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REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**

**GENERAL CONSIDERATIONS FOR  
PATIENT PREFERENCE STUDIES**

**E22**

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# ICH HARMONISED GUIDELINE GENERAL CONSIDERATIONS FOR PATIENT PREFERENCE STUDIES

## E22

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1 **1. INTRODUCTION**

2 **1.1 Background**

3 Patient preference studies (PPS) aim to assess the relative desirability or acceptability of actual  
4 or potential health interventions, or their characteristics and outcomes. PPS can generate  
5 structured insights about the relative importance of characteristics, also referred to as attributes,  
6 that are considered by patients when making decisions about drugs.<sup>1</sup> These attributes may  
7 include, for example, efficacy or safety outcomes or any other potentially relevant  
8 characteristics.

9 Understanding these qualitative and quantitative insights is important for various aspects of  
10 drug development, such as identifying unmet needs, designing clinical studies, and interpreting  
11 results.

12 PPS may be particularly valuable when seeking to understand how patients perceive and  
13 prioritise potential treatment outcomes and other characteristics, and their views on different  
14 aspects of their condition.

15 Patients who experience a disease or use drugs can provide relevant perspectives on the disease  
16 outcomes and effects of drugs and other health interventions. For diagnostic or preventive  
17 interventions, or possible future treatments, healthy and at-risk individuals may also contribute  
18 informative perspectives. While the information provided by PPS does not replace the  
19 information provided by efficacy and safety studies, the PPS information may be useful across  
20 the different phases of drug development, pre- and post-marketing, and may be considered  
21 together with the efficacy and safety information in the benefit-risk assessment of drugs and  
22 related regulatory decisions, as described in ICH guideline documents ICHM4E(R2) and ICH  
23 E2C(R2).

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<sup>1</sup> The term "drug" should be considered synonymous with investigational product, therapeutic, medicine, medicinal product, biological product, pharmaceutical product, preventive, or diagnostic medicinal products. The term "drug approval" refers to obtaining marketing authorisation for the drug.

24 **1.2 Purpose of the Guideline**

25 This harmonised guideline outlines general considerations about the use, design, conduct,  
26 analysis, and submission of PPS aimed at informing drug development, regulatory submission  
27 and evaluation, drug approvals and maintenance of such approvals.

28 **1.3 Scope and Direction**

29 This guideline focuses on methods called stated-preference methods. Stated-preference  
30 methods involve collecting preference data through surveys or interviews where participants  
31 are asked to express (state) their choices or acceptable thresholds for trade-offs for specific  
32 outcomes or treatment alternatives. Unlike revealed-preference methods, which rely on actual  
33 observed behaviour, stated-preference methods use hypothetical scenarios to understand how  
34 patients might behave under different conditions. Revealed-preference methods are outside the  
35 scope of this guideline.<sup>2</sup>

36 PPS may have applications in many situations, including, but not limited to, those described in  
37 this guideline. The emphasis throughout the document is on applications to drugs intended for  
38 treatment; however, this guideline also applies to drugs intended for prevention or diagnosis in  
39 healthy individuals or prospective patients.

40 Caregiver preferences are different from, and not a replacement for, patient preferences. While  
41 caregiver preferences may be informative for the regulatory assessment, they are not addressed  
42 further in the guideline.

43 When the objective is to gather preferences from other stakeholders such as healthcare  
44 professionals instead of patients, it is important to recognise that their preferences may differ  
45 from those of patients. Healthcare professional preference studies should not be confused with,  
46 or used to replace, PPS and are outside the scope of this guideline.

47 This guideline addresses PPS and the value that patients place on characteristics of drugs. It  
48 does not focus on patient reported outcome measures.

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<sup>2</sup> Revealed preference methods are those in which patient preferences are obtained from the actual observed behaviour or choices made by patients (e.g., which drug was actually used).

49 The placement of PPS data in labelling is considered a regional matter outside the scope of this  
50 guideline.

51 Many methods are available for designing PPS. Recommendations about choice of method and  
52 consequently how to conduct the PPS, beyond the general principles outlined below, are outside  
53 the scope of this guideline.

