

D2.1 Desires, expectations, concerns and requirements of stakeholders about methodologies for patient-preference elicitation and their use in making well-informed decisions regarding medicinal products

115966 – PREFER Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle

[WP2 – Patient preference elicitation issues and approaches]

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Publishable Summary

BACKGROUND: The patient perspective is increasingly considered to be an essential component of healthcare research and decision-making. A growing area of focus is the measurement and use of patient preferences regarding different medical treatment options or their properties.

OBJECTIVES: Task 2.1 aimed to identify stakeholders' desires, expectations, concerns and requirements regarding the measurement and use of patient preferences throughout the medical product life cycle.

METHODS: A four-step approach was used. First, exploratory interviews were conducted with 16 stakeholders. Second, a literature review of scientific publications and other publicly available documents was performed. Third, semi-structured interviews were conducted with 142 stakeholders (patients, informal caregivers, patient representatives, physicians, regulators, reimbursement agency representatives, health technology assessment representatives, industry representatives, academics) from eight different countries (7 EU, USA). Fourth, eight focus group discussions with representatives from the same stakeholder groups were performed to discuss topics identified during the interviews more thoroughly.

RESULTS: The **exploratory interviews** revealed the heterogeneity in how interviewees defined the concept of patient preferences. Interviewees agreed that there was value in measuring and using patient preferences in all stages of the medical product life cycle. The **literature review** showed numerous roles for patient preferences to inform industry, marketing authorization, health technology assessment and reimbursement decision-making. Echoing the exploratory interviews' results, interviewees during the **semi-structured interviews** spontaneously used different terms to define patient preferences. Although interviewees were positive regarding the general concept of patient preferences in the medical product life cycle, mixed opinions were expressed regarding the implementation of patient preferences in industry, regulatory marketing authorization, health technology assessment and reimbursement decision-making. Stakeholders recognized the need for greater awareness, acceptance and education regarding the concept, measurement and use of patient preferences throughout the medical product life cycle. Concerns amongst stakeholders were a lack of standardization and consensus regarding methodological aspects of measuring patient preferences. This lack of consensus may reflect the fact that use of patient preferences in the medical product life cycle is still relatively novel. The focus group discussions with patients revealed: i) key issues that matter to patients, related both to their healthcare in general and to properties of medical products and ii) topics to consider in designing and conducting patient preference studies such as factors influencing their participation in preference studies and how preference information coming forth from such studies should be handled. The **focus group discussions** with regulators, health technology assessment/payer representatives and industry representatives identified: i) topics to consider when designing, conducting and reporting on patient preference studies such as factors to consider regarding the sample in patient preference studies and ii) current and potential applications of patient preferences in industry, marketing authorization and health technology assessment.

CONCLUSIONS: Patient preferences can serve to inform various stakeholders in many ways, however more awareness, acceptance and education regarding the concept, measurement and its implementation is needed throughout the various steps in the medical product life cycle. The lack of standardization and consensus on methodological aspects of methods to measure patient preferences needs special attention in follow-up research.

Information within this report that may influence other PREFER tasks

Linked task	Points from this report that are of particular relevance to the linked task
2.8: Develop study synopses and preliminary research questions for empirical case studies and simulation	Results of this task generate insights into the preliminary research questions addressed by PREFER, as task 2.1 highlights gaps in our knowledge base as well as key topics stakeholders are concerned about.
3.2: Translate the preliminary research questions identified in WP2 to concrete study designs	As this task can provide input for the design of the preliminary research questions addressed by PREFER, it indirectly also provides input into the concrete study designs.
4.1: Define the scope of the recommendations	Results of this task provide input into the content items for the scope of recommendations document created in task 4.1 within PREFER.
4.2: Preparation of operational requirements and best practices for conducting of case studies	Results of this task such as the section operational requirements in the literature results can serve as a knowledge base for the preparation of operational requirements for conducting case studies within PREFER.
4.3: Creating draft recommendations and testing these for extrapolation to other disease areas and decision points with stakeholder advisory groups	Results of this task can provide input into the content items for the recommendations created in task 4.3 within PREFER.

Abbreviations

Abbreviation	Description
AC	academic
BRA	benefit-risk assessment
CA	caregiver
CVD	cardiovascular disease
DM	myotonic dystrophy
EMA	European Medicines Agency
EU	Europe
FDA	US Food and Drug Administration
FGD	focus group discussion
HTA	health technology assessment
IDM	industry decision-making
IN	industry representative
INT	interviews
LIT	literature review
MA	marketing authorization
MeSH	medical subject headings
MPLC	medical product life cycle
PA	Patient
PDUFA	Prescription Drug User Fee Act
PH	physician
PO	patient organization representative
PP	patient preferences
QALY	quality adjusted life year
RA	rheumatoid arthritis
RE(G)	regulator
UK	United Kingdom
USA	United States of America

Introduction

The patient perspective is increasingly considered essential on all levels of healthcare research and decision-making (2). This growing attention is demonstrated by an accumulating amount of literature on the role of the patient perspective in medicinal product and medical device development (3-5), regulatory assessment (6-9), health technology assessment (HTA) (10-13) and clinical practice guideline development (14, 15). The term 'medical product' will be used hereafter as an umbrella term for human medicinal products (or drugs) and medical devices as defined by the European Commission (16, 17) and the US Food and Drug Administration (FDA) (18). This increased focus on patients' perspectives has led to direct involvement of patients in decisions regarding treatment (19-22), medical product development (4, 23, 24), regulatory decision-making (7, 25, 26) and reimbursement decision-making (27). Direct involvement occurs through the participation of patients or patient representatives in a group of decision-makers (28). Direct patient involvement has been shown to be informative for decision-making, but has also been criticized for not representing the entire patient population (25, 28, 29).

A particular area of focus is the measurement and use of patient preferences (25, 30). Methods for eliciting patient preferences allow for the inclusion of patient insights in decision-making by eliciting their preferences regarding a medical product or its properties and then including those results in the different decision-making processes along a medical product life cycle (MPLC). Although no consensus exists regarding the definition of patient preferences across research fields and disciplines (24, 28, 31-33), patient preferences have been defined by the FDA as "the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions" (18). Patient preferences might play a role in various decision-making processes along the MPLC, such as: i) in medical product design and clinical trial design (34), ii) in regulatory benefit-risk assessment (BRA) and marketing authorization (MA) (25, 29, 35-37), iii) in HTA and reimbursement decision-making (33) and iv) by physicians in the context of individual treatment decision-making (14).

Due to this wide possible applicability of patient preferences, different stakeholders are interested in measuring and using them at various points in the MPLC. Aside from one study focusing on integrating patient preferences in reimbursement decisions and clinical practice guideline development (38), to our knowledge, few studies have formally investigated stakeholder views towards measuring patient preferences and their broader use in decision-making along the MPLC. Consequently, stakeholders' desires, expectations, concerns and requirements for measuring and using patient preferences in medical product decision-making remain unclear.

For these reasons, the PREFER ('Patient Preferences in Benefit and Risk Assessments during the Treatment Life Cycle') project, and more specifically, task 2.1 of work package 2 (WP2) was initiated. The aim of PREFER is to strengthen patient-centric decision making throughout the life cycle of medical products by developing expert and evidence-based recommendations to guide the different stakeholders (industry, regulatory authorities, HTA bodies, reimbursement agencies, academia, health care professionals and patient organizations) on how and when patient preference studies should be performed, as well as how the results can be used to inform decision-making. The PREFER project consists of four WPs jointly addressing these issues. In WP2, task 2.1 aimed to explore stakeholder perspectives towards the role of patient preferences throughout the MPLC and the nature of these stakeholders' desires, expectations, concerns and requirements regarding the measurement and use of patient preferences in decision-making within the MPLC. Insights of this task will show opportunities and potential barriers for the use of patient preferences in decision-making along the MPLC by all stakeholders, thereby paving the way for subsequent tasks within PREFER. Task 2.1 was organized in a four-step approach:

1. exploratory interviews,
2. a literature review,
3. semi-structured interviews and
4. focus group discussions.

The present report is therefore also organized into four parts. In the first part, results from exploratory interviews are included. These results informed the study presented in the second part of the report, namely a literature review. Together, the results from the exploratory interviews and literature review informed the third study described in part three, namely stakeholder semi-structured interviews with stakeholders. Finally, the results of the semi-structured interviews informed the fourth and final study of task 2.1, namely focus group discussions with stakeholders, which

are described in the final part of this report. The final section integrates insights from all four steps. The appendices of the report provide additional information related to the methodological approach or supplementary information from the studies.

Methods

General design

This task applied a four-step approach: exploratory interviews, a literature review, semi-structured interviews and focus group discussions.

1. Exploratory interviews

To get an initial view on stakeholders' opinions about the use of patient preferences throughout the MPLC, 16 semi-structured exploratory interviews were conducted during the PREFER kick-off meeting in Basel on Oct 28th, 2016, using a preliminary interview guide. A non-probabilistic sampling strategy was used: interviewees were selected based upon: 1) our judgment on their ability to provide guidance with regard to the research questions (purposive sampling) and 2) whether they were able to attend the kick-off meeting and if so, whether they had time to participate in an interview during the kick-off meeting (convenience sampling). Interviews were conducted with HTA/payer representatives (n=4), regulators (n=2), industry representatives (n=3), patient organization representatives (n=4), physicians (n=2) and academics (n=1). Data were analysed through qualitative content analysis, with the frequency of observations compared against the six stakeholder groups.

2. Literature review

Objectives and research questions

The aim of the literature review was to explore stakeholder perspectives towards the role of patient preferences throughout the MPLC and the nature of these stakeholders' desires, expectations, concerns and requirements regarding the measurement and use of patient preferences in decision-making within the MPLC. This literature review was therefore guided by the following research questions:

1. Is the use of patient preferences and/or patient preference methods in the MPLC desired and what is described as added value and/or limitations for the use of patient preferences and/or patient preference methods in the MPLC? **(desires);**
2. What is expected to happen when patient preferences and/or patient preference methods are used in the MPLC? **(expectations);**
3. What are concerns for the use of patient preferences and/or patient preference methods in the MPLC? **(concerns);**
4. What are requirements for the use of patient preferences and/or patient preference methods in the MPLC? **(requirements).**

Search strategy

The authors (RJ, IH, JV, EvO, CW) developed search queries (Appendix 1) based on the main three concepts of these research questions. These concepts are: i) the desires, expectations, requirements and concerns; ii) the different stakeholders: regulatory authorities, HTA bodies and reimbursement agencies, patient organizations, caregivers, physicians and researchers and medical product industry and iii) the use of patient preferences or patient preference methods in the MPLC. The search queries consisted of Medical Subject Headings (MeSH) terms and free text words to ensure a comprehensive search (Appendix 1). The free text search was limited to the fields title and abstract (Appendix 1). Based on the search queries, a systematic search was carried out with support from a research librarian from Erasmus Rotterdam University through November 2016. The consulted scientific databases were: Guidelines International Network, Embase, PubMed, PsycINFO and EconLit. Other scientific publications (white literature) was included via hand searching and snowballing. All members from the PREFER project were asked to share and other publicly available documents (grey literature) in the form of regulatory

documents, HTA reports, project reports or workshop reports.

Inclusion and exclusion criteria

The following inclusion criteria were applied:

1. *Study types.* Because a preliminary scoping exercise revealed a lack of qualitative primary research articles on our research topic, we broadened our scope and considered also other types of literature (grey literature): regulatory documents, HTA reports, (systematic) reviews, quantitative primary research articles, project reports, workshop reports and perspective articles were also eligible.
2. *Perspective.* Only literature describing the view of at least one of the above-mentioned stakeholder groups was found eligible. To define the type of stakeholder upon which the opinion in a particular article is based, each record was assigned to a certain stakeholder group: for primary research articles, (systematic) reviews and perspective articles, the background of the first author was used to assign a stakeholder perspective. For regulatory documents, the regulatory agency perspective was assigned. HTA reports were assigned to the HTA body perspective. For project reports, since those are written from a multitude of stakeholder perspectives, they could not be assigned to only one stakeholder perspective.
3. *Interest.* Included literature had to describe the use of a patient preference method in the MPLC or the use of patient preferences from a patient preference method in the MPLC. As this review focuses on the use of patient preferences in the MPLC and not on their use in individual treatment decision-making, literature describing only the use of patient preference methods in the context of individual treatment decision-making were excluded.
4. *Evaluation.* Only literature describing the role or specific use of patient preferences in the MPLC and one of the proposed research questions was found eligible.

The following exclusion criteria were applied: i) not in English, ii) no full text available, iii) published before 2011, v) country outside of US/EU and vi) conference abstracts, conference notes, book reviews and presentations.

Selection protocol

A two-step screening strategy was used. First, three authors (RJ, EvO, CW) screened: i) title and abstract of white literature or ii) table of contents or headings of grey literature for relevance to the research questions and exclusion criteria. Each record was independently screened by two authors to minimize selection and data bias. Disagreements were resolved by discussion between three authors (RJ, EvO, CW). Second, one author (RJ) applied inclusion and exclusion criteria to the full text.

Data extraction

An adapted form of 'qualitative content analysis' as described by Lohrberg et al. (39) was performed for data extraction by one author (RJ). In contrast to the qualitative content analysis described by Lohrberg et al., deductive codes were applied for data extraction (Appendix 2). These codes were developed before data extraction and were derived from: i) the research questions and ii) themes that emerged during the exploratory interviews (Appendix 2). New codes were also created during data extraction and text was recoded subsequently. We coded text in the results section, discussion and conclusion of the included qualitative primary research article. We coded text in the discussions and conclusions of the included primary quantitative research articles, (systematic) reviews and perspective articles, because we anticipated that in these sections, the author gives his personal opinion. For regulatory documents, HTA reports, project reports and workshop reports, we coded the full text. The NVivo PRO 11 software (QSR international) was used for coding.

3. Semi-structured interviews

One hundred and forty-three semi-structured interviews were conducted between April 2017 and August 2017, although initially 144 interviews were planned. The following stakeholders were interviewed: HTA/reimbursement agency representatives (n=24), regulators (n=23), industry representatives (n=24), academics (n=24), physicians (n=24), patient representatives and patients (or their caregivers when appropriate, n=24) (Table 7). Interviewees were recruited from seven European countries (Sweden, Romania, Italy, the UK, the Netherlands, Germany, France) and the U.S. An online form was sent to all PREFER consortium members where they could suggest potential interviewees and provide reasons for interviewing them (Appendix 3). Inclusion criteria and quota per stakeholder group were set to allow for a heterogeneous sample (Appendix 4). Interviewees were selected based on these predefined inclusion criteria and were sent an invitation with an information form via e-mail (Appendix 5,6).

