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Committee for Medicinal Products for Human Use (CHMP)

Draft Qualification Opinion of IMI PREFER

Draft agreed by Scientific Advice Working Party (SAWP)	30 September 2021
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Comments should be provided using this template. The completed comments form should be sent to ScientificAdvice@ema.europa.eu

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[1] Last day of relevant Committee meeting.
[2] Date of publication on the EMA public website.
[3] Last day of the month concerned.

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Based on the rapporteurs' reports the CHMP gave the following answers:

In this follow-up procedure to a previous qualification advice, IMI PREFER seek qualification for a **framework** (see documents in Annex provided by the applicant for qualification opinion by the CHMP) intended to provide suggestions on how patients' perspectives could be measured through patient preference studies and then incorporated into regulatory decision processes, as applicable. Relevant considerations include what matters to patients, how much it matters, and how e.g., trade-offs between benefits and harms as well as other study object attributes of interest can be identified and addressed from the patients' perspective. A structured approach to this qualification built on systematic literature searches and comprehensive stakeholder interviews. The foundational work also informed the research and operational plans of PREFER, which led to a series of case studies to address selected methods that were assessed as most promising.

The objectives of the PREFER framework are to:

1. Inform on key considerations when designing, conducting and applying the results of a fit-for-purpose patient preference study (PPS);

2. Support regulatory decision-making when assessing and using preference study results;

3. Support the discussion between industry and regulators about preference studies.

The PREFER framework consists of three main components, see Fig.1 below: 1) defining the preference study purpose and objectives, 2) planning, designing and conducting the preference study, and 3) interpreting and applying preference study results:

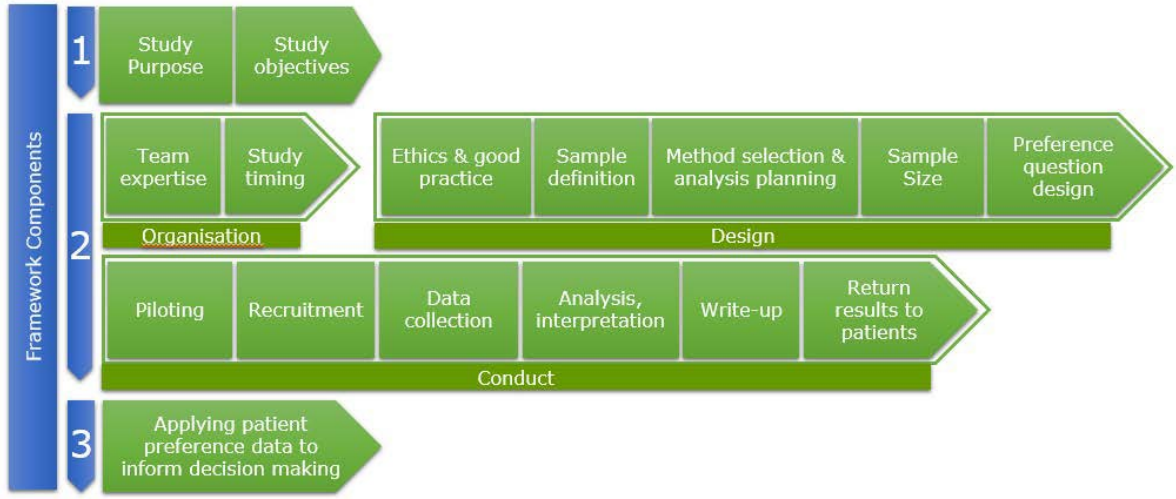

Fig. 1: The PREFER framework

The qualification package further presents five methods for eliciting preferences: discrete choice experiment, two types of best-worst scaling, threshold technique, and swing weighting. This list represents an example set of suitable methods that have been used in the past in the context of development and evaluation of medicinal products and should not be viewed as comprehensive or prescriptive.

A 'points to consider' section on method selection complements the framework and describes methodological, participant and feasibility factors that are considered relevant for the selection of a suitable method. These factors can also be used to evaluate additional methods beyond those presented.

