications, and *de novo* requests. This draft guidance also provides recommendations on
65 how patient preference information should be incorporated into device labeling for patients
66 and health care professionals. This draft guidance is applicable to both diagnostic and
67 therapeutic devices that are subject to these review processes.

68
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandguidance/guidanceDocuments/UCM296379.pdf>.

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

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

80

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

92

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

100

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

105 Additionally, this draft guidance may be informative to other stakeholders such as patient
106 groups and academia who may wish to consider conducting patient preference studies. The
107 Agency encourages sponsors and other stakeholders considering conducting patient
108 preference studies for regulatory purposes to FDA to have early interactions with the relevant
109 FDA review division.

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111 III. Background

112

113 Historically, some patients have brought their views to FDA regarding the approval or
114 clearance of FDA-regulated medical products. Their views have influenced regulatory
115 decisions by providing additional insight and helped to provide the public with faster access
116 to safe and effective medical products, such as those for patients with HIV³ and multiple
117 sclerosis.⁴

118

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

124

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

129

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

140

141 3.1 What is patient preference information?

³ Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS,
<http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm134331.htm> (last visited, October 1, 2014).

⁴ See FDA’s *Guidance for Industry; Expedited Programs for Serious Conditions—Drugs and Biologics*, issued
May 2014

(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>).

⁵ See Public Workshop - The Patient Preference Initiative: Incorporating Patient Preference Information into the
Medical Device Regulatory Processes, September 18-19, 2013,
<http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm361864.htm> (last visited January 15,
2015); see also The Patient Preference Initiative: Incorporating Patient Preference Information Into Medical
Device Regulatory Processes: Public Workshop; Request for Comments (78 FR 45538) (July 29, 2013)
([https://www.federalregister.gov/articles/2013/07/29/2013-18080/the-patient-preference-initiative-
incorporating-patient-preference-information-into-the-medical](https://www.federalregister.gov/articles/2013/07/29/2013-18080/the-patient-preference-initiative-incorporating-patient-preference-information-into-the-medical)).

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

146
147 This draft guidance focuses on ***patient preference information***, which for the purposes of
148 this draft guidance, is defined as qualitative or quantitative assessments of the relative
149 desirability or acceptability of attributes that differ among alternative diagnostic or
150 therapeutic strategies.⁶

151
152 Attributes of a device are features such as effectiveness, safety, means of implantation,
153 duration of effect, duration of use, and other device characteristics that may affect benefit-risk
154 considerations.

155
156 In the context of benefit-risk assessments, qualitative information may be useful in
157 identifying which outcomes, endpoints or attributes matter most to patients and which factors
158 affect patients' risk tolerance and perspective on benefit. Quantitative information can
159 provide estimates of *how much* different outcomes of features matter to patients and the
160 tradeoffs that patients state they are willing to make among them. Patients may be queried
161 about their risk tolerance and benefit-risk preferences *a priori* (to prospectively report their
162 preferences without prior experience with a particular device) or after receiving treatment.

163
164 Patient-centric assessments should take into account both the patient's willingness and
165 unwillingness to tolerate risks associated with device use. Both willingness and
166 unwillingness are helpful in determining patient tolerance for risk and perspective on benefit
167 and may be informative in FDA's assessment of the benefit-risk profile of a device.⁷

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

168
169 It is important to acknowledge that individual patient preferences may vary, and that a patient
170 may not assign the same values to various risks and anticipated benefits as his/her health care
171 professional, a family member, regulator, or another individual. Furthermore, patient
172 preferences may vary both in preferred modality of treatment/diagnostic procedure (e.g.,
173 often devices are one option to be considered in a treatment care path, which may include
174 surgery or medication) as well as in risk tolerance. Some patients may be willing to take on
175 higher risks to potentially achieve a small benefit, whereas others may be more risk-averse,
176 requiring more benefit to be willing to take on certain risks.

177
178

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

⁷ See Footnote 1.

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

187
188 Furthermore, it may be appropriate to approve a PMA, approve an HDE application, or grant
189 a *de novo* request for use of a device by a subset of the population for which an indication is
190 requested when valid scientific evidence shows that the probable benefit of a device
191 outweighs probable risks of the device for that subset. In making such a determination, FDA
192 would consider patient preference information along with the totality of evidence from
193 clinical and nonclinical testing. If FDA determines the device would expose patients to an
194 unreasonable or significant risk of illness or injury, or the benefits do not outweigh the risks
195 for some definable target population, FDA would not approve such a device.