Upon agreement, interviewees received a consent form (Appendix 7). Interviewees were asked to read the information form and sign the consent form. Interviews took approximately one hour and were conducted via telephone or face-to-face. Interviews with patient representatives, patients, caregivers and physicians were conducted in their native language. Interviews with HTA body/reimbursement agency representatives, regulators, industry representatives and academics were conducted in English. Only if interviewees indicated that they did not feel comfortable with an interview in English was the interview conducted in their native language.

An interviewing protocol was developed to minimize variability and enhance comparability across the interviews, since they were conducted by eight different interviewers. The interviewers group was composed of members involved in the 2.1 sub-task as well persons outside of the PREFER project in order to be able to conduct the interviews with patient representatives, patients, caregivers and physicians in their native language. Online meetings and were held and emails were exchanged among the interviewers to exchange experiences and advice and to discuss the overall progress of the interviews. At the start of the interview the purpose of the interview was explained. Two interview guides were used: one version for HTA/reimbursement agency representatives, regulators, industry representatives and academics; and one version for physicians, patient representatives, caregivers and patients (Appendix 8). Two guides were designed as we anticipated a large variety in knowledge and familiarity with the topics of the interview guide and to ensure the same topics were addressed in all interviews. These interview guides were developed based upon the research questions, the outcomes of the literature review and feedback from the exploratory interviews. Both versions of the interview guide were pilot tested. Participants were asked to express their opinions on the measurement and use of patient preferences in all possible decision-making processes (including but not limited to product development, marketing authorization (MA) and reimbursement decision-making) during the MPLC with a focus on the participant's field of expertise. Ethical approval was obtained in all countries where interviewees were recruited (Appendix 7). Interviews were audio recorded and transcribed verbatim. The framework method, as described by Gale et al. (1), allowing the inclusion of a priori as well as emerging themes was used for analysis. The framework method consists of seven stages: transcription, familiarization, coding, developing an analytical framework, applying the analytical framework, charting and interpreting (Appendix 9). NVivo qualitative data analysis software by QRS International Pty Ltd Version 10, 2012 was used for analysis. During the last stage of the framework method, we analysed results per theme and stakeholder group, which is also how the results section of the interviews is structured. Differences that were identified during the analysis that are country-specific or disease-specific (for patients) within a particular stakeholder group are indicated in the results section.

4. Focus group discussions

A total of 8 focus group discussions (FGDs) of 3-10 participants were conducted. Four patient FGDs were conducted; one with rheumatoid arthritis patients in Sweden, one with cardiovascular patients in Romania, one with lung cancer patients in Italy, and one with myotonic dystrophy patients and caregivers in the UK. In addition, four expert FGDs were conducted; one with European industry representatives, one with European regulators, one with US regulators and one with European and Canadian HTA/reimbursement representatives. Participants were recruited via patient organizations, hospitals, the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the HTA advisory group of PREFER. Participants were selected on the basis of predefined inclusion criteria, depending on their experiences or expertise being able to inform our research questions.

Patient FGDs were conducted face-to-face and expert FGDs via teleconferences. FGDs took between 45 minutes and two hours. Expert FGDs were conducted in English and patient FGDs in the native language of the patients. Written informed consent was obtained from all participants. Focus group discussions were recorded, transcribed verbatim and pseudonymized. Non-English transcripts were translated to English.

The analysis was conducted by a small subset of moderating team members (EvO and RJ) in order to minimize variability and enhance comparability across the focus group discussions. Thematic analysis, as described by Howitt (40), was used to analyse the FGDs and consisted of five stages: data familiarization, initial coding generation, search of themes, review of themes and theme identification and labelling. NVivo qualitative data analysis software by QRS International Pty Ltd Version 10, 2012 was used in the final two stages of the analysis.

Results

1. Exploratory interviews

A variety of definitions for patient preferences was given by interviewees. Interviewees of all stakeholder groups agreed that there was value in measuring and using patient preferences in all stages of the MPLC. Interviewees mentioned different possible roles of patient preferences throughout the MPLC. Most interviewees agreed that a systematic approach of eliciting patient preferences with the purpose of informing MA and reimbursement is not widely adopted. Concerns were raised for the methodological requirements of patient preference methods. The preliminary interviews revealed that the interview guide contained several questions that interviewees did not understand or could not answer. The exploratory interviews informed the coding tree of the literature review and the interview guide of the semi-structured interviews: i) the new guide focused on topics raised in the exploratory interviews, ii) questions that that interviewees did not understand or could not answer work during the exploratory interviews were removed or adapted ([read full report](#)).

2. Literature review

The database search of the literature review yielded 636 records. One hundred thirteen other records were included via hand searching, snowballing (i.e. retrieving literature via scanning and examining texts and bibliographies) and grey literature. After exclusion of duplicates, 592 records were screened on title and abstract or table of contents. From these, 125 full texts were screened, resulting in 52 records which were included for analysis (Appendix 11,12).

First, the general desires, expectations, concerns and requirements regarding patient preferences applicable to all decision-making processes will be described. Afterwards, the specific aspects for different decision-making processes along the MPLC will be discussed for: i) industry processes and decision-making, ii) regulatory BRA and MA decision-making and iii) HTA and reimbursement decision-making. Per decision-making process, the results are graphically presented in figures. Under the figures, the results are described at length.

2.1 General desires, expectations, concerns and requirements regarding patient preferences in processes and decision-making along the medical product life cycle

The use of patient preferences in multiple stages and for multiple purposes throughout the MPLC is often **desired** (18, 34, 41-46). Overall, many authors agree that patient preferences are useful for several decision-makers and stakeholders, such as industry, healthcare professionals, regulators and health technology assessors (18, 43, 44, 46, 47). Selig (45) notes that while it is important to incorporate input from the patient community throughout the life cycle, the choice of whether and when to conduct a patient preference study depends on different factors (e.g. the readiness of the community and the ability to adequately engage the appropriate patients). Factors influencing the utility and role of patient preference studies are described at length in the task 2.2 deliverable (see deliverable 2.2).

Different authors **expect** that measuring and using patient preferences in the MPLC will allow clinicians and policy makers to take into account issues most important to patients (48) as well as leading to more patient-centric care and a higher effectiveness of treatment (44). Additionally, the FDA guidance (18) states that measuring and using patient preferences throughout the MPLC will result in more patient-centric decision-making.

Despite the desired role of patient preferences and positive expectations, authors describe several **concerns** related to the use and measurement of patient preferences in the MPLC. First, there is no consensus on the definition for patient preferences. This might hamper the communication between stakeholders with differing backgrounds, which in turn might complicate integrating patient preferences in healthcare decision-making (2, 42). Second, although the existence of guidance on the use of patient preference methods (by for instance ISPOR and MDIC) is raised (34), some authors are concerned about the high number of available patient preference methods (49) and the lack of precise guidance as to which method to use in which circumstance (34, 50). Third, many patient preference methods are cognitively complex and attributes used in these methods can be misleading to patients (44). In this context, Hauber et al. (51) notes the problem of low numeracy among groups of patients. Fourth, the validity, reliability and transferability of patient preferences measured with different methods are questioned (42,

47, 51). Fifth, the question of whose preferences to measure in preference studies (34, 41, 52) and how to deal with subgroups having systematically differing preferences is often debated (52).

In general, the **requirements** mainly concern the need for clear guidance on when to use which patient preference method in the MPLC (50, 53). Some authors argue that the planning of preference studies should start early in the development of a medical product (24, 34) and that the choice of the method depends on many factors (e.g. the intended use of patient preference information: defining strategic requirements, informing the design of a clinical study, regulatory BRA or providing information to support reimbursement) (24, 45). Guidance is also needed on whose preferences (e.g. patient or public) to measure for informing a specific decision (52). According to Dirksen (42) future activities toward the use of patient preferences in healthcare decision-making should align with existing patient participation methods, such as scoping, appraisal, translation and communication activities in HTA. Further, future preference research should be undertaken with the same level of commitment to the principles of ‘good science’ applied to any clinical research effort (42, 45). Authors also raise a need for further patient preference research that: i) compares the performance of different patient preference methods in a given situation, ii) aims at developing guidelines as to sample adequacy and methods to validate preference studies and iii) determines the impact of changing the list of attributes with any given method (54). Finally, Selig (45) raises a general need to engage with partners and experts when undertaking preference studies and to have trust and written agreements about intellectual property and the use of data in this interaction.

2.2 Desires, expectations, concerns and requirements regarding patient preferences in industry processes and decision-making

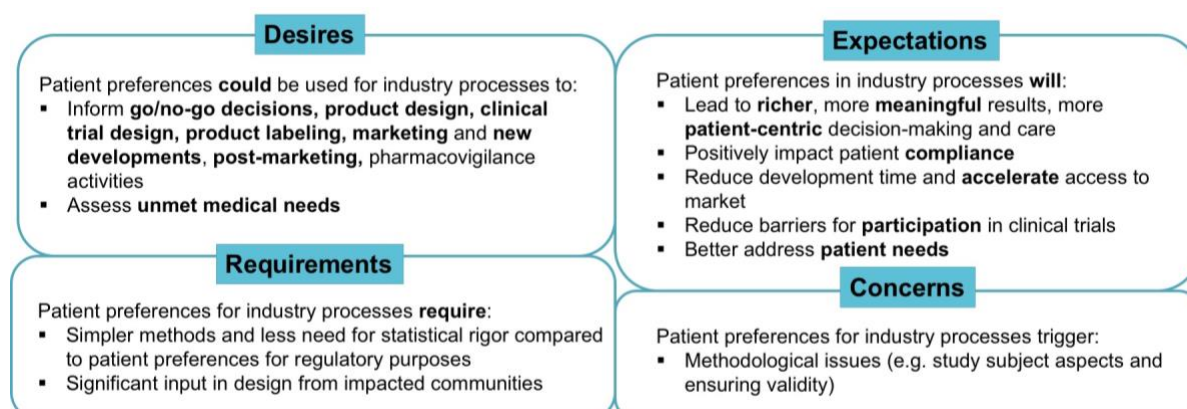


Fig. 1 Desires, expectations, concerns and requirements for patient preferences in industry processes

The use of patient preferences for industry processes and decision-making is often **desired** (18, 23, 45, 54-59). Authors elaborate on the specific **desired use** of patient preferences for industry processes and decision-making. First, patient preferences can inform ‘go/no-go’ decisions throughout the drug development (e.g. internal portfolio decisions among multiple disease settings or decisions about which assets to prioritize within a portfolio) and patient preferences about non-product-specific choices and priorities can inform resource allocation decisions (45). Second, patient preferences can help define areas of unmet medical need (18, 30, 45). Third, patient preferences can influence which medical product will be developed (45). Fourth, patient preferences can inform product design. For example, quantitative or qualitative information of patient preferences on treatment attributes can inform the design of a target product profile (18, 23, 24, 34). Fifth, patient preferences can be used as input for clinical trial design (18, 53, 56, 59-61) by indicating: i) which clinical (component) endpoints are of highest importance to patients (18, 56, 59, 61) and ii) which endpoints should not be considered (61). Patient preference information in this context can be used to inform: i) endpoint selection (24, 34, 45, 62), ii) enrolment criteria and sample populations (24, 56), iii) trial size (34), iv) analysis of clinical trials (18, 24) and v) defining subgroups with differing approaches for making trade-off decisions (24, 45, 54). This information of subgroups can suggest new markets for present indications (54) and can point to specific treatment opportunities for drug developers (45). Sixth, patient preferences for other aspects of treatment such as dosing administration options, dose timing, route of administration, dose frequency and treatment duration might also inform industry processes and decision-making (18, 23, 53). Seventh, patient

preferences can inform product labelling (18, 24, 54, 63) if that information played an important role in the approval decision (18, 24, 54). Eight, patient preferences in post-marketing processes can inform: i) new innovations (18), ii) redesign and improvement of existing products (18), iii) expanded indications or populations (18) and iv) risk assessments underlying product recalls (24). Ninth, patient preferences might also be used in pharmacovigilance activities (24, 46, 63), because the benefit-risk balance may change due to new evidence on adverse events (46). Smith et. al (63) describe that among pharmacovigilance activities such as adverse event reporting, signal detection and evaluation, risk management and BRA and risk communication, patient preferences can be integrated in BRA and risk management planning and evaluation. Tenth, patient preferences might be used in marketing to optimize promotional materials and to identify new feature sets and other product changes (24).

Besides the specific desired use of patient preferences in industry processes and decision-making, authors discuss what they **expect will happen** when patient preferences are used in industry processes and decision-making. Patient preferences for endpoint selection will result in richer and more meaningful results to future patients and patient preferences for study design and endpoints of the target population will impact the compliance of this population with the drug, once results are disseminated (50). Additionally, patient preference information is expected to help reduce overall drug development time and accelerate access to market by potentially accelerating clinical development (51). Furthermore, using patient preferences for industry processes and decision-making will allow for more patient-centric decision-making (18) and more patient-centric care (57). Additionally, using patient preferences for clinical trial design is expected to reduce barriers for participation and might affect willingness of participants to enroll and complete a clinical study (18) and using patient preferences to define treatment attributes is expected to better meet the needs of patients and deliver improved outcomes (23).

Concerns relating to the use of patient preferences in industry processes and decision-making are described at length in the MDIC report (24) and include methodological issues such as the selection of a method, a representative sample, attributes and how to ensure validity when measuring patient preferences.

The **requirements** of a patient preference study supporting strategic planning and informing clinical trial design are generally less than those required to support regulatory BRA and also the requirements regarding the type of method are less stringent: simpler methods, smaller sample size, less need for statistical rigor (24). Several bodies, including the FDA, describe that qualitative methods such as focus groups, social media, public meetings, workshops, might be informative to gather *patient input* in the early stages for industry processes and decision-making (18, 24, 30). According to Selig (45), it is important to identify the right research partners for the design and conduct of the patient preference study; patient preference studies aiming to inform internal strategic decisions are ideally conducted with significant input from impacted communities. According to Chow et al. (56), preferences for clinical endpoints should be measured from the patient population's perspective, rather from that of the general population because patients have insights into the disease experience and a vested interest in the outcome. Smith et al.(53) describe that when the medical condition affects infants, young children or the elderly, informal caregivers' preferences on clinical trial endpoints should be elicited. Lastly, a need for further research into the impact of the level of previous education on patient preferences for clinical endpoints is raised (56).

