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GENERAL CONSIDERATIONS FOR PATIENT PREFERENCE STUDIES

E22

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E22

ICH Consensus Guideline

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1. INTRODUCTION

1.1 Background

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

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

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

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

[1] 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.

1.2 Purpose of the Guideline

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

1.3 Scope and Direction

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

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

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

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

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

[2] 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).

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

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

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

2. GENERAL PRINCIPLES

2.1 Protection of Study Participants

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

2.2 Patient Input in the Development of PPS

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

- Identifying the use for a PPS;
- Designing a PPS;
- Identifying feasibility challenges in the conduct of a PPS;

[3] 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").

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

2.3 Preliminary Research

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

2.4 De Novo Work May Not Always be Justified

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

2.5 Global Applicability

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

2.6 Early Consideration and Planning are Critical

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

2.7 Quality Standards

- The research question(s) should align with the research objective, which drive the methods chosen, protocol, analysis plan, data management, and a report that is informative for the given purpose.

- PPS are expected to follow the principles of good study design and conduct. This includes generation of study documents such as informed consent forms, protocol, interview guide, analysis plan, (final) survey instrument, when applicable, and study report. It also includes ensuring that the study design and statistical analysis approaches are pre-specified and well-documented.

- It may be useful to pre-register protocols using a registry, a comparable platform, or other formal mechanisms to enhance research credibility and transparency.

- The conduct of PPS should align with the principles of the "quality by design" approach to clinical research, such as focusing on critical quality factors to ensure the generation of reliable and meaningful results and the management of risks to those critical quality factors, using a risk-proportionate approach (see ICH E8).

2.8 Ensuring Multidisciplinary Expertise in the PPS Team

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

3. PPS IN DRUG DEVELOPMENT AND POST-MARKETING EVALUATIONS

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

3.1 Types of PPS

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

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

3.2 How Might PPS Inform Drug Development and Evaluation

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

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

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

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

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

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

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

4. RECOMMENDATIONS AND PRACTICAL CONSIDERATIONS FOR PPS

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

[4] Applicants to regulatory authorities are ultimately responsible for all aspects of studies submitted to regulatory authorities.

4.1 Research Objective and Research Question

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

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

4.2 Study Design and Method Selection

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

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

[5] For the purposes of this guideline, we refer to "researcher" as those responsible for designing and executing the study.

4.3 Study Sample

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

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

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

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

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

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

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

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

4.4 Sample Size

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

4.5 Attributes and Levels

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

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

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

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

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

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

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

- These levels help to capture the plausible range of values for each attribute, depending on the context. The range of attribute levels included in a PPS should at least cover the attribute's relevant values expected in clinical studies (treatment and control groups). Otherwise, this could limit the ability to interpret the clinical results, diminishing the overall usefulness to support the PPS objective. Extrapolation of PPS data beyond the levels included in the study is generally not recommended.

- If the PPS objective is to inform benefit-risk assessment, expected efficacy and safety information from clinical studies (e.g., early clinical studies) may be available to inform the range of attribute levels.

4.6 Instrument Design

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

4.6.1 Context

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

4.6.2 Presenting the Information During the PPS

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

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

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

sequence).

4.6.3 Implementing Quality Checks

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

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

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

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

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

4.6.4 Pretesting

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

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

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

4.6.5 Piloting

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

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

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

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

4.7 Analysis Plan

Whether descriptive or inferential, the analysis should address the research objective and question(s) and follow recommended practices. Justification should be provided for the analytical approach. In some situations, patient preference data may be combined with clinical data.[7]

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

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

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

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

[6] Both ICH E6 (R3) and CDISC ODM v2.0 include recommendations related to data capture that are helpful to consider when designing a PPS.
[7] 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.

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

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

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

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

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

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