54 Preference research is a large and evolving field.<sup>3</sup> As such, this guideline provides general  
55 considerations and scientific principles rather than detailed technical instructions. When  
56 technical topics are described as examples, these reflect possible options based on current  
57 practice, but newer or alternative methods may also be appropriate. When available, interaction  
58 early in the process with regulatory authorities can be useful to ensure that the PPS meets  
59 regulatory expectations and scientific standards.

## 60 **2. GENERAL PRINCIPLES**

### 61 **2.1 Protection of Study Participants**

62 Principles applicable to other types of studies involving human subjects, such as ethical  
63 conduct, compliance with the protocol, and protection of personal data, are applicable to PPS  
64 as well. PPS participants should be protected in accordance with the applicable regulatory and  
65 legal requirements.

### 66 **2.2 Patient Input in the Development of PPS**

67 Patient input is valuable throughout drug development, including in the development of PPS.  
68 Patient input can support activities, including:

- 69 • Identifying the use for a PPS;
- 70 • Designing a PPS;
- 71 • Identifying feasibility challenges in the conduct of a PPS;

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<sup>3</sup> While not formally endorsed or qualified within this guideline, external resources that may offer relevant insights and supplementary information include the Innovative Medicines Initiative (IMI) PREFER Recommendations, the Medical Device Innovation Consortium (MDIC) Patient-Centered Benefit-Risk Framework, the Professional Society for Health Economics and Outcomes Research (ISPOR) best practice documents on Patient Preference Methods and Quantitative Benefit-Risk Assessment, and the Council for International Organizations of Medical Sciences (CIOMS) guidelines XI and XII (“Benefit-Risk Balance for Medicinal Products”, “Patient Involvement in the Development, Regulation, and Safe Use of Medicines”).

- 72 • Developing PPS protocols;
- 73 • Selecting attributes and levels;
- 74 • Contextualising the PPS findings and highlighting their practical implications.

### 75 **2.3 Preliminary Research**

76 Typically, it will be important to conduct thorough preliminary research (e.g., literature  
77 reviews, expert consultations, patient interviews) to ensure that all relevant information is  
78 identified and included in the PPS design. This step is critical for qualitative research (e.g.,  
79 interview guide development) and quantitative research (e.g., survey development).

### 80 **2.4 De Novo Work May Not Always be Justified**

81 Although most studies are designed for a specific set of attributes and therapeutic context, there  
82 may be existing relevant PPS literature that can address the intended research objective and  
83 question(s). Ongoing and future studies should take existing relevant literature of sufficient  
84 quality into consideration to avoid unnecessary burden on the patient community.

### 85 **2.5 Global Applicability**

86 In some circumstances, PPS conducted in other region(s) may be useful and may inform  
87 regulatory drug assessment and related decisions in the local region (i.e., the region not studied  
88 in the PPS). This has the potential to conserve resources and decrease burden for the patient  
89 community. The degree of applicability of PPS results from other region(s) to the local region  
90 should be evaluated. Applicants should justify why a PPS conducted outside of the local region  
91 is informative to the local region. The applicant may find this topic useful to discuss  
92 prospectively with the relevant regulatory authorities.

### 93 **2.6 Early Consideration and Planning are Critical**

94 Beginning as early as possible, the usefulness of PPS should be considered systematically  
95 throughout drug development. While detailed discussion about the timing of PPS is specific to  
96 a development program, the timing of the study typically will be influenced by the objective  
97 of the PPS, when enough information is available to design the PPS to support the objective,  
98 and when the results from the PPS are anticipated to be used.

99 **2.7 Quality Standards**

- 100 • The research question(s) should align with the research objective, which drive the  
101 methods chosen, protocol, analysis plan, data management, and a report that is  
102 informative for the given purpose.
- 103 • PPS are expected to follow the principles of good study design and conduct. This  
104 includes generation of study documents such as informed consent forms, protocol,  
105 interview guide, analysis plan, (final) survey instrument, when applicable, and study  
106 report. It also includes ensuring that the study design and statistical analysis  
107 approaches are pre-specified and well-documented.
- 108 • It may be useful to pre-register protocols using a registry, a comparable platform, or  
109 other formal mechanisms to enhance research credibility and transparency.
- 110 • The conduct of PPS should align with the principles of the “quality by design” approach  
111 to clinical research, such as focusing on critical quality factors to ensure the generation  
112 of reliable and meaningful results and the management of risks to those critical quality  
113 factors, using a risk-proportionate approach (see ICH E8).