2.3 Desires, expectations, concerns and requirements regarding patient preferences in regulatory benefit-risk and marketing authorization decision-making

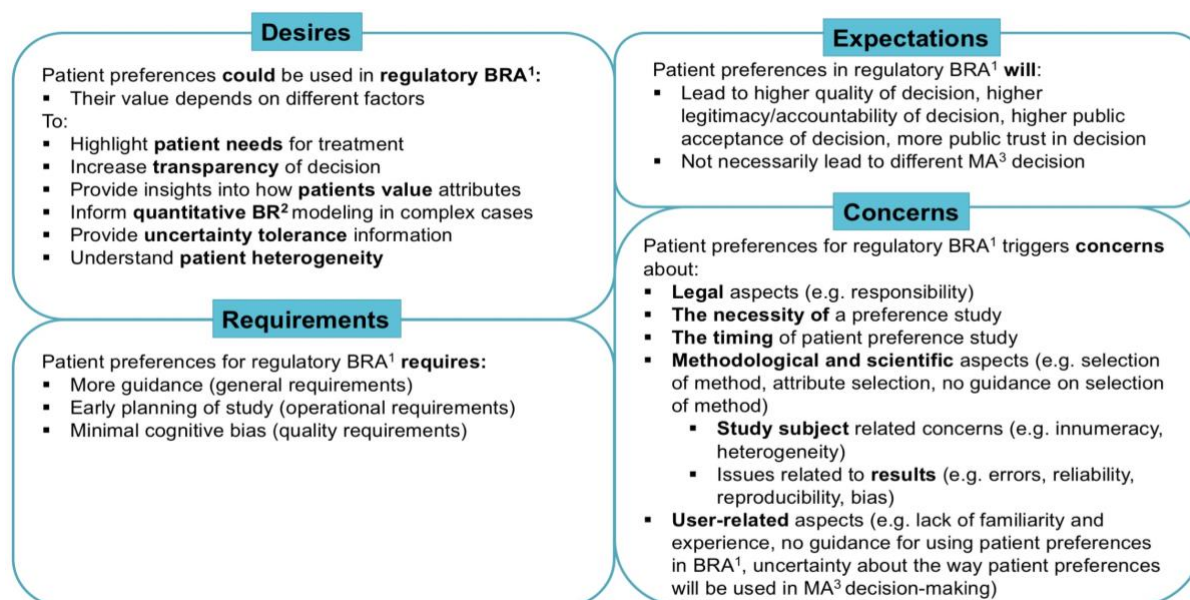


Fig. 2 Desires, expectations, concerns and requirements for patient preferences in regulatory benefit-risk assessments

¹BRA= benefit-risk assessment; ²BR= benefit-risk; ³MA= marketing authorization

Many authors **desire** the use of patient preferences in regulatory BRA and discuss their potential in MA decisions (18, 24, 25, 29, 43, 45-47, 52-54, 58, 59, 63-69). Authors discuss why using patient preferences in BRA could be useful (Table 1). Reasons put forward include because patients have the unique experience of the disease and benefits and risks of the treatment. Some authors also reason that *patient preferences* might be useful because *direct involvement of patient representatives* in regulatory decision-making processes might not be representative. At the same time, authors argue that direct involvement and the use of patient preferences from patient preference studies are not mutually exclusive and should complement each other (29, 46, 67).

Some authors argue that the value and role of using patient preferences for MA decisions is subject to a variety of factors (18, 24, 65, 70). The term “preference sensitive” has been used to refer to situations characterized by these factors (Appendix 13, box 1). Examples of factors pointing toward such situations are the clarity of the benefit-risk balance, the rarity of the disease and the degree of subjectivity of endpoints considered (Appendix 13, box 1, box 2). For example, patient preferences might be particularly useful when the balance of benefits and risks is not self-evident (24, 29, 45, 70). Conversely, the MDIC report describes “non-preference sensitive” situations, where the use of patient preferences is less relevant for regulatory BRA: when the benefit-risk trade-off is clear (e.g. high benefit, low risk), when the patient is not a major decision-maker, when assessors and sponsors are familiar with the disease state, technology, study design and clinical inputs, when the treatment is clearly superior to existing therapies or when the treatment addresses an unmet medical need with poor outcomes so that the risk of treatment will not be greater than the untreated disease (24). Factors influencing the utility and role of patient preference studies are described at length in the task 2.2 deliverable (see deliverable 2.2). Besides the general value of using patient preferences in BRA and MA decisions, many authors elaborate on their specific use and/or the specific type of information they could add to BRA and MA decisions (Table 2).

Although taking patient preferences into account in BRA and MA decisions might not necessarily lead to a different decision outcome (71), many authors **expect** that patient preferences in regulatory BRA and MA decisions will result in: i) a higher quality decision (46, 68, 72), ii) greater legitimacy or accountability of the decision (72) which would result in increased understanding and/or acceptance by the public and stakeholders (46, 49, 71, 72) and iii) more public trust in the licensing process (69).

Despite the desired use of patient preferences in BRA and MA decisions, authors discuss many **concerns** related to the measurement of patient preferences and their use in BRA and MA decisions. First, there are legal concerns such as who is responsible for collecting patient preferences, the reliability of preference data and the consequences of potential biases that may occur (46). A second concern relates to the necessity of patient preferences for a certain medical product: for which medical products should patient preference information be collected (24, 34, 54)? A third concern relates to the question when in the medical product development stage to design and implement a preference study to inform regulatory assessment (24, 53, 54). Fourth, methodological and scientific issues are raised: the innumeracy of the participants (46, 51), the challenge of communicating the quantitative aspects of health information to patients (18), heuristics, inert or flexible preferences and measurement errors³ (46), sample bias and the representativeness of the preferences elicited by a particular group on any given moment or occasion (24, 34, 45, 46, 66). One author describes however that many of the possible sources of bias are similar to those in clinical trials and can be resolved through the same solutions used in clinical trials (24). Furthermore, the hypothetical nature of the choice from which patient preference data are derived may weaken the validity and reproducibility of patient preferences (24, 45, 46). Besides the challenges of obtaining valid and reliable measures of patient preferences (51, 72), the issue of neglecting patient heterogeneity and variation among subgroups is raised (43, 46). Authors are also concerned about the cognitive burden for participants (66) and the tension between patient preference methods with strong methodological underpinnings and the cognitive difficulties that come with these methods (28): *"No method exists that has a low cognitive burden and strong methodological underpinnings and that can, at the same time, deliver enough and adequate information to support the decision."* However, others maintain that the cognitive burden of patient preference methods is acceptable to patients (69). Another concern raised is how to select a patient preference method for obtaining patient preferences that can inform regulatory decision-making (24, 34, 49). Fifth, concerns related to the use of patient preferences are discussed. Unresolved questions relate to: i) the way patient preferences information will be used and reviewed by regulatory agencies (24, 45, 46), ii) the way to submit patient preferences information to regulators (45) and iii) the standards for collection and submission of patient preferences information (45). According to some, patient preferences can be viewed as an additional form of evidence to be evaluated in conjunction with other regulatory considerations (24, 30, 54) and specific approaches are needed for using preferences in the evaluation of clinical evidence (46). Another user-related concern is the lack of familiarity and experience among regulators and sponsors with patient preference methods (24, 30, 45, 53). Lastly, some authors raise the issue that no guidance exists about: i) what method to use (24), ii) which attributes to use in a patient preference study (24), iii) how to assure validity in a patient preference study (24) and iv) whose preferences to measure in a patient preference study (24, 52).

Requirements related to the measurement and use of patient preferences for regulatory BRA can be divided into general requirements, operational requirements and quality requirements (Table 3). Authors describe that promising steps have been made by EMA (29) and FDA (18), but that the value of patient preferences in BRA still needs to be agreed upon by regulatory agencies, patients and sponsors (58, 72). There is a general need for: i) regulatory guidance on when and how in the drug development process patient preferences should be measured to inform regulatory evaluation (53, 58), ii) more experience and expertise with performing and evaluating patient preference studies (24, 49, 53, 66, 70) and iii) developing best practice standards for patient preference studies (24, 46, 51). Some authors note that regulatory agencies need to identify resources to evaluate patient preferences (66) and that a need exists to identify and engage the appropriate methodological expertise when designing and executing a patient preference study aiming to inform regulatory BRA (45, 49). Furthermore, many authors highlight the importance of a multi-stakeholder approach (18, 24, 29, 45, 54, 58, 67), which can be achieved through public-private partnerships (54) and some authors stress the need of: i) interaction between regulators and industry in the design phase of the patient preference study (18, 24, 45) and further in the development (45) and ii) involving patients, caregivers and patient organizations as active research partners in the design and conduct of patient preferences studies (29, 45, 58, 67).

Table 1. Arguments for the desired use of patient preferences in regulatory BRA and MA decision-making

³ For more information on these methodological issues, the reader is referred to the following papers referenced to in the publication cited in the text, Egbrink MO, 2014 (46): i) Mussen F, Salek S, Walker S. Benefit-risk appraisal of medicines A systematic approach to decision-making. Oxford, UK: Wiley-Blackwell; 2009, ii) Bridges JFP. Stated preference methods in health care evaluation: An emerging methodological paradigm in health economics. Appl Health Econ Health Policy. 2003;2(4):213-24, iii) Bridges JFP, Onukwughu E, Johnson FR, Hauber AB. Patient preference methods A patient centered evaluation paradigm. ISPOR Connections 2007;13(6):47-7, iv) Hauber AB, Fairchild AO, Reed Johnson F. Quantifying benefit-risk preferences for medical interventions: An overview of a growing empirical literature. Appl Health Econ Health Policy. 2013;11(4):319-29.

Arguments for desired use of patient preferences in BRA and MA	References
Patient preferences could be used because:	
Endpoints usually selected or considered do not sufficiently capture patient preference information	(46)
Patients have the unique experience of disease and benefits/risks of treatment	(30, 45, 51)
Patients are directly affected by the decision	(51)
Regulators and patients might have differing preferences	(71)
Direct involvement of patient representatives in regulatory decision-making processes might not be representative	(45, 46, 51, 64, 72)
It would facilitate integration of patient concerns into BRA	(70)
It enables a more patient-centered drug development	(43, 65)
It allows regulators to decide on MA for subpopulations	(68)
It leads to a better understanding about the decision made among stakeholders	(46, 49, 71)
It enhances consumer empowerment if patient representatives are confronted with evidence on patient preferences	(46)
It solves issue of which patients to involve directly	(46)
It allows for a formal, transparent, evidence-based, consistent consideration of patient perspectives and values	(43, 45, 46, 51, 68)

Table 2. Desired use of patient preferences in regulatory BRA and MA decision-making.

Desired use of patient preferences in BRA and MA decision	References
Highlighting the need for a treatment from a patient perspective	(48, 72)
Highlighting potential differences in views between patients and others	(24, 29, 45, 65)
Highlighting situations with need for transparent and accessible communication about the MA decision	(29)
Providing insights into how patients value clinical outcomes and other attributes	(18, 24, 46, 51, 53, 54, 66, 72)
Giving insights into how people weigh benefits and risks as the disease progresses	(45)
Providing a quantitative measure of how patients view their choices	(45)
Weighing of outcome measures/attributes	(7, 43, 62)
Weighing of different outcomes/attributes (such as risks and benefits)	(7, 24, 46, 54, 60, 68)
Providing insights into the most meaningful/most relevant outcomes to patients	(18, 24, 45, 48, 54, 66, 67)
Identification of outcome measures with less perceived meaning	(62)
Patient perspectives on other aspects of treatment (e.g. dosing)	(53)
Offering insights into the benefit-risk trade-offs that patients accept (risk tolerance information)	(24, 28, 45, 46, 48, 53, 54, 58, 67, 68)
Support for regulators to understand whether people are likely to use therapy if approved	(65)
Giving insights into how patients compare benefits and risks between treatment options	(45)
Possibility for quantitative benefit-risk modelling in complex cases and inclusion of weights to scale benefits and harms	(24, 54)
Provision of uncertainty tolerance information	(45, 67)
Support of understanding patient heterogeneity regarding outcomes	(18, 24, 29, 43, 54, 68) (29, 43, 45)
Tailoring MA decision based on subgroups with homogeneous preferences	(18, 29, 54, 68)

The desired uses are grouped into a hierarchy. This hierarchy is indicated by grey shaded cells, (=1st level of the hierarchy), no shaded cells (=2nd level of the hierarchy), tab (=3rd level of the hierarchy).

Table 3. Requirements for patient preferences in regulatory BRA and MA decision-making

Operational requirements related to patient preferences in BRA and MA	References
General operational requirements for patient preference studies	
Study objectivity	(45)
Independent design of study	(72)
Similar requirements to those of clinical trials	(24, 45)
Extensive and forward planning	(66)
Objectives and attributes should be determined before design of study	(45)
Designed based on prior literature and preference information	(24)
Clear definition of the patient sample and characteristics	(24, 45, 67)
Requirements regarding whether to conduct a patient preference study	
Decision depends on: patient population, disease community, sponsor environment, scientific issues	(45)

and process results issues	
Needs to be evaluated on case by case basis	(34)
Factors that help in this decision: drug/device and preference sensitivity of decision	(34)
Whether or not to conduct a patient preference study needs to be decided by the sponsor	(45)
Requirements related to timing of patient preference study	
Decision is appropriate topic for sponsor/FDA discussions	(24)
Decision depends on: characteristics of treatments and the disease	(24)
Needs to be decided by sponsor	(24)
Before or after pivotal trial: pros & cons	(24)
Appropriate time points during product development, possibly before pivotal studies	(29)
If in pivotal trial itself, pre- and post-evaluation of patient preferences should be done	(29)
In phase 2 or 3, although not clear what specific potential harms are and how much tolerance patients have for risk	(45)
Requirements related to the results of the patient preference study	
Stakeholders must be prepared for disappointing outcomes	(45)
Study results must be provided to patient community and public	(45)
Quality requirements related to patient preferences in BRA and MA	References
Same standards and requirements for patient preferences information as for clinical data	(24, 58)
Requirements regarding sample characteristics	
Patient should be the focus , not health care professional	(18)
If not possible to elicit from patients: eliciting preferences from proxies	(24)
Elicit preferences from patients and not from public (although more pragmatic to use public preference)	(52)
Sample should be representative of population of interest	(18, 24)
Population of interest is determined by research question	(24)
If not feasible to draw truly representative sample: sample that can yield reliable results	(45)
Preferences should come from patients enrolled in clinical trial	(69)
Preferences should come from broadier population than clinical trial population	(65)
Disadvantage when using preferences from patients enrolled in trial: bias	(24)
Sample should be diverse and heterogeneous (e.g. by large samples, setting quotas)	(24, 67)
Requirements regarding sample size	
Representative sample of adequate size so that results can be reasonably generalized to population of interest	(18)
Sufficient size to generate acceptably robust results	(45)
If subgroups: sufficient number in each subgroup	(18)
Requirements regarding the type of preference information	
Patient preference information should fit current process of drug approval	(72)
Type of patient preferences information is determined by research question	(24)
Both qualitative information and quantitative information are valuable	(18, 29, 45)
Use of clinical data to augment patient preferences data	(29, 51)
Both patient's willingness and unwillingness to accept the identified risks should be measured	(18)
Requirements regarding what type of method	
Patient preference methods should fit current process of drug approval	(72)
Authors discuss the value, appropriateness, limitations of various methods , and requirements when applying them	(18, 24, 25, 30, 48, 51, 54, 66, 67, 73, 74)
Authors refer to established good research practices by recognized professional organizations	(18, 30, 45)
Newer methods may also be acceptable	(18)
AHP and CA are appropriate and valid for submission purposes in Germany	(74)
DCE is preferred by PROTECT	(52, 73)
MDIC framework discusses factors that influence decision and a set of principles that could be used to guide the selection of methods	(24)
Requirements regarding the design, set-up and conduct of patient preferences studies	
Minimal cognitive bias by study participants	(18)
Survey by trained research staff , if self-administered: should go through tutorial	(18)
Ensure that study participants fully understand all (medical) information and features they evaluate	(18, 24, 51)
Therefore: important to define the context of the benefit-risk trade-offs, explain the level of effectiveness and the severity of treatment-related harms, and help patients conceptualize probabilities using numeric, verbal, and graphic representations of uncertainty	(18, 66)
Cope with generally low level of numeracy in general population if probabilistic measures are used	(51)
Requirements specific of type of patient preferences method are discussed	(29, 65, 66)
Requirements regarding attribute selection	