During the procedure, the applicant has raised three questions that serve as basis for subsequent discussion, i.e.:

Q1: *The intended objectives of the PREFER framework for patient preference studies are to:*

- *Inform a preference study research team on key considerations when designing, conducting and applying the results of a fit-for-purpose preference study*
- *Guide decision-makers when assessing and using preference study results to inform decision-making*
- *Support the discussion between industry, regulators, HTA bodies and payers about preference studies intended to inform medical product decision-making*

Does EMA agree that these are the ***appropriate principal objectives*** *for the framework? Does EMA agree that the* ***framework*** *achieves its intended objectives?*

Q2: *Does EMA agree that the '****points to consider****' on method selection, together with the additional details of five key quantitative methods, when applied appropriately within the PREFER framework, can support generating patient preference evidence to inform decision-making throughout the* medicinal product lifecycle*?*

Q3: *Does EMA agree that if preference study results inform a regulatory decision or a HTA, then (for regulatory decisions) the corresponding data could be included in the* ***drug label*** *as applicable, and the manner in which the study informed the decision could be included in the* ***public assessment report****?*

Discussion

Framework objectives

The systematic efforts by the IMI PREFER project to address gaps in approaches to incorporating patients' views into decision making and to develop a framework for patient preference studies are acknowledged. The project steps (assessing stakeholders' views, classifying and selecting methods, identifying research questions, searching historical case studies and conducting case studies) are considered in principle appropriate to come up with a proposal for a framework together with a discussion on selected methods that could be fit for application to future patient preference studies.

Expert judgment has been the cornerstone of regulatory evaluation during the authorisation and life-cycle of medicinal products. More systematic approaches to benefit-risk assessment, however, have been subject to regulatory science activities (EMEA/108979/2009). Quantitative and semi-quantitative methods designed to weigh relevant efficacy and safety data together with value judgements have been proposed in the past (see report of the CHMP working group on benefit-risk assessment models and methods, doc. ref. EMEA/CHMP/15404/2007), but implementation in regulatory practice has been very limited so far. These activities resulted in the implementation of structured templates to support regulatory assessments (https://www.ema.europa.eu/en/about-us/support-research/benefit-risk-methodology), and which are the basis for the information integrated in public assessment reports (EPAR) to make key aspects of the regulatory decision transparent. Transparency of regulatory decision-making is considered of major public health importance. Currently, patient views are regularly included in a qualitative, non-systematic way by considering patient and/or patient organisation input in scientific advice procedures and assessments of marketing authorisation applications. There is a shared interest in structuring patient involvement, including patient preference studies, in regulatory decision-making processes.

The potentially concerned (decision) scenarios are diverse and can range from: whether to transition an investigational medicinal product from preclinical to human research, deciding on the specifics and design of the target product profile (e.g., indication, dose, presentation, etc.), informing study planning (e.g., endpoint selection and ranking, etc.) to identify and value trade-offs for benefits and risks, and/or informing a post-marketing strategy. Consequently, the scenario where PPS are used will determine the regulatory impact and criticality of a given PPS design and execution. Prospective, clinical data-agnostic use cases (e.g., to identify areas of unmet need) may also be distinguished from post-hoc use cases intended to assist the interpretation of clinical study data generated for a specific development.

The outlined 'principal objectives' of the framework with its components and sub-elements as defined in the sections 3.2 to 3.4 are agreed. The framework serves its objectives as indicated and its components 1 & 2 adequately address planning and conducting PPS on a meaningful level of detail. Many aspects, e.g. sample definition, method selection, experiment/question design, analysis, etc., are in line with important considerations during *clinical* study design and subject to regulatory assessment. These aspects may qualify as topics for seeking Scientific Advice for a specific development programme. It is furthermore agreed that these aspects are generally applicable, regardless of a specific PPS method chosen.

Framework component 3, i.e. application of PPS data to inform decision-making, in turn offers several example objectives as well as application and presentation modalities. The relevance/applicability and thus supportive value of PPS may not be uniform across these objectives (see above). The outlined use cases and applications to decision-making are to be strictly understood as examples and should not pre-empt future decisions on acceptability of PPS for regulatory decision-making by CHMP (or other committees). Nevertheless, the provided information on technical methods for application of PPS data and examples for implementing these are considered valuable information to guide future PPS applications. The applicant notes that the objectives as defined are not prescriptive with regard to circumstances under which patient preference data would be needed to support decision-making. This is supported. The framework may furthermore support interactions between industry, regulators (and HTA bodies/payers, as well as patients) and could guide decision-makers during assessment of PPS while using PPS results to inform decision-making.

Introducing the concept of 'preference sensitive situations' (section 2.1 in the briefing documentation) was questioned with regards to its added value and necessity during interaction with the applicant. It is found of limited value in assisting in the identification of relevant contexts of use in the regulatory setting. The conditions/categories listed to describe PP-sensitive situations appear rather soft and any eventual judgment of whether they would apply in a certain situation would remain subjective (as well as dependent on the experimental design). Furthermore, assessing the "*willingness to accept uncertainty*" was not considered a straightforward context of use. This was accepted by the applicant during the Discussion Meeting and a reference in this respect is added to the qualification opinion.