114 **2.8 Ensuring Multidisciplinary Expertise in the PPS Team**

115 The design, conduct, analysis, and submission of a PPS should be undertaken by a cross-  
116 functional study team with the relevant PPS methodology and clinical expertise.

117 **3. PPS IN DRUG DEVELOPMENT AND POST-MARKETING EVALUATIONS**

118 Different types of PPS can inform several aspects of clinical trial design, benefit-risk  
119 assessment and post-marketing evaluations.

120 **3.1 Types of PPS**

121 PPS can be conducted using different methods and can be broadly categorised as quantitative,  
122 qualitative, or mixed methods preference studies, although the distinction between these  
123 categories is not always clear-cut. Qualitative PPS focus on non-numerical approaches (e.g.,  
124 narrative information) to explore preferences and may be useful, for example, in the form of  
125 interviews, to identify which attributes are important to patients. Quantitative PPS focus on  
126 numerical measures and statistical analysis of preferences. Quantitative PPS can be used, for  
127 example, to produce numerical estimates of the importance patients assign to attributes or the

128 degree to which patients state they are willing to make trade-offs among different attributes.  
129 Such studies can also be used to describe the distribution of preferences and of these estimates  
130 in a population (“preference heterogeneity”). Quantitative PPS are designed based on insights  
131 gained from previous qualitative research. Qualitative and quantitative approaches may be  
132 combined using a mixed methods approach.

### 133 **3.2 How Might PPS Inform Drug Development and Evaluation**

134 Examples of the use of PPS in the different phases of development are described below. These  
135 examples are meant to illustrate potential uses of PPS.

136 Common uses of PPS include, but are not limited to:

- 137 • Identifying treatment priorities;
- 138 • Informing outcome/endpoint selection for a subsequent clinical trial;
- 139 • Interpreting the relative importance of different components of an endpoint with  
140 multiple components;
- 141 • Informing meaningful change of an endpoint;
- 142 • Providing information on the acceptability of benefit-risk trade-offs;
- 143 • Identifying treatment characteristics that matter to patients such as mode of  
144 administration;
- 145 • Informing acceptability of protocol visits and procedures;
- 146 • Informing recruitment and retention strategies;
- 147 • Informing acceptability of risk management or mitigation strategies.

148 PPS conducted at an early stage of development could also provide information about unmet  
149 needs, priorities for disease management, and patients’ willingness to participate in clinical  
150 studies, among others. This type of early information is often, but not always, qualitative and  
151 may be used to inform the development of subsequent PPS.

152 In terms of clinical trial design, PPS may be used as the basis for informing the development,  
 153 selection, and prioritisation of endpoints. When an endpoint combines multiple events or items  
 154 to generate a single measure, patients may not view each of the constituent items as equally  
 155 important. PPS potentially can inform weighting or scoring of individual endpoint elements.  
 156 PPS can provide the patients' perspective on the relative importance of the constituent elements  
 157 to inform the interpretation of the endpoint and potentially inform the development of  
 158 algorithms for weighting constituent elements to generate a score reflecting patient preferences.  
 159 PPS can also help inform whether the magnitude of change in an endpoint is considered  
 160 meaningful from the patients' perspective.

161 At a later stage in drug development, PPS can be used to help inform interpretation of the trial  
 162 results. PPS can also provide information about the trade-offs patients are willing to make  
 163 among specific attributes of the drug or the likelihood that patients would consider the benefits  
 164 of a drug to outweigh the risks. When treatment choices are associated with high risks or high  
 165 uncertainty (e.g., rare but life-threatening adverse effects, treatments with uncertain long-term  
 166 safety outcomes), PPS can provide measures of risk thresholds that can inform benefit-risk  
 167 assessment. In addition, PPS may be used to inform the development of risk-mitigation  
 168 strategies and risk management plans.

169 Because preferences are expected to differ among patients, PPS may also help describe  
 170 preference heterogeneity, which is the distribution of preferences within a population, or to  
 171 compare distributions between pre-specified subpopulations (i.e., subgroups) with  
 172 characteristics potentially associated with differences in preferences. For example, patients  
 173 with a more severe form of a disease may be more willing, or less willing, to tolerate drug risks  
 174 than patients with a less severe form.