3.3 Are there established quantitative methods to elicit patient preferences?

196
197 There are a variety of quantitative approaches to eliciting patient preferences. Such
198 approaches attempt to quantify the whole patient-preferences spectrum from individual
199 patients, which requires careful study design, conduct, and analysis. For straightforward
200 decisions regarding risk tolerance and patient preference, qualitative input may be sufficient.
201 Complex questions regarding such issues, however, may require quantitative evidence to
202 ensure that different outcomes are properly weighed in the same scale and therefore can be
203 compared.
204

205
206 Multiple studies have identified and compared a variety of methods to measure patient
207 preferences on benefits and risks and derive preference weights in a scale that allows for
208 direct comparison.^{9,10,11} The majority of these studies have used a class of methods called
209 stated preference, in which preferences are elicited by offering choices to participants. Other
210 studies have used revealed-preference methods, in which patient preferences are obtained
211 from the actual clinical choices made by patients. Both stated-preference and revealed-
212 preference methods may be informative for understanding patient preferences. Some stated-
213 preference and revealed-preference methods are outlined in Appendix B to this draft
214 guidance.

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

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

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

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

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215

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

223

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

228

229 3.4 How is patient preference information different from patient-reported outcomes?

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

236

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

248

249 3.5 Is the submission of patient preference information required?

¹² See FDA's *Guidance for Industry; Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, issued December 2009 (<http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>).

¹³ See Footnote 9.

¹⁴ M Agapova, *et al.*, "Applying Quantitative Benefit-Risk Analysis to Aid Regulatory Decision Making in Diagnostic Imaging: Methods, Challenges, and Opportunities," *Academic Radiology*, 1138-1143 (2014).

¹⁵ See Footnote 10.

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

260

261 Such circumstances may exist for devices with the following attributes:

262

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

269

270 **3.6 When and how might FDA consider patient preference information during the** 271 **review of PMAs, HDE applications, and *de novo* requests?**

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

278

279 ***FDA’s Evaluation of PMAs.*** In the PMA approval review, FDA determines whether a
280 device provides a “reasonable assurance of safety and effectiveness” by “weighing any
281 probable benefit to health from the use of the device against any probable risk of injury or
282 illness from such use,” among other relevant factors (section 513(a)(2)(C) of the FD&C Act
283 (21 U.S.C. 360c(a)(2)(C))).¹⁶ A reasonable assurance of safety occurs when “it can be
284 determined, based upon valid scientific evidence, that the probable benefits ... outweigh any
285 probable risks,” and the valid scientific evidence adequately demonstrates “the absence of
286 unreasonable risk of illness or injury associated with the use of the device for its intended
287 uses and conditions of use” (21 CFR 860.7(d)(1)). Moreover, a reasonable assurance of
288 effectiveness occurs when “it can be determined, based upon valid scientific evidence, that in
289 a significant portion of the target population, the use of the device for its intended uses ...
290 will provide clinically significant results” (21 CFR 860.7(e)(1)). The evidence used to

¹⁶ See Footnote 1.

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

293

294 **FDA’s Evaluation of HDE Applications.** An HDE application is similar to a PMA, but is
295 exempt from the effectiveness requirements of sections 514 and 515 of the FD&C Act (21
296 U.S.C. 360d and 360e). FDA approval of an HDE authorizes an applicant to market a
297 Humanitarian Use Device (HUD), a device intended to benefit patients in the treatment or
298 diagnosis of diseases or conditions that affect fewer than 4,000 individuals, subject to certain
299 profit and use restrictions set forth in section 520(m) of the FD&C Act (21 U.S.C. 360j(m)).
300 To approve a HUD under the HDE pathway, FDA must determine, among other things, that
301 “the device will not expose patients to an unreasonable or significant risk of illness or injury”
302 and “the probable benefit to health from the use of the device outweighs the risk of injury or
303 illness from its use, taking into account the probable risks and benefits of currently available
304 devices or alternative forms of treatment” (section 520(m) of the FD&C Act (21 U.S.C.
305 360j(m)).

306

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

316

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

328

329 **3.7 Can FDA or sponsors use or consider patient preference information be used at**
330 **times other than during the submission and review of PMAs, HDE applications, and *de***
331 ***novo* requests?**

¹⁷ See Footnote 1.