Preferences should be measured over relevant clinical domains	(18)
Clinical centered attributes versus patient centered attributes:	
Broader than clinical centered attributes to inform regulators about meaningful benefit-risk trade-offs	(65)
Patient centered attributes allow exploration of attributes meaningful to participant	(67)
Choice of attributes is critical and should be informed by:	
Literature search, qualitative studies, asking group of medical/regulatory experts to identify attributes	(24)
Patient preference study to identify attributes	(24)
Requirements regarding survey instrument	
Survey instrument should be developed with input from multiple stakeholders	(45)
Survey instrument should include screening questions, informed consent provisions, background information, training and definitions, piloting, survey questions, follow-up survey questions	(45)
Requirements regarding the analysis of results	
Sources of uncertainty be reported through CI/standard error	(18)

The requirements are grouped into a hierarchy. This hierarchy is indicated by grey shaded cells, (=1st level of the hierarchy), no shaded cells (=2nd level of the hierarchy), tab (=3rd level of the hierarchy).

2.4 Desires, expectations, concerns and requirements regarding patient preferences in health technology assessment and reimbursement decision-making

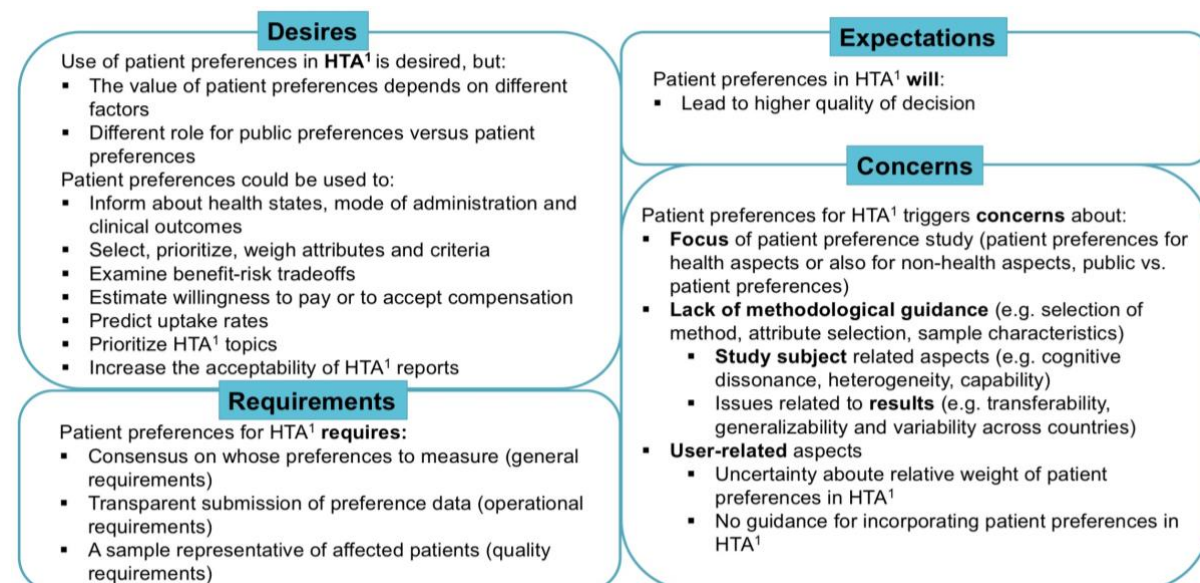


Fig. 3 Desires, expectations, concerns and requirements for patient preferences in health technology assessments

¹HTA= health technology assessment

The integration of *patient* preferences in HTA is clearly **desired** (7, 24, 25, 42, 43, 47, 55, 57, 59, 61, 74-77). Authors elaborate on reasons why integrating patient preferences could be useful in this decision-making context (Table 4). Although some authors question the representativeness of direct involvement in HTA (42, 76), it is also put forward that direct patient involvement and patient preferences are not mutually exclusive and should complement each other (42, 46). The value of patient preferences is often described to be dependent of factors or by referring to cases when including patient preferences in HTA is mostly desired. Examples include when interventions have only marginal benefits or involve trade-offs with significant positive and negative consequences (42, 76), in decisions about rare disease therapies (59), if existing research does not evidently point toward one treatment being superior or if treatment processes vary markedly (2, 62) (see deliverable 2.2). Besides the general value of using patient preferences in HTA context, many authors elaborate on their specific desired role and/or the specific type of information they could add to HTA such as the use of patient preferences to calculate Quality Adjusted Life Years (QALYs) that are then used for cost-utility analyses (52) or patient preferences to determine weights to calculate net benefit (28, 60) (Table 5). One argument against the use of patient preferences for HTA regarding

reimbursement decisions is that *public* preferences should be used instead, because HTA guides decisions about the allocation of public resources, obtained from the general public who bear the costs associated with healthcare decisions (Appendix 13, box 3) (42, 52).

Including *patient* preferences in HTA is **expected** to lead to a higher quality of the decision made and decisions that will be more likely to be accepted by the public because the ones affected by the decision are involved in the decision-making process (46). Additionally, the use of patient preferences “*will provide an extra source of evidence for the existing value dossier required for drug reimbursement*” (28).

Despite the possible role of patient preferences in HTA and reimbursement decisions, authors discuss many **concerns** relating to the use of patient preferences in HTA and reimbursement decisions. First, it is questioned whether patient preferences should only be measured for health aspects or also for non-health aspects (2). Second, there is an ongoing discussion about the use of public preferences versus patient preferences for reimbursement decision-making (2, 42, 52) which is an “*important debate because preferences might differ and making decisions based on one groups’ preferences may be suboptimal for the other group*” (52). Third, it is unclear what type of patient preference evidence (quantitative or qualitative) should be considered in reimbursement decisions; if patient preferences are incorporated in economic evaluations, quantitative preferences are recommended, whereas if they are disconnected from economic evaluation, patient preference information can also be qualitative in nature (2). Fourth, the usefulness of patient preferences information is discussed, since the transferability and generalizability of patient preferences information is limited across countries when characteristics of healthcare service and its associated benefits are being valued (i.e. these characteristics are more likely to be system, country or culture specific than data on effectiveness) (42, 77). Other factors raised by authors that might limit the usefulness of patient preferences relate to: i) the variability in patient preferences methods and results (42, 75), ii) the “*low quality of patient preference information*” (42), the validity of patient preferences information that might be endangered because of hindsight bias (42), cognitive dissonance and mechanisms of adaptation to side effects (42, 77), “*the fact that patients would not know what is good for them*” or are “*not capable of expressing their preferences*” (42) and the fact that “*patient preferences are constructed, shaped by how information is presented, influenced by many external factors and not helpful*” (42). Factors influencing the utility and role of patient preference studies are described at length in the task 2.2 deliverable (see deliverable 2.2). Fifth, the selection of a patient preference method and the lack of guidance on good research practice are mentioned (2, 28, 34). Sixth, some methodological concerns are raised: the selection of endpoints in a patient preference study and the potential negative impact of overlap between criteria (60, 62), the way questions are asked in patient preference surveys is discussed because this can affect the estimation of utilities (68) and the difficulty to balance between understandability and accuracy of questions (68). Ensuring that the sample is representative is challenging (34, 62) and treatment selection bias must be accounted for in this context (77). Neglecting patient heterogeneity is another methodological concern (43). Other concerns are: i) the lack of clear direction on where and how to incorporate research evidence on patient preferences in current procedures (2, 28, 42) and how to align with the traditional QALY calculation (42), ii) the difficulties with conducting systematic reviews on patient preferences for informing HTA (76), iii) what should be the weight of patient preferences in relation to other decision criteria (2, 42), iv) under which conditions to integrate patient preferences in HTA and reimbursement decisions (2) and v) the availability of time, funding and staff required for incorporating patient preferences in HTA and reimbursement decisions (2).

Authors discuss general **requirements**, operational requirements and quality requirements related to the use and measurement of patient preferences for HTA and reimbursement decision-making (Table 6).

Table 4. Arguments for the desired use of *patient* preferences in HTA and reimbursement decision-making

Arguments for desired use of patient preferences in HTA and reimbursement	References
Patient preferences could be used in HTA because	
Direct involvement of patient representatives in HTA and reimbursement processes is not always representative	(42, 76)
It would increase the effectiveness of patient involvement strategies	(42)
It allows readers of HTA reports to recognize that an optimal decision is not uniform across patients	(76)
It challenges the opinions on the importance of endpoints	(43, 60)
It improves the effectiveness and efficiency of healthcare interventions	(42)
It enhances consumer empowerment	(42)
Patients are the “end-consumers” of health technologies and services	(61)
It assures patient-centric reimbursement decisions	(24, 43)

It increases the transparency of decisions	(43)
Reimbursement decision-makers might not fully understand how patients see the benefit-risk trade-offs or have different perceptions about it	(24)
Patient perceptions of the added value of a technology may differ from those of physicians or other providers or decision makers	(24)

Table 5. Desired use of *patient* preferences in HTA and reimbursement decision-making

Desired use of patient preferences in HTA and reimbursement	References
Patient preferences could be used to:	
Inform HTA about preferred treatments/technologies/healthcare services and:	(50, 52, 75, 77)
Preferred health states (quality of life)	(43)
Preferred mode of administration	(43, 50)
Preferred clinical outcomes (including benefit/risk)	(43, 60, 62)
Select, prioritize or weigh endpoints and criteria	(25, 28, 60, 62)
Examine relative benefit-risk trade-offs	(52)
Estimate willingness to pay or willingness to accept compensation	(52)
Predict uptake rates	(52)
Indicate the general acceptability of a technology to patients	(24, 50, 76)
Perform cost-utility analyses	(52)
Perform cost-effectiveness analyses	(55, 60, 62)
Prioritize HTA topics	(60)
Tailor reimbursement decisions based upon patient heterogeneity	(43)

The desired uses are grouped into a hierarchy. This hierarchy is indicated by grey shaded cells, (=1st level of the hierarchy), no shaded cells (=2nd level of the hierarchy), tab (=3rd level of the hierarchy).

Table 6. Requirements for *patient* preferences in HTA and reimbursement decision-making

General requirements related to patient preferences in HTA	References
Taxonomic work for patient preferences research needed	(2, 76)
Guidance needed on:	
Good research practice and quality assessment criteria	(2, 42)
Study population: ex ante or ex post perspective	(2)
Study design	(2)
Timing of preference study	(2)
Patient preferences method	(2, 50)
Which methods to use for data retrieval and evidence synthesis	(2, 42)
Which methods to use for integrating clinical evidence into the patient preference analysis	(50)
Consensus needed on:	
The type of study population (i.e. should public or patient preferences be used) and scope of preferences (should preferences be measured for health aspects only or for issues beyond health)	(2, 42)
The conditions for use of patient preferences in reimbursement decisions	(42)
The position of patient preferences in assessment	(2, 42)
Further research needed on:	
Methods to use for integrating clinical evidence into patient preference analysis	(62)
Methodological issues such as hindsight bias, cognitive dissonance and regret	(42)
Operational requirements related to patient preferences in HTA	References
Requirements related to timing of patient preference study	
Patient preferences should be measured during marketing phase to assess long-term side effects and burden	(2)
Requirements on how to submit patient preferences data	
Description of patient preference study should be transparent: approach, choice, characteristics of participants and analysis	(50)
Quality requirements related to patient preferences in HTA	References
Quality requirements are the same requirements that apply to all research: validity and representativeness of sample	(2)
Requirements regarding sample characteristics and sample selection	
Patient preferences should come from the same population as data of effectiveness	(2)
Sample should be representative of the affected patients	(50)
Both patients in remission as well as patients in recovery should be included	(62)
Sociodemographic characteristics and characteristics of the disease should be considered in the sample selection	(55, 62)

Requirements regarding the type of preference information	
Quantitative patient preferences are more useful	(76)
Type of preference information (qualitative or quantitative) depends on whether they are needed in assessment or appraisal phase of HTA	(2)
Requirements regarding what type of method	
General requirements for each method used for HTA decisions/policy decisions:	(28)
Methods should adhere to utility theory	(28)
Methods should account for several patient-relevant attributes and outcome measures	(28)
Methods should be easy and simple for patients to understand	(28)
Choice of method depends on:	
Research question, whether disease-specific or generic measurement is needed and on interested in average patient preferences or spectrum of patient preferences	(2)
Practical considerations: e.g. ease of application	(78)
Decision context	(78)
Usefulness, advantages and disadvantages of specific patient preferences method in HTA/reimbursement decisions are discussed	(25, 28, 60, 61, 77, 78)
Requirements discussed that depend on type of patient preference method	(60, 62)
Requirements regarding selection of outcome measures	
Outcome measures should come from existing clinical trials	(62, 79)
Patient representatives, patients and experts should inform selection of outcome measures	(42, 62)
Outcome measures should not overlap	(62)
Requirements regarding survey instrument	
Questions have to be asked in an open and understandable way	(28, 50)
For choice-based preferences measures, options should:	
Be clearly described	(50)
Have realistic advantages and disadvantages	(50)
Be communicated to patients together with their characteristics	(78)

The requirements are grouped into a hierarchy. This hierarchy is indicated by grey shaded cells, (=1st level of the hierarchy), no shaded cells (=2nd level of the hierarchy), tab (=3rd level of the hierarchy).