#### 175 **4. RECOMMENDATIONS AND PRACTICAL CONSIDERATIONS FOR PPS**

176 Like any scientific study, PPS should follow internationally recognised scientific standards and  
 177 recommended practices. Recommendations outlined in this section should be given special  
 178 consideration when designing or evaluating a PPS. It is up to the applicant<sup>4</sup> to explain how the  
 179 results are intended to support their regulatory submission, and to justify that the data submitted  
 180 meet the regulatory requirements.

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<sup>4</sup> Applicants to regulatory authorities are ultimately responsible for all aspects of studies submitted to regulatory authorities.

**181 4.1 Research Objective and Research Question**

182 As in all research, PPS have a distinction between research objective and research  
183 question(s). The research objective describes what the PPS is intended to inform in drug  
184 development and evaluation. The research question(s) refine the research objective into  
185 answerable question(s).

186 As an example, a research objective may relate to identifying efficacy endpoints most important  
187 to PPS participants with a specific disease. Corresponding research question(s) could be  
188 related to (i) assessing the relative importance of attributes that align with the proposed efficacy  
189 endpoints; (ii) assessing the relative importance per unit change in attributes; and (iii)  
190 determining whether the relative importance varies by disease stage and key subgroups. As  
191 another example, if a research objective is related to informing a benefit-risk assessment, the  
192 corresponding research question(s) might relate to (i) assessing levels of risks PPS participants  
193 would accept in exchange for specified degrees of benefit and (ii) determining whether these  
194 results vary by prior experience with specific drugs or side effects.

**195 4.2 Study Design and Method Selection**

196 The choice of method can depend on several factors, including the research question(s), the  
197 patient population, and the number of attributes or scenarios to be assessed. A PPS is not limited  
198 to one method and can include both quantitative and qualitative approaches. There are different  
199 methods to conduct qualitative PPS, including interviews, focus groups, and Delphi panels.  
200 Similarly, there are a variety of quantitative approaches to eliciting patient preferences,  
201 including discrete choice experiment, best-worst scaling, threshold technique, and swing  
202 weighting.

203 Researchers<sup>5</sup> are encouraged to refer to published literature for more information on the  
204 methods available, points to consider for method selection, and the respective strengths and  
205 limitations of various methods. There should be a clear rationale for the choice of methods used  
206 in the PPS. This includes explaining why a specific preference elicitation technique was  
207 selected and how it supports answering the research question(s). In small populations such as  
208 in very rare diseases, some methodologies may not be feasible.

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<sup>5</sup> For the purposes of this guideline, we refer to “researcher” as those responsible for designing and executing the study.

**209 4.3 Study Sample**

210 The PPS sample should be guided by the research objective and question(s) and is defined  
211 through a set of inclusion and exclusion criteria. Typically, the PPS would include a sample  
212 that is representative of the target population of the regulatory submission. A mismatch between  
213 the PPS sample and the target patient population can limit the generalisability and applicability  
214 of the PPS findings. If the PPS planned to include different populations than the target  
215 population of the regulatory submission, the study report should include a discussion  
216 supporting the relevance of the PPS (see Section 4.8).

217 Key characteristics to consider when developing a sampling plan include those potentially  
218 associated with differences in preferences, such as:

- 219 • Participant characteristics, including demographic diversity of participants;
- 220 • Disease characteristics, including stage of the disease;
- 221 • Treatment characteristics, including experience with treatment or treatment outcomes;
- 222 • Other relevant characteristics (e.g., risk attitudes, health literacy) to describe the sample  
223 or define subgroups.

224 Particular attention should be paid to any subgroups with potentially different preferences who  
225 may be less likely to participate in the PPS.

226 When data are used across regions, the similarity of culture and health care of a local region to  
227 other region(s) should also be carefully considered if they impact preferences (see also Section  
228 2.5). Having some indication (e.g., qualitative preference information) from the local region to  
229 support the use of quantitative results from other region(s) studied is helpful.

230 There are different types of recruitment strategies, and the choice of strategy can depend on the  
231 objective of the study. It is important to consider how recruitment strategies can impact the  
232 representativeness of the target population. For example, people who are part of panels,  
233 advocacy groups, clinical trials, recruited online, or receive care at speciality clinical sites, may  
234 have different characteristics compared to the target population.