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

336

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

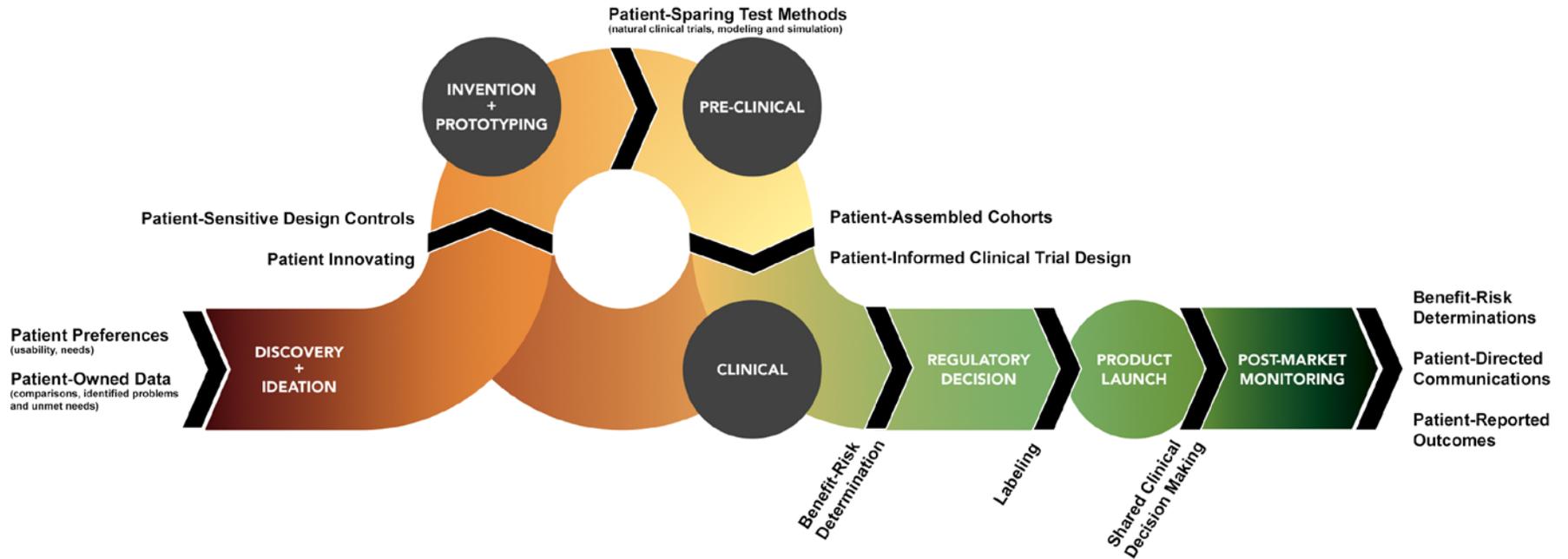
365

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

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374

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

IV. Recommended Qualities of Patient Preference Studies

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

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

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

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

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

¹⁸ See Footnote 9.

¹⁹ F.R. Johnson, *et al.*, *Quantifying Patient Preferences to Inform Benefit-Risk Evaluations in Benefit-Risk Assessment in Pharmaceutical Research and Development*, CRC Press (2013).

²⁰ F. Mussen, *et al.*, *Benefit-Risk Appraisal of Medicines*, John Wiley & Sons Ltd (2009).

²¹ See Footnote 11.

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414 help identify a subgroup of patients (e.g. patients with higher pain and functional
415 limitation) who consider the benefit-risk profile of a medical intervention favorable,
416 and FDA can take this information into account in its benefit-risk determinations.
417 These quantitative methods may help the Agency identify this subgroup and estimate
418 its relative size with respect to the overall surveyed patient population.
419

420 c) **Established Good Research Practices by Recognized Professional Organizations:**

421 The quality of a study may be established if it follows guidelines for good research
422 practices established by a recognized professional organization. For example, the
423 International Society for Pharmacoeconomics and Outcomes Research published a set
424 of good research practices for discrete-choice experiments.^{22, 23} Newer methods may
425 also be acceptable, and FDA intends to consider these on a case-by-case basis.
426

427 d) **Patient Centeredness:** Patient preference studies should ensure that the patient, not
428 the health care professional, is the central part of the study. The study should aim to
429 measure inherent attitudes and values of well-informed patients. This could also
430 include evaluating caregiver, parent, or guardians' preferences in situations when the
431 patient may not be able to provide the patient preference perspective.
432