3. Semi-structured interviews

Introduction to results

Structure of results section. Results were analysed per theme and per stakeholder group, which is also how the results section below is structured. Below each theme, a summary describing the interview results for that specific theme across all stakeholder groups is given (blue boxes). Below the blue boxes, the same theme is discussed per stakeholder group in more detail. Any differences that were identified during the analysis that are country-specific or disease-specific (for patients) within a particular stakeholder group are indicated. Codes following the quotations refer to the interviewee's characteristics and are formatted in the following way: i) stakeholder group in which the interviewee was labelled, ii) country the interviewee was recruited from and iii) ID number of the interviewee (e.g. AC_NL_12 means Dutch academic with ID number 12).

Preference terminology. It is important to denote that interviewees had a variety of definitions in mind when talking about 'patient preferences', which might have coloured the results described below. Furthermore, differences in familiarity with patient preferences and methods might have contributed to differences in definitions of 'preferences' interviewees were referring to when talking about preferences throughout the interview. A definition derived from the FDA definition⁴ was provided to interviewees in the beginning of the interview to denote patient preferences in a more precise way.

Demographics of interviewees. One hundred and forty-three semi-structured interviews were conducted. The following stakeholders were interviewed: HTA/reimbursement representatives (n=24), regulators (n=23), industry representatives (n=24), academics (n=24), physicians (n=24), patient representatives and patients (or their caregivers when appropriate, n=24). Interviewees were recruited from seven European countries (Sweden, Romania, Italy, the UK, the Netherlands, Germany, France) and the U.S. (Table 7).

Table 7. Demographics of interviewees (n=143)

	Stakeholder group									
	PA, PO and CA (n=24)					IN (n=24)	REG (n=23)	HTA/ reimbursement (n=23)	PH (n=24)	AC (n=24)
	PA (n=14) n %	PO (n=8) n %	CA (n=2) n %			n %	n %	n %	n %	n %
Country										
Italy	3 21%	1 13%	0 0%			4 17%	4 17%	4 17%	4 17%	4 17%
Romania	3 21%	1 13%	0 0%			4 17%	3 13%	4 17%	4 17%	4 17%
Sweden	3 21%	1 13%	0 0%			4 17%	4 17%	4 17%	4 17%	4 17%
the UK	2 14%	1 13%	1 50%			4 17%	4 17%	4 17%	4 17%	4 17%
France	1 7%	1 13%	0 0%			2 8%	2 9%	2 8%	2 8%	2 8%
Germany	1 7%	1 13%	0 0%			2 8%	2 9%	2 8%	2 8%	2 8%
the Netherlands	1 7%	1 13%	1 50%			2 8%	2 9%	1 8%	2 8%	2 8%
the U.S.	1 7%	1 13%	0 0%			2 8%	2 9%	2 8%	2 8%	2 8%
Disease area										
LC	4 29%	2 25%	0 0%			NA	NA	NA	6 25%	NA
RA	4 29%	2 25%	0 0%			NA	NA	NA	6 25%	NA
MD	2 14%	2 25%	2 100%			NA	NA	NA	6 25%	NA
CVD	4 29%	2 25%	0 0%			NA	NA	NA	6 25%	NA

Abbreviations: PA= patients; PO= patient organization representatives; CA= caregivers; IN= industry representatives; REG= regulators; HTA= HTA/reimbursement representatives; PH= physicians; AC= academics; LC= lung cancer; RA= rheumatoid arthritis; MD= myotonic dystrophy; CVD= cardiovascular disease; PP= patient preferences; NA= not applicable.

⁴ Academics, regulators, HTA/reimbursement representatives and industry interviewees were presented with the following definition: "The relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions. In other words, patient preferences are the basis of how patients choose a particular treatment over others. To make a choice, patients make trade-offs between a treatment's characteristics, weighing its advantages and disadvantages collectively." Patients, physicians, patient organization representatives and informal caregivers were presented with the following definition: "Patient preferences reflect why patients choose a particular health treatment over other available options. This health treatment can be a drug or a medical device. A preference can be stated for a health treatment as a whole or for the advantages and disadvantages of one treatment. In order to make a choice or state a preference, patients need to weigh up the advantages and disadvantages and compare them to those of other health treatments."

3.1 Stakeholders' definition of patient preferences

First, when asked about their spontaneous definition of patient preferences, stakeholders across different stakeholder groups and countries used a variety of related terms to define patient preferences; patient preferences were defined as patients' choices, decisions, trade-offs, perspectives, values and priorities. Amongst different stakeholder groups, a polarization could be made regarding the scope of the term patient preferences; with the majority of them spontaneously adopting a broad definition (e.g. patient preferences are patient perspectives regarding medical products) rather than a focused definition (e.g. patient preferences are trade-offs regarding treatment outcomes). The majority of stakeholders agreed to the definition³ they were presented with afterwards. Stakeholders from all stakeholder groups pointed out the challenge of defining patient preferences.

First, when asked about their spontaneous definition of patient preferences, **three out of twenty-four academics** pointed out the challenge of defining patient preferences. Academics spontaneously defined patient preferences in a variety of ways, with several terms returning multiple times. According to academics, patient preferences evolve around patients' choices, trade-offs, patients' perspective, patients' values, priorities, decisions. The majority of academics embraced a broad definition of patient preferences and thought of patient preferences as a synonym for the **patients' perspective, attitudes, desires and what patients find important**. Two academics adopted a more focused definition of patient preferences and referred to economical terms such as **utilities and "trade-offs patients are willing to make between favourable and unfavourable effects of treatments"** (AC_NL_12). A similar polarization among academics was observed about the subject of patient preferences: while the majority of academics defined patient preferences around patient choices and the final decision outcome of the decision-making process: *"what everybody is choosing when they need to use a drug or a medical device"* (RO_AC_21), three defined patient preferences as the decision-making process leading up to the final decision made: *"I would think about the process that individual will follow in order to reach that particular decision"* (AC_UK_22). When presented with the definition⁵, a similar categorization could be made, with the majority of academics agreeing to the definition. Reasons why the other academics did not agree to the definition³ they were presented with included the focus of the definition and/or the fact that according to them, the definition is guided too much by the benefit-risk framework: *"I think I would prefer a definition saying the relative desirability to patients of specified alternatives among alternative health interventions. Then the patient has to do the inference about outcomes because in this definition outcomes is considered as certain"* (AC_SE_24). Three academics underlined the importance of not singling out a specific patient preference elicitation method in the definition: *"they've got through exactly the same thinking as I was trying to go for and they've avoided putting it down too much to one methodology or another, which I think is also necessary"* (UK_AC_23).

Also among HTA/reimbursement representatives, four out of twenty-four underlined the difficulty in defining patient preferences. HTA/reimbursement representatives defined patient preferences in different ways, with the majority of them defining patient preferences **broadly**, around what patients want and value in medical products: *"how the patients perceive the technologies and what this technology gives to them in terms of quality of life, of better health, better way of living"* (HT_IT_14). Only three adopted a more **specific** definition and used terms like 'weight' and 'trade-offs' to define patient preferences: *"the expression of patients concerning the weight they give to certain dimensions of treatment"* (HT_FR_7). One HTA/reimbursement representative considered the definition of patient preferences to be **completely integrated** in their existing definition of the QALY: *"so my definition of patient preference, all the questions of preference, (are) included in the health outcome in the QALY"* (HT_FR_8). Although most HTA/reimbursement representatives agreed to definition³ they were presented with, they also pointed out the importance of having an expanded definition, not implying only quantitative methods: *"maybe this definition implies an attempt to measure quantitatively the patient preferences. This is my impression because if you are think about a trade-off I think that this kind of definition is really, really connected to a quantitative view of patient preferences which is not the only one existing"* (HT_IT_14).

⁵ Academics, regulators, HTA/reimbursement representatives and industry interviewees were presented with the following definition: *"The relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions. In other words, patient preferences are the basis of how patients choose a particular treatment over others. To make a choice, patients make trade-offs between a treatment's characteristics, weighing its advantages and disadvantages collectively."*

Among industry representatives, a **variety** of definitions was used but with many terms in common; patient preferences were defined as patient perspectives, patient needs, patient feelings, patient choices, patient priorities. Four industry representatives had **difficulties** in exactly defining patient preferences, with a majority defining patient preferences **broadly**, e.g. *“around how they are most impacted by the treatment or the disease and then how does that impact their quality of life. It is really understanding their life experience and then figuring out, well what’s up?”* (US_IN_10) Only one industry interviewee defined patient preferences in a more focused way: *“To me that’s how patients trade off different attributes of treatments in health-related interventions”* (IN_UK_19). Overall, industry representatives agreed to the definition³ they were presented with, with three of them pointing out that it needed simplification when presented to patients and two of them pointing out that definition³ they were presented with is more about existing therapies than with development of new therapies: *“it has less to do with development of new therapies and more to do with existing therapies”* (IN_NL_11).

Six out of twenty-four regulators underlined the **difficulty** in defining patient preferences and used different but related terms to define the concept; patient preferences are patients’ perspectives, patient expectations, patient acceptance, patient priorities towards medical products. The majority of regulators stated a **broad** definition: *“a subjective feeling of the patient concerning the medical intervention”* (RE_FR_6). Conversely, three of them employed a more **focused** definition: *“You might ask [...] what aspects of your disease would you most like to have treated by a drug and we are not thinking of that as preferences”* (RE_US_6). Three regulators stated they did **not have a definition of patient preferences**, with one regulator stating it was because he was against the operative concept of patient preferences: *“To me patient preference means nothing. So, I don’t have a definition”* (RE_IT_10). The majority of regulators agreed with the definition³ they were presented with but many pointed out the complexity of it, and that it needed to be simplified when communicated to patients.

Patients and caregivers defined patient preferences broadly around **patient choices** regarding medical products: *“I’m thinking it’s when the patient has to choose between several medicines for the same disease”* (PA_RO_9). Three of them defined preferences as the eventual result of the decision-making process; *“The collected data are symptoms”* (PA_DE_1). Most patients agreed with the definition⁶ they were presented with. **The majority of patient organization representatives** defined patient preferences around the choices patients would make and what patients would like to see as regards to their treatment. Overall, they agreed to the simplified definition³ with one pointing out that the definition is based on the fact that there are multiple available treatment options for a certain disease, which is not always the case.

The majority of physicians defined patient preferences broadly around treatment choices: *“what my patient chooses and say is preferable when discussing the alternatives”* (PH_SE_8). Two physicians were completely **new to the topic** and had not thought about it prior to the interview. Similar to patients, two physicians tended to define patient preferences as the **actual** preferences patients have: *“Patient preferences is the wish to be cured”*. (PH_NL_3) One physician specifically related patient preferences to quality of life, and two physicians stated that patient preferences are actually related to or mirror the **physicians’ preferences**: *“Preference is actually related to what the doctor proposes”* (PH_IT_8) Physicians overall agreed to the definition⁴ they were presented with, with three suggesting to include the no-treatment option. One physician was explicitly against the definition⁴ presented, as it assumes patient knowledge: *“Patients cannot express a preference because they are not properly informed of the prognosis for their illness [...] So, if understanding of the prognosis is lacking, how would they be able to come to a correct understanding of the drug and the drug’s efficacy?”* (PH_IT_5)

⁶ Patients, physicians, patient organization representatives and informal caregivers were presented with the following definition: *“Patient preferences reflect why patients choose a particular health treatment over other available options. This health treatment can be a drug or a medical device. A preference can be stated for a health treatment as a whole or for the advantages and disadvantages of one treatment. In order to make a choice or state a preference, patients need to weigh up the advantages and disadvantages and compare them to those of other health treatments.”*

3.2 Stakeholders' general attitudes towards integrating patient preferences in decision-making throughout the medical product life cycle

The majority of stakeholders across different countries had a positive attitude towards the general concept of “patient preferences” in the MPLC, as patients are the final user of health care and have unique insights and disease experience. However, diverging opinions were expressed about implementing patient preferences in industry, regulatory MA, HTA or reimbursement decision-making. Patients' lack of knowledge about scientific and technical aspects, as well as questions regarding how patient preferences could be incorporated into current decision-making processes, and whose preferences should be used to inform decision-making were reasons why stakeholders from all stakeholder groups doubted the usefulness and feasibility of including patient preferences in decision-making. Industry participants appeared to be the most positive stakeholder group towards using patient preferences in the MPLC. All stakeholders, particularly regulators, agreed that the value of patient preferences in decision-making depends on factors such as the development stage and the type of medical product.

Although most **academics** were positive about considering patient preferences at some point along the MPLC, six out of 24 academics were hesitant or against including those in regulatory MA or HTA/reimbursement decision-making. Reasons why academics advocated using patient preferences at some point in the MPLC included the fact that patients are the **final user** of healthcare, using patient preferences would **increase adherence**, and because it would **prevent resource misallocation**: *“I think products that have been developed using patients in the entire process will be more warmly greeted within the group of patients that are supposed to use it” (AC_SE_22)*. Several academics underlined that patient preferences are just one piece of evidence and their use in decision-making has to be determined on a case by case basis: *“It's a bit like putting on the shelf so that people can buy something or can use it, that's not the same thing as they absolutely should in all circumstances” (AC_UK_23)*. One reason mentioned by academics for not considering patient preferences in decision-making is the **lack of technical knowledge among patients**: *“I don't think this will ever be possible, because of the differences in the knowledge” (AC_RO_23)*. Furthermore, one academic stated that for reimbursement decision-making, the added value of including patient preferences is compromised because patient preferences are **influenced** by emotional aspects and therefore are a less reliable source of information: *“The problem in the case of reimbursement, (is that) patients are too much emotional so to say” (RO_AC_22)*. Moreover, one academic was doubtful because of the **unresolved question of whose** preferences should be elicited for decision-making: *“Until you can define 'patient' properly I'd struggle to know that that would be generalizable and like I think I personally would have a preference for doing public so - I feel like preferences are important it's just whose preferences then I'm worried about” (UK_AC_21)* and one academic doubted the relevance of patient preferences for MA decisions as there is *“enough evidence to make this decision without the preference aspect” (AC_FR_12)*. Another academic explained how the value of patient preferences in the current MA procedure **depends on the role of regulators** and because in the current system, regulators are in charge of performing benefit-risk assessments instead of patients, the value of patient preferences is low: *“If you are looking at the current system where regulators are doing the benefit risk assessment, I think there is not that much value in having patient preference studies conducted because I don't think it will affect many of the decisions being made [...] but if it is becoming a bit more liberal and the role of the regulators would change then it could be more useful” (AC_NL_12)*. Nine academics **advocated** using patient preferences **in all decisions** across the MPLC, including early development decisions, MA and HTA and reimbursement decisions, as *“there is a benefit risk trade off and that's a value judgment and these value judgments should not be done by expert panels, they should be informed by evidence which is elicited from patients” (DE_AC_11)*.