235 With these challenges in mind, researchers should justify the recruitment strategy, which  
236 includes sources from where participants are recruited and how their eligibility is determined.

237 The limitations of the chosen strategy and potential bias should be described. Researchers  
238 should also consider how diagnosis should be assessed and justify the approach.

#### 239 **4.4 Sample Size**

240 Determining sample size for qualitative and quantitative PPS varies based on research  
241 question(s) and methods. While the sample size for qualitative PPS tends to be smaller than  
242 quantitative PPS, it should include diverse perspectives to capture variability in preferences  
243 within the target population. In quantitative studies, sample size should be large enough to  
244 ensure the desired level of precision, which depends on the research objective. If the research  
245 question(s) includes assessing differences in preferences between subgroups of interest, the  
246 sample should include a sufficient number of participants in each subgroup of interest. The  
247 sample size also depends on the complexity of the PPS, such as the number of attributes and  
248 levels being tested. Provided that sources of bias are adequately minimised, a larger sample  
249 generally provides more precise estimates of preferences and better generalisability to the target  
250 population.

#### 251 **4.5 Attributes and Levels**

252 If a PPS is based on the attributes and levels of a drug or treatment, particular attention should  
253 be paid to the development of the attributes and levels. Attributes are specific characteristics of  
254 a drug or treatment that patients consider when making treatment decisions (e.g., efficacy  
255 outcomes, side effects, frequency of dosing, and route of administration). In general:

- 256 • Attributes included should be relevant for the patients, research objective and  
257 question(s);
- 258 • It is important to avoid attributes known to be irrelevant that might increase burden;
- 259 • Omitting relevant attributes from the PPS may limit the usefulness of the results,  
260 depending on the objective of the study.

261 Methodologies rely on assumptions that should be considered when selecting attributes (e.g.,  
262 attributes are viewed as independent by participants); these assumptions if not met may limit  
263 the interpretability of the PPS results.

264 When selecting the attributes to include in a quantitative PPS, researchers are encouraged to  
265 engage patients in the selection process. Semi-structured interviews or focus groups could be

266 conducted among a sample of patients where a list of attributes and their respective descriptions  
 267 are presented to the participants to solicit feedback.

268 Generally, it is important to consider alignment between attributes and endpoints. It is  
 269 particularly important when the objective of the PPS is to inform benefit-risk assessment (see  
 270 ICH M4E(R2)). Applicability of the PPS to the clinical data may be limited if key endpoints  
 271 from the clinical studies are not included in the PPS. It is acknowledged that sometimes, perfect  
 272 alignment may not be possible. In some cases, limitations can be managed (e.g., using generic  
 273 attributes when trial endpoints are not known at the time of designing the PPS).

274 Levels of attributes refer to the different values of each attribute that are presented to  
 275 participants:

- 276 • These levels help to capture the plausible range of values for each attribute,  
 277 depending on the context. The range of attribute levels included in a PPS should  
 278 at least cover the attribute’s relevant values expected in clinical studies  
 279 (treatment and control groups). Otherwise, this could limit the ability to interpret  
 280 the clinical results, diminishing the overall usefulness to support the PPS  
 281 objective. Extrapolation of PPS data beyond the levels included in the study is  
 282 generally not recommended.
- 283 • If the PPS objective is to inform benefit-risk assessment, expected efficacy and  
 284 safety information from clinical studies (e.g., early clinical studies) may be  
 285 available to inform the range of attribute levels.

286 **4.6 Instrument Design**

287 Instruments (e.g., interview guides, surveys) should be clear, comprehensible, and relevant to  
 288 participants. When designing instruments for preference elicitation, researchers should take  
 289 actions to minimise potential bias.

290 **4.6.1 Context**

291 Instruments should define the PPS context by providing a clear description of the scenario that  
 292 participants are expected to think about when stating their preferences. This is important as  
 293 preferences may differ based on the context. The information should be adequately presented  
 294 and described in a manner that is realistic and does not bias responses.

295 **4.6.2 Presenting the Information During the PPS**

296 Attributes and other relevant information should be described such that they are interpreted as  
297 intended, consistently, and unambiguously across all participants.