433 e) **Effective communication of benefit, harm, uncertainty, and risk:** Health numeracy
434 means the ability to understand and use numbers in making health-related decisions.
435 Given the level of numeracy in the general population, it is important for patient
436 preference studies to define the context of the benefit-risk tradeoffs, explain the level
437 of effectiveness and the severity of treatment-related harms, and help patients
438 conceptualize probabilities using appropriate numeric, verbal, and graphic
439 representations of uncertainty.
440

441 In a typical patient preference study, a patient may be asked to consider various
442 combinations of health outcomes and to indicate which combination is preferred and
443 by how much. The patient should understand and cognitively process these health
444 outcomes, and the benefits, harms, risks, and uncertainties associated with them.
445 Communicating the quantitative aspects of health information has been widely
446 recognized as a challenge.^{24, 25} Examples of formats used to communicate numerical
447 values include:
448

²² J.F.P. Bridges, *et al.*, "Conjoint analysis applications in health—a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force," *Value in Health*, 403-13 (2011).

²³ F.R. Johnson, *et al.*, "Constructing experimental designs for discrete-choice experiments: Report of the ISPOR conjoint analysis experimental design good research practices task force," *Value in Health*, 3-13 (2013).

²⁴ B. Fischhoff, *et al.*, "Communicating Risks and Benefits: An Evidence Based User's Guide," U.S. Food and Drug Administration (2011).

²⁵ L.M. Schwartz and S. Woloshin, "The Drug Facts Box: Improving the communication of prescription drug information," *Proceedings of the National Academy of Sciences*, 14069-14074 (2013).

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

457

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

461

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

476

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

487

²⁶ See Footnote 24.

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

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- 488 g) **Logical soundness:** The data should include internal-validity tests of logic and
489 consistency and should be verified for conformity with logic and consistency.
490
- 491 h) **Relevance:** Critical aspects of risk, benefit, and uncertainty should be included in the
492 elicitation of preferences, and omission of any should be well justified. Preferences
493 should be measured over relevant clinical domains to be useful in evaluating available
494 evidence. If clinical endpoints take the form of surrogate markers (e.g., liver
495 enzymes) that may be asymptomatic, the study should help patients understand how
496 such measures affect the likelihood of more serious outcomes.
497
- 498 i) **Robustness of Analysis of Results:** After measurements are made in a scientific
499 study, an analysis of these results should ensure appropriate interpretation of the
500 collected evidence. Quantitative analyses often involve development of statistical
501 models, which in turn provide estimates of the parameters of interest. It is important
502 that the sources of uncertainty are well understood because decisions may be made
503 based on these estimates. The uncertainty of an estimate can be reported through a
504 confidence interval and standard error. Sensitivity analysis is an effective method to
505 determine the value of the parameter that would change the final decision.²⁸ For
506 example, if the parameter does not affect the final decision regardless of its value,
507 then its uncertainty may not be important to the overall analysis.
508
- 509 j) **Study Conduct:** The validity and reliability of study results depends in large part on
510 compliance of research staff and study participants with the study protocol. A patient
511 preference study should be administered by trained research staff. If the preference
512 study is self-administered by patients, they should go through a tutorial and a quiz
513 before answering questions, to help to ensure compliance with the study protocol.
514
- 515 k) **Comprehension by Study Participants:** Efforts should be made to ensure that study
516 participants fully understand the risk and other medical information being
517 communicated to them. For example, if a survey instrument's presumed reading level
518 of the target patient population is too high, some respondents may not understand a
519 question. In this case, the respondents may use heuristics or mentally turn the
520 question at hand into an easier but different question to answer, which would render
521 an invalid measurement.
522

523 Example: CDRH Patient Preferences of Weight Loss Devices Study

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

²⁸ A.H. Briggs, *et al.*, "Model Parameter Estimation and Uncertainty Analysis A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6," *Medical Decision Making*, 722-732 (2012).

²⁹ M. Ho, M. Gonzalez, H. Lerner, C. Neuland, J. Whang, M. McMurry-Heath, A. Hauber, and T. Irony. "Incorporating patient-preference evidence into regulatory decision making." *Surgical endoscopy* (2015): 1-10.