The importance of transparency with regard to PPS is emphasised and it is generally recommended to publish PPS in a register (e.g. the access health preference study and technology registry), even when the clinical trial in which the patient preference study might be embedded is already registered as clinical trial in EudraCT or *clinicaltrials.gov*. Applicants of the studies should be encouraged to publish results of the research.

Overall, it is agreed that the framework is suitable for informing on objectives, design and conduct, and reporting of PPS.

Points to consider on content & methodological aspects

The high-level structure of the points to consider (PtC) chapter, i.e. the three categories: methodological factors, participant factors, and feasibility factors, can be agreed. Understanding well-described limitations and potential mitigation strategies (where possible) requires cross reading with the framework as well as external literature. However, it is evident that no definitive solution may be found for all inherent challenges of PPS (e.g., mitigating certain biases, assuming generalisability of results, etc.). Each use scenario for PPS differs by the question(s) posed and/or by the method and design elements chosen accordingly. Asking the right questions at the design stage is important, but a general acceptance of concept and approach cannot obviate scrutiny with regard to assessment of design, conduct and analysis.

The in-depth discussion of possible PPS methods considers only a selection of available methods (discrete choice experiment, best-worst scaling variants, swing weighting, threshold technique). These methods (described in chapter 4 of the framework) differ with regard to the experimental setup, the design space as well as regarding the associated tasks for study participants to express their preferences. In this way, the presented set of experiments displays a relevant spectrum when it comes to method selection for most efficient PP-elicitation, given a specific research question. As regards optimal methodological approach, and as also indicated by the applicant, flexibility should be kept for PP research should other /related concepts turn out to be more suitable. The approach to identifying methods is not documented as systematic but based on a review of available methods by Soekhai et al. (Pharmacoeconomics 2019). Although not covering all available methods for patient preference research, it leads to a documentation that is helpful for selecting an appropriate one for a given research setting. It is emphasized that a systematic approach to selecting an appropriate method is not limited to the presented and discussed methods, and the provided list should not be considered prescriptive. Retrospective application of the points to consider to completed case studies is valuable and can guide future application of the documentation annexed to this qualification opinion.

Several general methodological aspects need thorough consideration for understanding the validity and generalisability of data generated within a specific PP experiment and should be addressed as early as at the planning stage. These include, but are not limited to, representativeness of the study sample and susceptibility of any PP elicitation method to bias related to the choice of experimental setup, selection of attributes and attribute levels and way of their presentation/framing.

From the methodological perspective, the goal to generate evidence for PP by using targeted elicitation methods primarily corresponds to an "estimation task". In this context, the question of the target of estimation is hence relevant.

Population heterogeneity is an important issue. Disease-related aspects (such as time since onset, severity, etc.) as well as disease-unrelated aspects (such as attitudes, cognitive abilities, education & knowledge and/or experience with expected AEs, etc.) warrant consideration in study planning as well as interpretation of results. This may prove difficult in certain instances, but expectations as regards relevantly different preference profiles across subgroups within the target population should nonetheless be formulated and explored. Furthermore, the participants' ability to think about and express preferences will often only be triggered by the explicit confrontation with choice options. This is particularly so when confronted with never experienced or unfamiliar choice attributes. Aside from the more general issue of trial participant's competence to judge presented options, the fact that experimental conduct directly influences the research objective has a non-negligible impact on how PP-results should eventually be interpreted.

By its nature, the research target of a given PPS is intrinsically dependent on the offered options/alternatives which represent the core of any experimental PP setup. No single objective research approach seems possible which would be void of the potential to influence the experiment's outcome by the specific choice of "preference options/items" as well as by the way these options are presented to the trial participant. This fact has direct implication on concepts to address validity as well as reliability of elicited preferences. Meaningful PPS results should be robust to variability in how choice profiles are set up (see e.g., Veldwijk et al., Value Health 2016; Vass & Payne, Pharmacoeconomics 2017 for critical discussion) or at least enable an understanding as to the magnitude and direction of potentially introduced biases due to the experimental design. Qualitative preparatory work with PPS participants and/or background scenarios intended to enhance understanding of the concerned subsequent preference elicitation task need to be carefully considered for their potential to affect PPS results. In addition, participating in a PPS may have the potential to negatively affect subjects depending on information presented and appropriate care/measures should be in place to mitigate respective concerns.

The appropriate choice of an analysis method and pre-specification of a model and variable selection procedure is of major importance. Some elements of the points to consider section (as described in section 5) are closely related to general aspects addressed in the framework part of the documentation (section 3) and specifically the steps in table 3-4, addressing potential bias, should be considered when applying the points to consider. It is also stressed that (cross-)validation efforts would be critical to assess robustness of patient preference data. Robustness would be a criterion that has an impact on which information would be valuable for decision-making and communication, and respective (sensitivity) assumptions and analyses as well as alternative experiment specifications should be addressed at the planning stage (potentially also involving scientific advice).