Most **HTA/reimbursement representatives** were supportive of using patient preferences for HTA and reimbursement decisions. Reasons why they believed patient preferences are important included the following: patients are the **end user** of healthcare; **patient's adherence** to treatment will increase; patient preferences are part of the definition of **evidence-based healthcare**; patient preferences provide **critical information** that is not captured in clinical evidence and patients are the **ones affected by those decisions**: *“In the world of HTA, where we are, it is very difficult and also societally unacceptable to not take patient perspectives into account because we are making decisions on policy on a national level which involves patients themselves” (HT_NL_8)*. The remaining reimbursement representatives doubted using patient preferences in HTA and reimbursement decisions for different reasons: i) objective decision criteria such as **efficacy, cost-effectiveness and sustainability** are more

important: “I believe that outcomes should be more objective measures than asking the patient” (RO_HT_14), ii) the **societal perspective** is more important and should be considered instead of the individual patient preferences and iii) **methodological shortcomings** for measuring patient preferences: “So if the preferences [...] could be verified with respect to validity of the research methods to the generalizability, the reliability of the questions, then they could be used as another knowledge source to be added to critical literature” (IT_HT_13). Two reimbursement representatives were unsure about using patient preferences for HTA and reimbursement decisions because of the question **how** patient preferences could step into the HTA/reimbursement **process** and what weight they should receive: “What is difficult in this question is the question of measure. It is obviously important to have some information about preferences, and in what circumstances this would make good measure if it is possible, or if it is not too difficult” (HT_FR_7).

The majority of industry representatives agreed on the importance of using patient preferences across the MPLC: “So if we don’t include their preferences, I mean, why on earth would we bring something to the market [...]” (IN_NL_10) Reasons why patient preferences according to them should be considered include: patients are the **end user** of healthcare and **only the patient knows** what is best for him/her: “I think there is a paternalistic view that everybody has had so far that we know what is best for others. And the same can be applied to regulators and other groups. We cannot read patients’ minds. We need to ask them” (IN_US_9). Despite their positive attitude towards considering patient preference along the MPLC, seven industry representatives were hesitant about actually using them for decisions regarding MA or pricing and reimbursement, mainly on the grounds that patients **lack knowledge** about the scientific aspects of medical products and budget implications: “I don’t think there is time enough out there to actually engage the patient and to involve it, and sometimes it’s not possible because the educational level of a patient is maybe low” (IN_SE_18). Twelve industry representatives underlined that the **value and weight of patient preferences in the decisions** depends on several factors (e.g. the stage of the MPLC, the decision-making context, type of medical product and disease area) and remains an unresolved question, as we “have to put some weighting on the patient preferences” (FR_IN_10).

Although the majority of **regulators** adopted a positive attitude towards the concept of patient preferences in the MPLC, half of the regulators explained how and which factors impact the importance and relevance of using patient preferences for regulatory MA decisions such as the **clarity of the B/R balance**, **type of product**, the **severity and type of condition**, the **disease area**, the **regulators’ familiarity** with the product or disease area (e.g. when the MA decision has to be made about a medical product in a saturated market space) and related to that, the **rarity** of the disease of the medical product under review: “For some products it will be absolutely important, probably the crucial decision-making issue, for others it is probably nice to have but not that important, we could well do without” (RE_DE_5). Factors influencing the utility and role of patient preference studies are described at length in the task 2.2 deliverable (see deliverable 2.2). Ten regulators were clearly positive and argued that considering patient preferences for the regulatory MA decision “is necessary and probably is - should be one of the points in every decision” (RE_RO_9), as “it improves the credibility of your overall system” (NL_RE_6). Conversely, two regulators explicitly refused the idea of including patient preferences in the regulatory context on the grounds that patients lack technical knowledge and that their preferences are subjective and prone to emotional biases: “I think at the moment at least I see no major role for them to be honest [...] I think patients in general will overemphasize the benefits and reduce the side effects” (RE_NL_5). Two regulators doubted the **feasibility** of including patient preferences into the current **framework**: “I’m not really clear [...] where patient preferences would fit in with our evaluation of benefit-risk” (RE_UK_9). Several regulators underlined the necessity of educating patients prior to asking about their preferences.

All patients and caregivers found patient preferences to be important as patients are the **end-user** of healthcare, it would **empower patients** and it is in line with **democracy** principles: “The patient is a sort of client and the opinions of this ‘client’ should also be taken into account” (PA_RO_2). On the other hand, two patients were doubtful about using patient preferences in scientific discussions because of the perceived **patients’ lack of technical knowledge**: “I’m not a lab technician so asking me my preference on how something is done in a lab [...] would be almost detrimental” (PA_UK_3). Similarly, one patient stated that as a condition for using patient preferences, patients should **educate** themselves about the treatment and its side effects. The majority of patient organization representatives advocated using patient preferences in decisions across the MPLC, as patients are the concerned people and the ones with the disease experience. However, one patient organization representative doubted the role of patient preferences in the **economic sphere** because patients do not look at price and budget implications: “He would say, the best for me and what helps me the most, no matter how expensive” (PO_DE_2). One patient

organization representative was unsure about the role of patient preferences because of the difficulty in finding a **representative patient group**.

Mirroring physicians' definition of patient preferences, physicians thought about patient preferences mainly in the context of **individual treatment decisions**, rather than in the context of using them for developing and evaluating medical products. The majority of physicians thought having the patients' views on treatment decisions is important, because it affects compliance to medical regimens. However, when talking about using patient preferences for medical product development and evaluation decisions, four physicians doubted their relevance on the grounds that **objective criteria are more important**, the fact that there is **no space** for using patient preferences in the current system, that patients are **not realistic**, that they **lack scientific knowledge** and that patient preferences have a lot of **subjective** elements: *"But how can the patient interfere in these processes? They have no opportunity to. The process is an obligatory process because it is a pharmacological process, that is, there is no opportunity for the patient to have an influence"* (PH_IT_5).

3.3 Stakeholders' needs for integrating patient preferences in decision-making throughout the medical product life cycle

Stakeholders emphasized the following needs for integrating patient preferences in decision-making throughout the MPLC: i) a higher awareness and acceptance amongst stakeholders of the concept of patient preferences and ii) more education towards stakeholders on the concept of patient preferences, their potential role in the MPLC and how to collect and take into account patient preferences. This need was raised by all stakeholders across different countries, except for physicians. Another requirement which represents a common ground between stakeholders was a strong demand for scientifically sound methods that can function as methodological standard and can lead to valid, reliable and generalizable preference information. The importance of these methodological aspects was stressed by all stakeholders except patients and was considered particularly important by academics, industry members and HTA/reimbursement representatives who called for clear guidance on quality criteria to evaluate patient preference studies. HTA/reimbursement representatives, industry members and patients highlighted the need for a change in legislation and a clearer regulatory framework.

Academics raised a need for a higher **awareness and acceptance** of the concept of patient preferences among stakeholders: *"generally just openness from the research society I guess. Researchers need to acknowledge the possible effect that it can actually have to include patients"* (AC_SE_22). More specifically, a need for more **education** and training opportunities for decision-makers and researchers was called for by three academics: *"so a lack of training opportunities which means that the demand for these studies is growing faster than our capacity to satisfy the demand. I think that is a serious problem"* (AC_US_12). One academic raised a need for a **clear terminology** about patient preferences: *"a kind of general alignment of what patient preferences are"* (AC_IT_24). Academics also raised a need for **clear methodological standards** and **guidance** that helps answering the question: what constitutes a good patient preference study aiming to inform decision-making?: *"if those studies are used to inform real life decision-making, then I think there should be a sort of Vade Mecum in which we say these are the pros and cons of different methods"* (AC_IT_21). This guidance should come from **regulators**, according to three academics: *"we need to have some rules, clearly defined, telling you in what process you involve the patients, how representative they should be, I mean how large a sample population should be, to what extent you involve them and so on. So, I think that the regulatory framework is most important"* (AC_RO_22). Correspondingly, five academics underlined the need for a better characterization of the **reliability, validity, reproducibility, generalizability** of patient preference methods: *"we know little about the reliability, the reproducibility etcetera. So, we need to have a better understanding there. Today it is an academic work, sometimes it is a commercial work but it has little weight on policy decision making because of those reasons"* (AC_FR_11). Finally, three academics highlighted a need for **more best practices** of patient preference studies.

Similar to academics, **HTA/reimbursement representatives** expressed a need for a better **understanding, awareness and education** about the meaning and possible role of patient preferences among stakeholders: *"it is a general understanding and a general acknowledgement of the importance of patients' preferences [...] the usual understanding is that it is not in the heads of the decision-makers"* (HT_DE_8). Four HTA/reimbursement representatives felt that incorporation of patient preferences in HTA and reimbursement decisions requires a cultural

change: *“I think there is a big cultural issue about the value that is placed on this kind of data” (HT_UK_14).* Furthermore, HTA/reimbursement representatives underlined the need for **scientifically strong methods** and talked about the need for **validating** and **standardizing** the methods for collecting patient preferences: *“there are a lot of questions on methodology, there are a lot of questions on consensus among a wider stakeholder group and standardizing the methods” (HT_NL_8).* HTA/reimbursement also expressed a need for a **better understanding of the quality criteria** for patient preference studies. Next, two HTA/reimbursement representatives spoke about the need for **more** patient preference studies to be conducted and **published** in order to validate the methods and to be able to use them as input for HTA and reimbursement decision-making. Five HTA/reimbursement representatives expressed a need for a **higher understanding on how to integrate** patient preferences in the current decision-making frameworks: *“so it will be important to have ideas concerning the connection between patient submission or patient preferences, and the traditional criteria of the Committee. Also, [...] the articulation of the economic evaluation [...] It would be interesting to have a clear speech, a clear explanation to articulate the two to explain how it is complementary and not a substitute. [...] I mean that there is a pedagogic effort to explain the complementary between the two” (HT_FR_7).* Lastly, five HTA/reimbursement representatives stressed that a **clear framework** is needed to integrate patient preferences in decision-making: *“so we need to develop a framework that explicitly can be used as such pilot guidelines [...] I think that we are now not in the intermediate phase but we are in the first phases of pilot studies. We need more and more pilot studies in order to read this framework” (HT_FR_8)* and one reimbursement interviewee stated integrating preferences would require a change in the **law**: *“I don't see a way where for example the [name of HTA body] would start introducing something - an extra dimension regarding evaluation, unless they are told to do so by the government” (HT_SE_14).*

The majority of **industry representatives** stressed the need for a **higher acceptance** of the concept of patient preferences by all stakeholders: *“I think without the buy-in or without the alignment of all the different stakeholders in the development chain, you will not succeed” (IN_SE_20).* More specifically, four industry representatives raised a need for a **clear recognition of patient preferences by decision-makers** and a higher certainty that industry investments in patient preference data would not be a waste of money: *“If it's completely unclear whether the patient preference study will be considered by the regulators and the HTAs, it is more difficult to invest the money in this study than investing it in the pharmacokinetic study that is required by guidelines or in another study that will be more accepted by the regulator” (IN_DE_9).* For this very reason, two industry representatives suggested that patient preference studies should be made **mandatory** by decision-makers. Four (among which 3 Romanian) industry representatives suggested this recognition could be achieved via the set-up of a **clear regulatory or legislative framework**. Furthermore, eight industry representatives highlighted a need for **standardization** and **harmonisation** of patient preference methods, enabling all sponsors to collect patient preferences in the same way. Four industry representatives mentioned this **standardization** could be achieved by setting-up (regulatory) **guidance** on how to measure patient preferences for decision-making. Lastly, three industry representatives spoke about the need to **reduce barriers for industry to approach patients** for patient preference studies: *“we have to make sure that we have legislation that makes sure that you prevent, protect the individual rights of patients but that is also assisting us to make sure that we can include patient preferences in a decent manner at every level. So, regulatory and compliance and the whole framework over there should be able to help us out and not just always make it harder to do so” (IN_NL_10).*

Regulators were adamant about the need for **scientifically strong methods** that yield **robust and high-quality** preference data: *“I think we are still confronted with questions on how valid is you know patient data, patient input so I think that there is a need to validate the data as much as possible [...] If we were provided with robust, validated patient preference data, we would use it more systematically” (RE_UK_10).* More specifically, regulators highlighted a need for **validating and practicing the methods** to measure patient preferences and underlined the importance of eliciting patient preferences from a **representative** sample: *“more practical examples where this has been formalized and also have more insight and validation of the methodologies to be used” (RE_NL_5)* Moreover, four regulators underlined that patient preferences need to be **unbiased** and free from any **conflict of interest** between patients, patients' advocacy groups and pharmaceutical companies: *“So it's all about conflicts of interests, so all patients interviewed and asked should be free of potential conflicts of interests. That's one major aspect” (RE_DE_6).* Two US regulators specifically raised the need for patient preference data to be applicable for the **MA decision**: *“It would have to sort of be applicable to the considerations that are being looked at in the context of a given review” (RE_US_6).* One regulator raised a need for **more proof** of the added value of including patient preferences in medical product development and decision-making: *“the most important things will be to be able to show that those decisions [...] that are taken with patients are better decisions in terms of given end points and in*

*the interest of patients themselves as compared to decisions that are taken [...]without patient involvement” (RE_IT_10) Finally, three regulators underlined a need for more **education** about the concept of patient preferences: “And then as an education piece; I have no formal training on what a patient preference is [...] So I think it’s something that most regulators have heard of, but I don’t think we have a formal understanding of what it is” (RE_UK_9).*

Needs were addressed and discussed by six **patients**, as several patients perceived the topic as very technical and therefore outside their ability to contribute. Two patients raised a need for **patient education**, one patient underlined that the added value for patients needs to be made clearer when entering the study and one caregiver mentioned the need to **disclose data to patients** of patient preference studies. Needs expressed by patient organization representatives included: a **flexible approach** and **combination of different methods** to measure preferences, a **change in legislation** in so that patients are numerically more represented in decision-making instead of one patient representative for all patients, strategies **to incentivize patients** to participate in preference studies and the need for a **cultural change among physicians**, namely a shift in attitude towards a greater acceptance of preferences: “I am not saying that they will say “Ah, of course, I want patients” but they start to think ‘maybe the patient is not so useless and maybe they actually have something to tell me’, but this is a cultural change, and this is absolutely the most difficult thing” (PO_IT_1). Lastly, one patient organization representative claimed the need to make preference studies **diagnosis-specific** and **to involve patient organizations** in the design of preference studies.