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

531
532 The study's stratified sampling by Body Mass Index (BMI) ensured that estimates were
533 precise across the whole BMI range of interest. Moreover, the study used a preference
534 elicitation method that not only allowed investigators to identify and divide patients into
535 different segments by patients' risk-tolerance level, but also provided the estimated
536 percentage of patients that would prefer receiving the device to the status quo.

537
538 Design, conduct, and analysis of the study followed good research practices endorsed by an
539 international professional society representing health outcome researchers across the world.
540 Research conducted at the study design stage and during the face-to-face interviews with
541 patients helped ensure that the survey instrument was patient-centered, the communication of
542 benefits, harms, risks and uncertainty was clear, and the format of the questions would keep
543 potential cognitive bias to a minimum. Rigorous internal validation tests were conducted to
544 make sure the data quality was sufficiently high. The benefits (weight loss amount and
545 duration, improvement in comorbidities), harms (type of surgery, diet restrictions) and risks
546 (mortality, adverse events, and hospitalization) of the device were carefully defined so that
547 the tradeoff among the benefits and risks would be comprehensible to patients, health care
548 professionals, and the Agency.

549
550 The study showed that a substantial portion of obese patients would accept the risks
551 associated with a surgically implanted device if they lost a sufficient number of pounds. The
552 data generated from this study could also be used to inform clinical trial design, to estimate
553 the tradeoffs in risks that obese patients are willing to accept in exchange for a certain
554 amount of weight loss, or the minimum number of pounds they would have to lose to tolerate
555 the risks of a weight loss device.

556
557 Studies like this may provide information on the relative importance of certain device
558 attributes to patients as well as how benefits and risks are weighted, enabling more patient-
559 centric regulatory decision-making and potentially informing the design and analysis of
560 clinical trials.

561

V. Additional Considerations

562

563
564 The discussion below addresses additional considerations regarding patient preference
565 information.

566

5.1 Maintaining the Integrity of Patient Preference Information

567
568 As with other data submitted for premarket review, efforts should be made to ensure that data
569 integrity and validity are maintained. For example, participating investigators of IDEs are

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570 responsible for maintaining accurate, complete, and current records of each subject's case
571 history and exposure to the device. See 21 CFR 812.140(a)(3). Such case histories may
572 include patient diaries, assessments, electronic patient diaries, and other electronic patient-
573 reported outcome tools (ePRO).³⁰

574

575 **5.2 Conditions of Approval**

576 FDA may impose conditions of approval in certain situations, including for approvals where
577 it takes patient preference data into account. In some cases where FDA determines a product
578 has reasonable assurances of safety and effectiveness in a subset of patients (e.g., based on
579 disease severity) but the device poses potentially serious or life-threatening risks, FDA may
580 determine that conditions of approval are warranted. Patient preference studies may help
581 FDA identify a subset of patients in whom the benefits outweigh the risks, and the approval
582 would not be for the general population but instead would be limited to the population where
583 FDA determines the benefits outweigh the risks. In such cases, certain conditions of
584 approval³¹ may be appropriate to mitigate risk and facilitate use in patients in whom benefits
585 are expected to outweigh risks. As with other PMA approvals, HDE application approvals or
586 *de novo* classifications for certain devices, FDA may require the collection of postmarket
587 evidence through a post-approval surveillance study or “522 study.”³²

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

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

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

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

VI. Submission of Patient Preference Information

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

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

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

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

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

VII. Communicating Patient Preference Information in Device Labeling

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

that meets certain criteria. For more information, see FDA's *Draft Guidance for Industry and Food and Drug Administration Staff; Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act* issued on August 16, 2011

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268064.htm>).

This draft guidance, when finalized, will represent FDA's current thinking on this topic.

³³ MDDTs are scientifically validated tools created to support device development and regulatory evaluation. Qualification reflects CDRH's expectation that within a specified context of use, the results of an assessment that uses an MDDT can be relied upon to support device development and regulatory decision-making. See FDA's *Medical Device Development Tools; Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff*, issued on November 14, 2013

(<http://www.fda.gov/MedicalDevices/GuidanceRegulationandGuidance/GuidanceDocuments/ucm374427.htm>).

This draft guidance, when finalized, will represent FDA's current thinking on this topic.

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

626

627 This section includes recommendations for incorporating patient preference information into
628 device labeling and suggestions to help prepare such labeling consistent with the
629 requirements of 21 CFR Part 801.³⁴ For additional information on developing labeling,
630 please consult [FDA Guidance: Labeling - Regulatory Requirements for Medical Devices](#)
631 [\(FDA 89-4203\)](#).