Potential limitations with regard to conventional inferential interpretation also mean that a trial planning approach – as usually adopted for clinical trials based on power calculations in relation to statistical hypotheses testing – can generally not be assumed to be appropriate when planning PP experiments. The statistical models used to evaluate PPS data typically impose limitations on the number and type of preference statements that can be investigated using the available data. In more technical terms, it is usually necessary to impose parameter constraints to ensure identifiability of the statistical model and estimability of key model parameters. In this context, the number of comparable alternatives (attribute vignettes), the number of attributes, the number of attribute levels, as well as the number of choice tasks per respondent will likely determine the minimum required number of respondents to be included in a specific experiment. Interaction concerning the adequacy of methodological aspects in planning and sizing PPS might eventually be based on efficiency and estimability aspects. However, the focus of advisory interaction with regulatory bodies could be on the choice of the set of comparable alternatives (attribute vignettes), the range and presentation of attributes and their different levels. For these aspects, the PtC offers limited information at present. Janssens and co-authors (Janssens et al., BMC Med Inform Decis Mak 2019), part of PREFER, address in a helpful brief way "opportunities and challenges" for including PPS and provide a comprehensive qualitative review including lists of *concerns* associated with PPS and, related to these, *requirements* for making use of them in decision support.

In conclusion, although the method selection is not exhaustive, the points to consider chapter can support designing future PPS to generate evidence on patients' views with the goal of informing decision-making. As discussed above, a number of important methodological considerations require that specifically generated PP evidence will always need careful interpretation in the context of the experimental setup in which the PP data was collected and analysed.

Inclusion of PPS data in regulatory documents

In principle, information on PPS may be included in the Clinical Overview or the EPAR and other relevant documents. This would pertain to cases for which the information was either relevant to the regulatory decision and the benefit-risk assessment, and/or where PPS data are relevant to inform prescribers and users of the medicinal product. The decision will be made on a case-by-case basis. More generally, the value of conveying information on group-level preferences to individual patients in relevant documents would have to be carefully considered for situations where individual choice is paramount (i.e., for prescription or administration/use). If the primary intent was to reflect and justify the decision processes considered at the time of clinical programme planning and during MAA assessment, the EPAR would appear a more appropriate place for PPS-related descriptions and/or data. As said, a final decision by CHMP would only be possible at the time of an assessment of a MAA on a case-by-case basis, taking into account the validity and robustness of the data.

Qualification opinion:

The proposed research *framework* and *points to consider* document is generally endorsed as a comprehensive reference document for planning and conducting patient preference studies (PPS). However, specific comments are made and several potential limitations are addressed above, specifically also with regard to identification of preference sensitive situations. PPS may serve to inform regulatory decision-making in certain instances, and support the interpretation of clinical data and/or the planning of clinical development and clinical studies. The framework shall however not be considered as equivalent to an EMA guideline or reflection paper. Regulatory experience with PPS is currently limited and therefore formal EMA guidance how PPS can be applied and should be performed to successfully support marketing authorisation applications (MAA) cannot be given.

Potential PPS applications are manifold and may vary in importance for medicinal product development-related and regulatory decision-making (ranging from supporting the choice of endpoints for clinical studies to generating information on efficacy and safety trade-offs). Whereas the use of PPS shall not be constrained to specific scenarios, the scrutiny in assessment of PPS data, their relevance and eventual reliance on these data will be scenario-dependent.

As a principle, and regardless of adhering to the framework, it is therefore considered that this qualification opinion cannot pre-empt a case-by-case decision on the weight put on specific PPS results submitted as part of a marketing authorisation application. Any PPS, regardless of adhering to the framework, needs to be assessed according to its objectives and specific use case, accounting for appropriate pre-specification of model and analyses, together with sensitivity and supplementary analyses as appropriate. Potential limitations to result interpretation should be pro-actively addressed upon submission. Several sources of potential bias have been described and experimentally shown in the abundantly available literature on PPS. Evaluation of potential bias hence needs to be expected as an integral part of any upcoming assessment of PPS data.

It is reiterated that the list of stated PPS methods is not exhaustive and shall not be considered prescriptive for PPS method selection.

Registration and publication of PPS protocols (and results) in analogy to clinical trials is strongly encouraged. Moreover, if PPS are to play an important part in building an MAA dossier, scientific advice at the planning stage of these studies is recommended.

ANNEX provided by the applicant for qualification opinion.

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