Needs were addressed and discussed by five physicians, of which two mentioned a need for more **work on the methods to measure** patient preferences: “I think we really have a lot of work to do on the methodology we select - all the questions that you’re asking, how to select patients, how to question them, what information we give them beforehand. Then this allows us first to work within the given framework and receive more substantial recognition for the studies that are carried out” (PH_FR_4). One physician spoke about the generic needs for conducting studies, applicable to all types of studies such as **money, logistics and collaboration**. Another physician underlined the need for a **clear benefit for patients** when entering a patient preference study.

3.4 Stakeholders’ concerns for integrating patient preferences in decision-making throughout the medical product life cycle

The most recurring concerns amongst stakeholders were lack of standardization and consensus on methodological aspects due to the novelty of the field. This was mentioned by all stakeholders and across different countries except patients and patient organizations representatives. Concerns about not having a clear guidance on how to incorporate patient preference data in the existing framework and on how to weight this data with the traditional criteria were commonly mentioned by academics, HTA/reimbursement representatives, physicians and regulators. Apprehension about a possible risk of pharmaceutical companies influencing patient preference studies or direct them to conform to their finically driven agenda was expressed by physicians, regulators and patients/patient organization representatives. Finally, a lack of patients’ knowledge and education was considered a concern by regulators and patients/patient organization representatives.

Academics were mainly concerned about **methodological aspects**. Their concerns mostly related to: i) the **novelty of the research field** (e.g. a lack of **guidance** and **consensus** on how to measure patient preferences), ii) the **study design** (e.g. risk of selecting the wrong endpoints, attributes and levels and the risk of introducing bias in the study and iii) traditional scientific aspects such as the **validity** and **robustness** of preference research: “it is very easy to, well maybe not very easy but I think it is easy, to get the results you are interested to and not the objective truth, but the way you formulate your questions and select your patients and so on” (AC_RO_22). Five academics expressed concerns about not reporting patient preference research **transparently** as well as concerns related to how patient preference data could align and should be **weighted** together with other decision criteria. In this context, one academic was concerned about the risk of **misusing patient preference data** to overcome other aspects of technologies in decision-making: “There could be a concern on misuse of patient preference when they are used to overcome other important aspects of the technology [...] we need to be careful and then put everything into perspective that there are also key addition endpoints that must be preserved and taken into account on top of

other elements of patient preference” (AC_IT_24).

Concerns of **HTA/reimbursement representatives** could be grouped into concerns related to i) the **novelty** of patient preference research (e.g. lack of **experience** among researchers), ii) the **design** and conduct of patient preference studies (e.g. **uninformed patients**, the risk of **influencing** preference research and **sample representativeness**), and iii) the methods for measuring patient preferences (e.g. a lack of **standardization** and **confidence in methods** to measure patient preferences): *“it has been show that if you repeat these methods with the same people that sometimes you get different answers each time; so the sort of reliability isn’t necessarily there [...] You also have the various forms of bias going on, so respondents may attach value to two attributes to make each decision simpler and that they are purely basing their decisions on one or possibly two dominant attributes” (HT_UK_13).* When talking about using patient preferences for HTA/reimbursement, two HTA/reimbursement representatives worried about the **risk of creating disparity between disease areas**: *“This is a situation which in my opinion is completely illogical because it favors that group of patients for the sole reason that they prefer it that way and they’ve been able to influence because of they have a very strong patient organization” (HT_SE_14).* Lastly, three HTA/reimbursement representatives were concerned about how patient preferences fit in the current HTA/reimbursement **processes** and with traditional decision **criteria**.

Thirteen out of 24 **industry** representatives reported concerns related to: i) a lack of **standardization** and **consensus** on how to measure patient preferences, ii) the **patient sample** (e.g. a lack of **knowledge and education** level of patients, **sample representativeness** and **sample size**) and iii) the **validity** and overall **quality** of patient preference information: *“I think that my concern would be that I’m not aware of a single tool, or any standardization amongst tools to help make patient preferences more comparable and therefore decision-making more consistent” (IN_UK_18)* One industry representative worried about how to deal with **unexpected results**: *“It would be easy if patient preferences studies match our own vision on what we are doing. But what if they don’t match? If they give a different point of view and it doesn’t really fit in our advantage, how will we deal with it?” (IN_NL_10)*

Four out of 19 **regulators** expressed concerns about pharmaceutical **companies influencing** patient preference research: *“we would also want to be somewhat careful [...] I think that you don’t frame questions in a way that people who are [...] fairly desperate for treatment are not [...] you are not playing into the biases and judgements that are well understood [...] if a company is trying to persuade the regulator that something that is actually quite potentially dangerous” (RE_US_6)* Two regulators particularly worried about **patients not understanding questions in patient preference studies**: *“My concern is that the patients do not have enough information on what they are asked to compare, or to trade off” (RE_UK_12)* Other concerns related to: i) the fact that patient preferences are influenced by **unreliable sources** (e.g. media), ii) the scientific aspects of patient preference methods (e.g. **generalizability**, **validity** and **robustness** of methods) and iv) the **weight** of patient preferences in the decision; four regulators stressed that patient preferences should not completely guide the decision and three regulators worried about pharmaceutical companies **misusing** patient preferences to *“circumvent the normal regulatory process” (RE_UK_9)* or as *“an element to have the easiest routes to starting the marketing of the drug” (RE_IT_11).* Conversely, five regulators were positive and did not express concerns related to using patient preferences in regulatory decisions: *“So no I don’t have any; anything preventing me from accepting the idea of patient preferences incorporated into the process” (RE_FR_5).*

Out of eight **patients and caregivers** expressing concerns about measuring and using patient preferences in developing medical products, three were concerned about the **industry’s financially driven agenda** that may drive patient preference studies instead of genuine interest in hearing patients’ perspectives for development: *“when it comes to research, of a purely general kind like this one, you can’t just ignore answers you don’t like. You’ve got to include them, even if they point to something you might not like. When it comes to making a profit, when companies start getting involved in things other than purely medical research, that’s where I think things tend to go wrong a little. I realize they’ve got to think of the finances, but I think it’s wrong” (PA_SE_2).* Three patients worried about **confidentiality** of patient preference data. Concerns that were mentioned only once by patients and caregivers included: i) a lack of **patient knowledge** due to a lack of **information given to patients** about the study objectives and results: *“patients may need to know more, but it may be impossible for us to find out what went on before the study started, what they’re researching, and what results they’ve come up with” (PA_SE_1),* ii) leaving out certain groups of patients from the preference study based on the hospital they go to, iii) patient preferences being used as the only determinant of decisions: *“A preference is important but that shouldn’t be the final decision-point,*

*obviously the scientific side of things needs to come to it.” (PA_UK_2), iv) the reliability of patient preferences as they are influenced and destabilized by different factors such as time and emotional aspects: “So it depends on the mind-set of the day, so actually talking about patient preference you might get a snapshot in time” (PA_UK_3), v) the burden of patient preference studies on patients and related to that, the effect of this burden to the data gathered in preference studies (PA_UK_3). Among nine patient organization representatives, three worried about the **wording and complexity of the questions** in patient preference studies and the **level of patient knowledge**. Two patient representatives worried about **data privacy and confidentiality** of patient preference information. Concerns that were mentioned only once included: the tight European regulation as a **barrier for interaction** between industry and patients, the **resistance of health care professionals** towards including patient preferences and **not including all relevant stakeholders in the design** of patient preference studies.*

Out of 13 **physicians** expressing concerns about measuring and using patient preference in developing medical products, seven were apprehensive about the **risk of influence** and bias in patient preference studies (e.g. by question framing) and the role of the **commercially driven agenda** of pharmaceutical companies conducting patient preference studies: *“There is a science to it and it is important but [...] it can be influenced; the answers can be influenced in a lot of different ways” (PH_US_3)*. Three physicians worried about the **reproducibility** of patient preference studies because patient preferences are influenced by factors such as socio-cultural status, disease status, psychological and emotional factors and time: *“I suppose of assessing the reproducibility as well of given responses (...) how can you measure how variable somebody's response may be from one day to another or one week to another?” (PH_UK_7)*. Furthermore, five physicians were concerned about **not informing or educating patients** prior to asking about their preferences and patients not understanding the purpose of the preference study. Finally, when talking about using patient preferences for decision-making, seven physicians were concerned about **how patient preferences relate to other decision criteria** and five of them declared that patient preferences should not outweigh the traditional objective efficacy criteria and that patient preferences should not completely guide decisions: *“It must be something that's thought-provoking for the industry or academia developing a drug or device, to see how it could possibly be improved, but not to conclusively decide, we're suspending the study, the development of a drug or device” (PH_FR_3)*.

3.5 Stakeholders' expectations related to integrating patient preferences in decision-making throughout the medical product life cycle

Overall, stakeholders across different countries expressed mixed expectations related to the possibility and feasibility to integrate patient preferences in decisions throughout the MPLC. Amongst the different stakeholders, industry members and HTA/reimbursement representatives were the ones with more positive expectations. Patients, caregivers and patient organization representatives voiced positive and neutral expectations while regulators, academics and physicians expressed mixed expectations with more sceptical positions amongst physicians and academics.

Academics voiced mixed positive, neutral and negative expectations. Eight academics were hopeful and expected **more patient-centred product development and by result a decision-making** process that is *“more patient orientated [...] it's just one decision depends on another, if the decisions in the companies are more patient-orientated, the companies will have more success in regulatory processes which are patient-orientated” (AC_DE_12)* Other academics did **not anticipate big differences for reimbursement and MA decisions**, as *“if you already approve 90% of all treatments then you cannot really make that much impact any more than in that sense” (AC_NL_12)*. Three academics predicted it would *“be very long way”* before patient preferences will affect and change how decisions are made about medical products (AC_FR_11) and one academic expected that taking into account patient preferences would create a **risk** *“to put pressure on you to take into account their preferences, even if their preferences are against security and health” (RO_AC_23)*.

The majority of **HTA/reimbursement representatives** expressed positive expectations about the inclusion of patient preferences in decision-making throughout the MPLC. Specifically related to reimbursement decision-making, seven HTA/reimbursement representatives expected an overall **improvement** of this decision-making procedure and two expected a **higher transparency** of the decision-making and a **higher understanding** of the decision among external stakeholders: *“in HTA reimbursement I think it would really help open up the discussion*

on societal considerations, so make it more transparent and make it more participatory approach so that everyone and all the important stakeholders feel like they contributed to the decision” (HT_NL_8). Regarding the impact of patient preferences on the final decision outcome of the reimbursement decisions, different opinions were expressed; while one representative expected that using patient preferences in HTA would allow for **more** and **different** decisions to be made: *“I think we would have more patient centred decisions, I think different decisions would be made because now some decisions [...] just can't be made simply because they don't have the proper data”* (HT_DE_8), four HTA/reimbursement representatives were more sceptical and did **not expect** *“a big influence”* on HTA and reimbursement decisions, and considered patient preferences as *“an additional end point that might influence or tip the balance in one direction or another”* (HT_DE_7). One HTA/reimbursement representative was rather pessimistic and argued that it would make the reimbursement decision *“more complex and more difficult”* (HT_RO_14). Using preferences for decisions regarding product development would lead to a product development **more tailored** around patient needs according to four HTA/reimbursement representatives. Finally, one reimbursement representative expected using patient preferences in this respect could lead to an **increase in the price** of medical products because *“if you have products that clearly are preferred by patients because they have attributes that patients value, then presumably manufacturers will charge more for those products”* (HT_SE_14).

All but one **industry representative** expressed positive expectations about including patient preferences in the development and evaluation of medical products. Eight industry representatives expected an **improvement** of the MA and reimbursement decision-making. Other positive expectations included: i) a higher **transparency** of the decision-making, ii) a **higher credibility** and ii) a higher **societal acceptance** of the decision. Two industry representatives predicted that including patient preferences would lead to a **faster and easier market access** as *“you would value the effects of therapy on patients and [...] the cost effectiveness of a therapy might be better and reimbursement might be easier to decide on”* (IN_NL_11). Eleven representatives predicted that using patient preferences in product development would lead to a **more patient-centered product development by changing the focus of the medical products being developed**: *“I think that it will change the portfolio as the aspects we develop and the indications that we consider important”* (IN_US_10). However, two industry members pointed out it might take a while before patient preferences would actually be taken into account as *“moving from “a nice to have” to a structured listening is a journey to do together”* (IN_IT_17). One interviewee **foresaw reluctance and difficulties among reimbursement decision-makers** especially for those situations, like the rare diseases, in which very expensive medical products are highly valued only by a small proportion of the population: *“it may be a problem for the people that decide the budget for example, because we today already in Sweden we are struggling with the rare diseases, very difficult treatments that are very expensive and that can be something of course that the patient evaluation and a very strong positioning patient - that can really be beneficial I think for the patients, but maybe have some effects that other stakeholders don't like so much”* (IN_SE_19).

Ten **regulators** were positive about including patient preferences in the MPLC and expected that including them in regulatory MA decisions would lead to a **higher acceptance** of the decision among external stakeholders and will lead to a better *“understanding the process, and maybe also of application of the guidelines of the process”* (FR_RE_6). Two regulators predicted a positive change in the way regulators view and **approach benefit-risk assessments** resulting in *“a broader mathematic change in the output of regulation, and a dramatic change in the concern of regulators [...], it would become normal when discussing the benefit risks, it would be part of the concern”* (RE_UK_11). One regulator predicted an overall **higher quality of the MA decision** because currently there is *“a lot of guess work there. And I think to have more of that would certainly improve the quality of the decisions”* (RE_DE_5). Five regulators were more neutral about the eventual impact of patient preferences on the decision and stated that many MA decisions (e.g. those with a clear benefit-risk balance), having information on patient preferences would **not necessarily make a difference in the decision** itself even if it could affect the *“application of the guidelines of the process but it won't change a lot the decision”* (FR_RE_6). Five regulators, among which three Italian, were not convinced about using patient preferences in the regulatory environment and predicted a **slow uptake rate** of patient preference information in the regulatory environment, and one regulator attributed this slow uptake rate to a lack of familiarity with the concept of patient preferences within the current generation and the fact that until now, patient preference research has mainly been an academic exercise: *“I think it is a matter of time. It also has to deal with my generation has not been educated in this way of thinking [...] A lot of this work has been conducted in an academic environment and that is also one of the reason I think that it is not accepted everywhere, over everywhere because the acceptance we are dealing with are academic acceptance but not always practical acceptance”* (RE_NL_6).