632

7.1 General Labeling Recommendations

633 Clear, accurate, and informative labeling helps patients and health care professionals
634 understand the potential benefits and risks of devices and thus allows them to make informed
635 choices.
636

637

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

641

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

649

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

654

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

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

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

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658

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

666

7.2 Additional Recommendations for Patient Labeling

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

675

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

677

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

687

688 When possible, the likelihoods of risks and benefits should be expressed in absolute terms
689 rather than relative terms that may be confusing. For example, doubling a risk means very
690 different things if that entails an increase from 10% to 20% rather than an increase from
691 0.001% to 0.002%.³⁸

692

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

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

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

693 **VIII. Hypothetical Examples**

694

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

701

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

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

706

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

713

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

720

721 **B. Patient preference data helps inform FDA reviewer considerations**

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

725

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

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

739

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

742

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

743 A permanently implanted aesthetic device is intended to improve body appearance. The
744 device is studied in a healthy patient population.
745

746

747 Data from the clinical trial suggest similar body improvement benefit as marketed
748 alternatives but faster recovery from the surgical procedure to implant the device. However,
749 a higher rate of meaningful adverse events was observed, including need for reoperation to
750 remove and/or replace the device, with typically lesser improvement in body appearance with
751 subsequent procedures. This difference may be attributable to lower device durability.

752 Patient preference information indicates that some patients place a high value on the
753 appearance enhancement the device provides and that some patients would accept the higher
754 level of risk observed in the study, in exchange for the benefits.

755

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

762

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

763 A permanent, fully implantable device is intended to improve hearing. The device is studied
764 in a patient population with advanced hearing loss.
765

766

767 Data from the clinical trial demonstrate rare but observed surgical risks with the implantation,
768 such as facial nerve injury, as well as subsequent device failures requiring
769 revision/reimplantation. These risks are not present with conventional, non-implanted
770 auditory aids. The effectiveness data demonstrate similar performance to a conventional air
771 conduction hearing aid (which is class I exempt, low risk). However, patient preference
772 information clearly indicates that there is a sizeable group of patients who, unhappy with the
773 inconvenience and poor cosmesis of conventional hearing aids, are willing to accept the
774 greater risks of the implanted device despite equivalent effectiveness as non-implanted aids.
775

776

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

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

783

E. Pediatric HDE and Patient/Parent Preferences

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

792

793
794 The new pediatric device includes smaller prosthesis sizes and is inserted via a surgical
795 procedure which has an initial risk of higher operative mortality, but with long term device-
796 related benefits of improved durability and lower reoperation rate compared to current
797 treatment options for these patients. As stated previously, due to unavailability of
798 comparable devices for these pediatric patients, treatment strategy typically entails waiting
799 until the child grows big enough for anatomy to accommodate larger, available prosthesis.
800 This information along with evidence from nonclinical testing on the device is shared with
801 FDA's Advisory Committee. Additionally, a patient group submits patient preference
802 information from a study of parents of patients. The parents of these pediatric patients are
803 typically the primary caretakers and health care decision makers. The study shows that a
804 majority of parents surveyed prefer the benefit-risk tradeoff of this new device compared to
805 the current treatment options, despite the operative safety concerns.

806

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

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

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

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

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Patient tolerance for risk and perspective on benefit	<ul style="list-style-type: none"> — Did the sponsor present data regarding how patients tolerate the risks posed by the device? - <i>Are data available regarding how patients tolerate the risks posed by the device?</i> - <i>Are the risks identifiable and definable?</i> - <i>Do patients understand the type of risk(s) and the likelihood of the risk(s)?</i> - <i>Do patients understand the type of benefit(s) and the likelihood of the benefit(s)?</i> 	
<ul style="list-style-type: none"> • Disease severity 	<ul style="list-style-type: none"> - <i>Is the disease so severe that patients may tolerate a higher amount of risk for a smaller benefit?</i> - <i>Does the patient preference information (PPI) include patients across the spectrum of disease severity?</i> <ul style="list-style-type: none"> ○ <i>If yes, how does the PPI vary (if at all) across the spectrum?</i> ○ <i>If no, for what level of disease severity is PPI available?</i> 	
<ul style="list-style-type: none"> • Disease chronicity 	<ul style="list-style-type: none"> - <i>Is the disease chronic?</i> - <i>How long do patients with the disease live?</i> - <i>If chronic, is the illness easily managed with less-invasive or difficult therapies?</i> - <i>If chronic, does the patient preference information (PPI) include patients across the spectrum of disease chronicity?</i> <ul style="list-style-type: none"> ○ <i>If yes, how does the PPI vary (if at all) across the spectrum?</i> ○ <i>If no, for what level of disease chronicity is PPI available?</i> 	