298 When presenting this information, the researchers should consider the following:

- 299 • Numeracy (i.e., ability to understand and use numbers in making health-related  
300 decisions);
  - 301 ○ Appropriate numeric, verbal, and graphic representations can help participants  
302 conceptualise probabilities;
- 303 • Complexity;
  - 304 ○ Readability and similar assessments can help verify if the instrument is  
305 understandable to patients with varying literacy levels;
  - 306 ○ Implementing comprehension questions can identify if study participants are  
307 interpreting the information as intended;
  - 308 ○ Cognitive burden;
- 309 • Multilingual studies;
  - 310 ○ Translation of instruments should emphasise conceptual equivalence across  
311 languages and cultures;
- 312 • Descriptions of attributes and levels;
  - 313 ○ Attribute and level definitions should be carefully designed to be factual and  
314 avoid bias (e.g., avoid describing a level as “good” or “bad”); and
- 315 • Minimising cognitive bias.
  - 316 ○ The instrument design should minimise potential cognitive biases such as  
317 framing (e.g., presenting changes as losses or gains), anchoring (e.g., signalling  
318 a reference value), simplifying heuristics (e.g., recoding numerical values or  
319 percentages as low, medium, and high), or ordering effect (e.g., influencing the  
320 response to a question depending on its relative position in the question

321 sequence).

#### 322 4.6.3 *Implementing Quality Checks*

323 Data quality checks are a critical aspect of PPS, which may highlight potential data and study  
324 limitations. This should be considered early in instrument design. What constitutes an  
325 appropriate check depends on the study population, the PPS method, and should not  
326 unnecessarily add to the overall burden of the survey instrument. The choice of quality checks  
327 should be justified. Possible checks might include, for example:

- 328 • Adding questions to the survey instrument that can be analysed to assess data quality  
329 such as:
  - 330 ○ Adding a dominated-choice task to check for illogical responses;
  - 331 ○ Using different questions to ask for the same information (e.g., year of birth and  
332 age); and
- 333 • Implementing the survey so that the time it takes the participant to complete the survey  
334 is captured to assess speeding (rushing through survey questions).

335 Additionally, analysis approaches (also see Section 4.7) can be used to check for issues such  
336 as:

- 337 • Attribute non-attendance (when participants consistently ignore specific attributes  
338 while making choices);
- 339 • Illogical responses (e.g., preferring an obviously inferior option);
- 340 • Fraudulent responses (e.g., completing the survey multiple times, or synthetic  
341 participants generated by artificial intelligence); and
- 342 • Inconsistencies in responses from the same participant.

343 Important issues highlighted by quality checks should be addressed. It should be noted that  
344 most data quality checks, in and of themselves, cannot definitively identify responses that  
345 should be removed from the analysis set.

346 **4.6.4 Pretesting**

347 In PPS, pretesting and piloting an instrument serve different purposes, and both are essential  
348 steps in developing the instrument. Pretesting is an initial evaluation phase where the  
349 instrument is reviewed by a set of patients to identify any issues with comprehension or  
350 interpretation of content, wording, or format. The goal is to refine the instrument, such that  
351 questions are clear, relevant, and understandable, before launching the larger study.

352 • For qualitative PPS, pretesting generally involves conducting a few initial interviews to  
353 evaluate the interview guide. The focus is on ensuring that the questions are clear,  
354 relevant, and capable of eliciting detailed, meaningful responses. The pretest helps  
355 identify any issues with the flow of the interview, the comprehensibility of the  
356 questions, and the overall structure. Feedback from these initial interviews is used to  
357 refine the guide, making it more effective for capturing rich qualitative data.  
358 Researchers are encouraged to consider the study population (e.g., if fatigue is  
359 common) and maximum length of interviews.

360 • For quantitative PPS using survey instruments, the process generally involves  
361 administering the survey to a small, representative sample of the target population via  
362 cognitive interviews. These are usually conducted iteratively, using think aloud  
363 techniques where study participants voice out thought processes as they complete the  
364 survey instrument. The goal is to assess if questions are understood as intended and to  
365 identify any ambiguities and biases that should be addressed. The feedback is used to  
366 make necessary revisions before the survey is rolled out on a larger scale.