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827 From page 28 of the Benefit-Risk Guidance:

828

Factor	Questions to Consider	Notes
<ul style="list-style-type: none"> • Patient-Centric Assessment 	<ul style="list-style-type: none"> — How much do patients value this treatment? - <i>What benefit(s) from this device is (are) of most value to patients?</i> <ul style="list-style-type: none"> o <i>Does the treatment improve overall quality of life?</i> — Are patients willing to take the risk of this treatment to achieve the benefit? - <i>What risk(s) from this device is (are) of most concern to patients?</i> — Does the treatment improve overall quality of life? - <i>How well are patients able to understand the benefits and risks of the treatment?</i> - <i>Are patients willing to take the risk(s) of this device to achieve the benefit(s)?</i> - <i>Do any of these issues vary according to the stage of disease severity or chronicity, and if so, how?</i> 	
<p><i>Risk mitigation and indication targeting</i></p>	<ul style="list-style-type: none"> - <i>Could you identify ways to mitigate the risks such as using product labeling (including restricting the indication for use to a subset of the requested population derived from patient preference information in whom probable benefit outweighs probably risk), establishing education programs, providing add-on therapy, obtaining informed consent, etc.?</i> - <i>What is the type of intervention proposed?</i> 	

829

830

Appendix B: Methodology

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

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

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

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

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

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

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

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871 **i. Stated-Preference Methods**

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

890

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

895

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

903

904 **ii. Conjoint Analysis (CA) Methods**

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

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

921

922 **iii. Discrete-Choice Experiments (DC)**

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

927

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

934

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

939

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

941 Health-state utility indicates the quality of a given health state. Utilities can be measured at
942 the population or individual levels. Changes in health states can be expressed as incremental
943 utility elicited by either standard gamble (SG) or time tradeoff (TTO) question formats.

944 Utilities can be converted to quality-adjusted life years (QALYs). QALYs facilitate health-
945 outcome comparisons across groups of people, health outcomes, and durations by expressing
946 the value of a condition as the sum of the utility of each health state weighted by the duration
947 of that state.

948

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

⁴⁰See Footnote 10.

⁴¹See Footnote 39.

⁴²See Footnote 22.

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

959

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

964

965 **v. Threshold Techniques**

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

977

978 **vi. Multiple-Criteria Decision Analysis**^{48,49,50}

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

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

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

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

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

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

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

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

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

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

987

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

994

995 New MCDA approaches have been developed to tackle multi-criteria decision problems,
996 including Analytical Hierarchy Process (AHP) and Stochastic Multi-criteria Acceptability
997 Analysis (SMAA). The standard MCDA approach for medical product benefit-risk decision
998 making lacks the ability to account for the uncertainty of the criteria measurements and its
999 validity can be adversely affected when consensus is not reached. SMAA was introduced as
1000 a way to overcome these limitations by modelling them through simulations.^{51,52}

1001

1002 AHP has been used to elicit patients' weights for the criteria considered.^{53,54} The AHP has
1003 been used to demonstrate that patient relevant endpoints can be prioritized and weighted by
1004 decomposing a decision problem into multiple criteria and by then applying pair wise
1005 comparisons of the alternatives on the criteria.^{55,56} Since MCDA methods are consensus
1006 building processes, the resultant weights of various treatment options may be sensitive to the
1007 way and the order of questions and given instructions throughout the process because
1008 decision makers can be subject to various cognitive biases, such as framing effect and
1009 anchoring effect. Therefore, an independent third party to conduct a MCDA study is
1010 recommended to avoid possible bias introduced to the process.

1011

1012 **vii. Contingent Valuation (CV) or Willingness to Pay (WTP) Methods**

⁵¹ T. Tervonen & J. Figueira, "A survey on stochastic multicriteria acceptability analysis methods," *J. Multi-Criteria Decision Analysis*, 1-14. (2008).

⁵² P. Salminen, *et al.*, "Comparing multicriteria methods in the context of environmental problems," *Eur. J. Operational Research*, 485-496 (1998).

⁵³ M. Hummel, *et al.*, "Using the Analytic Hierarchy Process to Elicit Patient Preferences," *The Patient*, 225-237 (2012).

⁵⁴ T. Sullivan, "Using MCDA (Multi-Criteria Decision Analysis) to prioritise publicly-funded health care," Doctoral Dissertation, University of Otago (2012).

⁵⁵ M. Danner, *et al.*, "Integrating patients' views into health technology assessment: Analytic hierarchy process (AHP) as a method to elicit patient preferences," *Intl. J. Tech. Assessment Health Care*, 369-375 (2011).

⁵⁶ M. Ijzerman, *et al.*, "A comparison of analytic hierarchy process and conjoint analysis methods in assessing treatment alternatives for stroke rehabilitation," *The Patient*, 45-56 (2012).

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1013 Contingent valuation (CV) or willingness to pay (WTP) method measures the monetary value
1014 decision makers place on hypothetical scenarios. In a CV survey, decision makers were
1015 presented with some hypothetical scenarios, such as outcomes of treatment options. The
1016 decision makers is then asked directly how much they are willing to pay for an option that is
1017 deemed to be more favorable than their status quo, and how much compensation they require
1018 to accept an option that is deemed to be inferior to their status quo. Due to the methods'
1019 known bias and different monetary valuations between people, CV and WTP methods are not
1020 considered to be valid evidence for regulatory consideration.

1021

1022 **viii. Best-Worse Scaling (BWS)**

1023 In best-worst scaling (BWS) studies,^{57,58} patients are presented with a set of options and ask
1024 them to choose the best (or most important or most desirable) option and the worst (or least
1025 important or least desirable) option. There are three types of BWS studies, or “cases”: object
1026 case, single-profile case, and multiple-profile case. These cases are defined by the nature of
1027 the options presented to the patients. In each set of options, patients can indicate which of
1028 the attributes (object case), the attribute levels (single-profile case), or the profiles of attribute
1029 level combinations (multiple-profile case) is best and which is worst. The response pattern of
1030 patients reveals the relative importance of each attribute or attribute levels. The BWS
1031 multiple-profile cases are similar to a discrete choice experiment and each set typically
1032 consists of three or more profiles.

1033

1034 **ix. Quality-adjusted Life Year (QALY)**

1035 Besides MaxR and MinB, utility and attitude are two other conventional indices that measure
1036 subjective value of an outcome or a health state to patients. The value of utility for a chronic
1037 condition ranges from 0 (being dead) to 1 (living with perfect health). As a patient goes
1038 through a series of health states with varying quality of life, the quality-adjusted life-year
1039 (QALY) of the patient is defined as the weighted duration of the health state by their
1040 respective utility values. Therefore, QALY reflects both the morbidity and mortality of the
1041 patient.⁵⁹ Commonly used utilities elicitation methods include standard gamble (SG), time
1042 trade-off (TTO), visual analog scale (VAS), and rating scales. QALY is widely used in cost-
1043 effectiveness studies and health technology assessment. Since QALY is already a measure
1044 combining both benefits and harms of a health state or treatment option, it can be used to
1045 facilitate direct comparison between different treatment options in the benefit-risk assessment
1046 context. Attitude measures a patient’s psychological tendency toward an entity expressed in
1047 some degree of favor or disfavor, and is usually measured through ratings or rankings such as
1048 importance ratings and best worst scaling. While QALY and other utility-related indices are
1049 used in cost-benefit analysis of treatment options as well as risk-benefit analysis of

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

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

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

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1050 oncological treatment, QALY results may be sensitive to the elicitation method. Moreover,
1051 QALY estimates may not be available for the rare events observed in clinical trials of novel
1052 technologies. In such cases, sponsors may need to conduct a separate study to elicit QALY
1053 for these events.

1054

1055 **x. Revealed-Preference Methods (RP)**

1056 Revealed-preference methods are used to analyze patients' choices and behavior in the real
1057 world. These methods can provide information on the number of patients for whom the
1058 benefits of a medical technology outweigh the risks and potentially the reasons why patients
1059 believe that benefits outweigh risks. However, unlike stated preference methods, revealed
1060 preference methods often cannot be used to derive weights for or the relative importance of
1061 individual features or changes in feature levels. Some examples of revealed-preference
1062 methods include patient-preference trials and direct questions in clinical trials.⁶⁰

⁶⁰ See Footnote 9.