367 **4.6.5 Piloting**

368 Piloting typically involves a more comprehensive test of the instrument under actual study  
369 conditions. This phase uses a larger sample than the pretesting phase. Piloting helps to identify  
370 issues regarding feasibility, data quality, and logistics:

371 • In qualitative PPS, piloting can help to identify issues with question wording, interview  
372 length, and the interviewer's approach; and

373 • In quantitative PPS using electronic survey instruments, piloting may help to detect  
374 technical or display issues with the electronic administration and presence of high

375 dropout rates<sup>6</sup>. Results from the quality checks in the pilot phase help to facilitate early  
376 identification of potential bias, which can be addressed before the instrument is rolled  
377 out. Pilot information may also inform revisions to statistical considerations.

#### 378 **4.7 Analysis Plan**

379 Whether descriptive or inferential, the analysis should address the research objective and  
380 question(s) and follow recommended practices. Justification should be provided for the  
381 analytical approach. In some situations, patient preference data may be combined with clinical  
382 data.<sup>7</sup>

383 Researchers should develop a pre-specified analysis plan that defines the research question(s)  
384 and the statistical methods to be used, including defining analysis sets, handling of missing  
385 data, defining subgroups, and where appropriate testing of hypotheses.

386 The analysis plan should specify all primary and exploratory analyses, the analytical models or  
387 modelling plan, when applicable, and the software package(s) that will be used to perform the  
388 analyses. If several analytical models are planned, the researcher can consider outlining the  
389 steps or any diagnostics that will guide the selection of the final model.

390 For quantitative PPS, the analysis plan also should include the plan for handling the outcome  
391 of quality checks. Specifically, the analysis plan should describe and justify the use of data  
392 quality checks in defining the analysis sets for the primary and sensitivity analyses, and how  
393 these will be used in the interpretation of study results (see Section 4.6). If the data quality  
394 checks result in removing observations to create the primary analysis set, the results of the full  
395 analysis set (including removed observations) should be presented to demonstrate the impact  
396 of removing these observations on the study results.

397 Aligned with ICH E17, pre-specified pooling of regions or subpopulations may help provide  
398 flexibility, facilitate the assessment of consistency in preferences across regions, and support  
399 regulatory assessment and decision-making (see also Section 2.5). The pooling strategy should  
400 be justified. Pooling strategies should be specified in the study protocol and analysis plan, when  
401 applicable.

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<sup>6</sup> Both ICH E6 (R3) and [CDISC ODM v2.0](#) include recommendations related to data capture that are helpful to consider when designing a PPS.

<sup>7</sup> Quantitative benefit-risk analysis (qBRA) may combine data from quantitative PPS and clinical trial data. Detailed discussion of qBRA is outside of the scope of this guideline.

402 Sensitivity analyses are used to assess the robustness of the primary analysis results and check  
403 if conclusions change under deviations in assumptions and limitations in the data. Justification  
404 should be provided for deviations from the pre-specified analysis plan.

#### 405 **4.8 Reporting and Submission to Common Technical Document (CTD) Modules**

406 The PPS should be included in CTD modules 2 and 5.

407 The PPS report should be included in CTD 5.3.5.4 “other clinical study reports”. The PPS  
408 report structure can be based on (with adaptations as appropriate) the structure of clinical study  
409 reports (CSRs) (ICH E3(R1)). A PPS report typically includes content that addresses the topics  
410 covered in ICH E22 e.g., research objective and question(s), study design, method selection,  
411 study sample, sample size. If a quantitative benefit-risk analysis is conducted using the PPS  
412 (e.g., combining patient preference and clinical results), it can be described in a stand-alone  
413 report or included with the associated PPS report.

414 The PPS may be referenced in multiple locations, most frequently within Module 2. For  
415 example, the PPS can be listed and described in Product Development Rationale (CTD 2.5.1),  
416 typically including a description of the PPS objective and design, at the same level of detail as  
417 for clinical studies. If the PPS was done to inform design of a clinical study, a description  
418 should be included in CTD 2.5.1 about how the PPS results were used.

419 If PPS results are used as evidence of medical need or included in the benefit-risk assessment,  
420 they can be included in Benefits and Risks Conclusions (CTD 2.5.6) along with a critical  
421 assessment of the PPS. Optionally, as described in ICH M4E(R2), a summary of key elements  
422 of PPS results and/or quantitative benefit-risk analyses can be included in the appendix to the  
423 Clinical Overview (CTD 2.5.6.5). (See ICH M4E(R2) for details on how to include the results  
424 of quantitative benefit-risk evaluations).