Patients voiced mixed positive and neutral expectations. One patient predicted that including patient preferences in product development would lead to **better industry investments** and one patient predicted an **enhanced patient recruitment** for clinical trials. Four patients were **unsure what the impact** would be of using patient preferences in development and evaluation and one patient was skeptical if patient preferences will ever be taken into account: *“purely spontaneously I think no, I do not think that it will be a change” (PA_SE_3)*. All patient organization representatives expressed positive expectations (e.g. better suited medicines, better patient acceptance after market entry, new research perspectives), stressing that considering patients preferences in developing medical products will lead to *“more treatments or medical devices that have made an impact on an individual's quality of life and their independence” (PO_UK_1)*

Amongst **physicians**, positive expectations expressed included: i) a change in research perspective leading to the development of medical products *“that are better suited to taking care of the needs of patients” (PH_US_4)*; ii) an increased compliance of patients to the medical product and iii) an increased autonomy of patients. Four physicians were more pessimistic and doubted whether patient preferences could affect development as, for instance one physician stated: *“I am doubtful about this, what it can do. I do not think one has so very, very different opinions, other than how the drugs look today anyway” (PH_SE_8)*.

4. Focus Group Discussions

Introduction to results

Structure of results section. Results were analysed per stakeholder group, which is also how the results section below is structured. Below each theme, a graphic representation of the identified theme is given. Below the figures, the identified theme is discussed per stakeholder group in more detail. Codes following quotations refer to participants' characteristics and are formatted in the following way: i) stakeholder group and ID number of the participant, ii) continent or country the participant was recruited from iii) disease area (only applicable to patients and caregivers). The following abbreviations are used: CA= caregiver, CVD= cardiovascular disease, HTA= health technology assessment/payer, IN= industry, LC= lung cancer, DM= myotonic dystrophy, PA= patient, RA= rheumatoid arthritis, RE= regulator.

Readers' perspective of results section. The focus group guides for the patient, industry, regulatory and HTA/payer focus group discussions (FGDs) were developed based upon specific topics raised during the semi-structured interviews; FGD topics were selected if they triggered conflicting views during the semi-structured interviews and/or if the topic required more clarification. Participants were asked open-ended questions on the topics included in the FGD guides as described below, but also had room to talk about other topics important to them. The patient FGD guide included open-ended questions related to the following topics: (1) aspects influencing participants' treatment preferences, including properties of medical products, (2) factors influencing participation in patient preference studies, (3) patient-friendly design of patient preference studies and (4) handling patient preference data. The results of the patient FGDs can be interpreted as important considerations for the design and conduct of preference studies. More specifically: (1) healthcare aspects influencing treatment preferences raised by patients and caregivers point toward characteristics of medical products and other healthcare options that could be examined in preference studies, (2) patient views towards designing and conducting preference studies highlight how preference studies should be undertaken from a patient and caregiver perspective, including what measures can be undertaken to enhance patient participation. The industry, HTA/payer and regulatory representatives FGD guides included open-ended questions related to the following topics: (1) representativeness of patient samples in patient preference studies, (2) design of patient preference studies to inform decision making, (3) parties involved in conducting patient preference studies, (4) handling unexpected results, (5) reporting on patient preference studies, (6) assessment of patient preference studies and (7) use of these studies in industry and regulatory decision making and in HTA/payer decisions. Results from the industry, HTA/payer and regulatory FGDs reveal stakeholder views on the design and conduct of preference studies (e.g. sample representativeness, handling unexpected results), which provide information that may support methodological and organizational choices when undertaking preference studies.

4.1 Results from patient focus group discussions

Participant demographics per patient FGD are presented in Table 1. The themes and sub-themes identified in the patient FGD discussions are graphically presented in Figure 1, 2 and 3 and described at length below. Any differences that were identified during the patient FGD analysis that are country-specific or disease-specific are indicated in the text.

Table 1 Participant demographics per patient FGD

Disease area (N)	Geographical area	Stakeholder	Number of participants
Myotonic dystrophy (N=4)	UK	Patients	2
		Caregivers	2
Lung cancer (N=8)	Italy	Patients	8
Cardiovascular disease (N=10)	Romania	Patients	10
Rheumatoid Arthritis (N=3)	Sweden	Patients	3

Abbreviations: N, total number of participants; UK, United Kingdom.

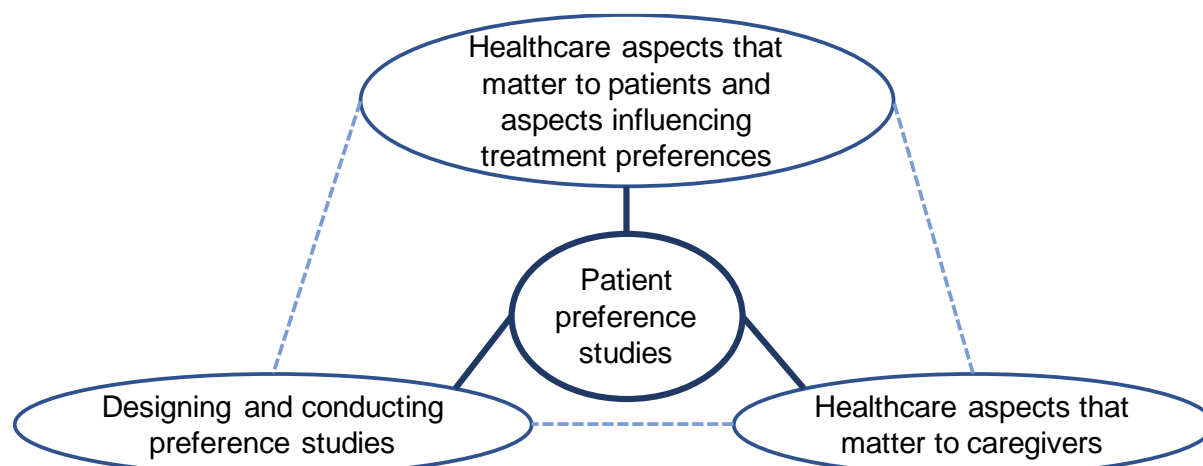


Fig. 1 Themes identified in patient focus group discussions are inter-related. Dotted line: indication of inter-relation between themes.

4.1.1 Healthcare aspects that matter to patients and aspects influencing treatment preferences

During the FGDs, participants across disease areas highlighted several healthcare aspects that matter to them and influence their treatment preferences. These aspects were both directly related to medical products, but also several other aspects were mentioned that were broader and not directly linked to medical products (Figure 2).

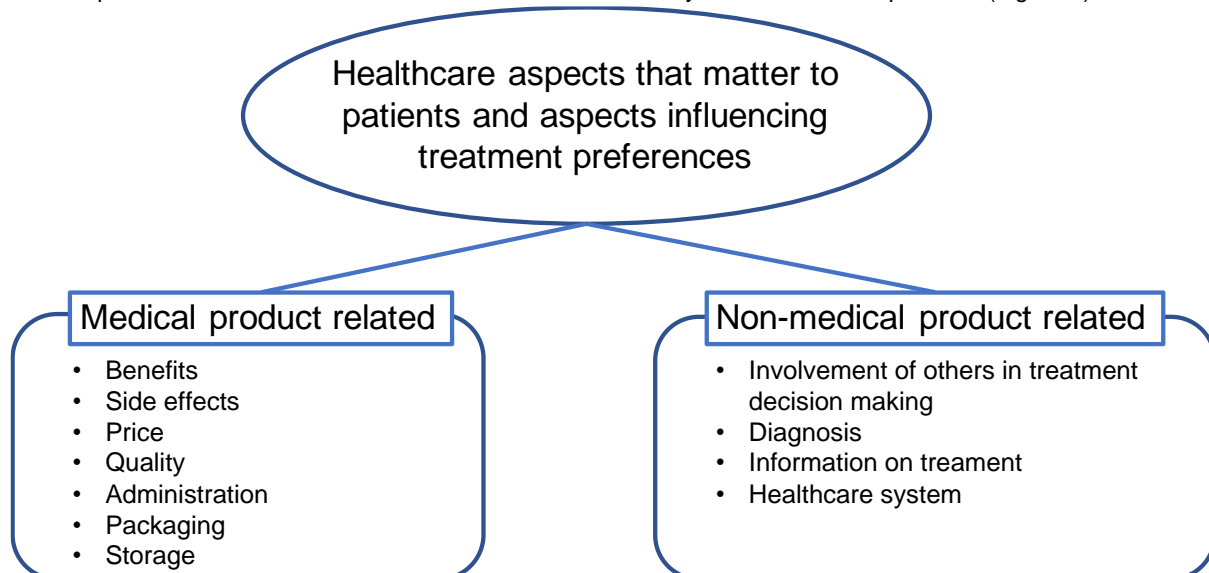


Fig. 2 Healthcare aspects that matter to patients and influence their treatment choices can be divided into aspects that related to their healthcare in general and to properties of medical products.

Medical product related aspects

Aspects influencing treatment preferences brought forward by participants directly related to medical products were: medical products' benefits, side effects, price, quality, administration, packaging and storage.

Benefits. Participants from all disease areas and countries explained that benefits and effectiveness of medical products are important for them and influence their treatment preference: *"To me, probably the most important aspect is the effectiveness of the therapy, this is the most important aspect."* (PA1_IT_LC) Some LC participants explained how ineffective treatments made them switch therapies: *"Finding a cure that was not effective anymore,*

I said that's it (...) now I must make a decision" (PA3_IT_LC) One LC participant explained that the benefit of their prescribed medical product outweighs the burden of the hospital visits that the treatment requires. The key benefits of medical products that participants spoke about differed across diseases: LC participants mostly cared about survival and decreasing tumour progression and size, RA participants spoke about reducing pain, and DM participants spoke about reducing mental issues, sleepiness, muscle weakness, bowel problems and preventing physical decline: *"Just to think that there would be something that held things as they are so they are not deteriorating, I think it's this deteriorating aspect that is the worst to deal with mentally and not knowing"* (PA1_UK_DM) Other medical product related aspects participants mentioned included the duration of the benefit (LC), how fast the medical product starts to work (RA), the impact of the medical product on their daily life and activities (DM, CVD, LC): *"It has an impact on your ability to work too, nowadays if you have a family and you are the only one who works, you take into account this too"* (PA5_IT_CVD)

Side effects. Participants from all disease areas and countries underlined how treatment side effects affect them: *"I think that side effects are a big problem, it hinders you a lot"* (PA3_SE_RA). The type of side effect participants worried about differed according to their disease. Injection site pain was a major side effect highlighted by RA and CVD participants. In addition, RA and DM participants mentioned mental side-effects such as depression (RA) and suicidal side effects (DM): *"She realised that it was affecting her mental state and she's just stopped it"* (PA1_UK_DM). LC and RA participants talked about how side effects affect them and some participants explained how this made them switch to another medical product or stop taking the medical product. Moreover, one LC participant reasoned that the expansion of his tumour might be attributed to the treatment itself. Further, one RA and one DM participant talked about how side effects of certain products exacerbate their disease-related symptoms limiting their treatment options: *"The cortisone is good, but I am a diabetic and then it is not a good combination to eat cortisone"* (PA2_SE_RA). Besides concerns on direct manifestation of side effects, one RA participant seemed to be specifically concerned with the uncertainty of postponed adverse events: *"What worries me is further along the way and old age and I eat a lot of cortisone and what will happen, my mother has also rheumatism. Look at her skin, it is just like paper. As soon as she touches it starts to bleed"* (PA1_SE_RA). Finally, LC, CVD and RA participants talked about the trade-off they made between treatment characteristics or between treatment options and how these trade-offs influenced their treatment preference: *"I would have rejected chemotherapy, it was useless and it would have destroyed me, being alive but unwell"* (PA1_IT_LC).

Price & quality. Participants from all countries, especially RO CVD and IT LC participants, articulated how medical product prices affect their treatment choices. Reasons why they attached importance to the price differed according to their country of residence. While RO CVD participants argued how the low disability allowance⁷ in Romania determines their preferences for medical products, IT LC participants specifically talked about how expensive immunotherapy is and how their insurance determines their ability to access this medical product: *"So, in any case I chose, I paid, and now I'm fine, I paid, but it isn't a preference (...), I was lucky because I was insured while other poor people couldn't do it, poor them"* (PA3_IT_LC). Moreover, one RO CVD participant attributed the high prices of medical products to the fact that medical products sold in Romania are not manufactured in Romania: *"It would be good if medicines for Romanians were made in Romania, in order to be cheaper"* (PA1_RO_CVD). The importance of price was placed in a broader perspective by SE RA, UK DM and RO CVD patients; one SE RA participant argued that the high cost protection⁸ in Sweden protects them from high medical product prices, and UK DM and RO CVD participants argued that besides the price, the medical products' quality is also important: *"Many times the price just doesn't matter anymore, it is the quality of the medicines that is important"* (PA1_RO_CVD).

Administration. Participants across disease areas raised several aspects related to the administration of medical products that matter to them and influence their treatment preferences. LC participants spoke about where they have to go to have the medical product administered, and how coming to the hospital to receive their treatment negatively impacts their daily life and confronts them with their illness: *"Honestly when I'm at home I can forget I'm ill, when I come here I have to cope with the awareness of being ill, so if I could avoid all this by taking a tablet at*

⁷ Disability allowance refers to the amount of money paid by the government to people who are unable to work because of a disability.

⁸ High cost protection in Sweden prevents patients from paying more than 1 100 SEK for healthcare over a period of twelve months.

home every fifteen days I would be very happy" (PA3_IT_LC). CVD, RA and DM participants worried about injections, more specifically about injection site pain and difficulty of using injections (RA, CVD) and needle phobia (DM): *"I have taken it for several months and, like, every time, it hurts like hell"* (PA3_SE_RA). Lastly, some DM participants worried about the large pill size of medical products combined with swallowing issues.

Packaging and storage. RA participants spoke about packaging problems and explained the difficulty of opening blister packs: *"But they are horrible these, yes, they are, yes I can't almost take them out, that is how much pain I am in"* (PA2_SE_RA). RA participants also addressed the problem that their biologic medical product takes up a lot of storage space and needs to be kept in the cold or dark.

Non-medical product related aspects

Participants brought forward aspects related to the following themes that matter to them, not directly related to medical products: involvement of others in treatment decision making, diagnosis, information on treatment and the healthcare system.

Involvement of others in treatment decision making. LC, CVD and DM participants noted how their healthcare and preferences were heavily impacted by healthcare professionals and family. Moreover, LC, CVD and DM participants talked about how their treatment choice and preference is determined by physicians: *"Interacting with doctors is fundamental for the choices we have to make. What is the main topic in this respect? The main topic is our preference, what do I prefer? If there's nothing to choose from, I prefer what they offer me"* (PA6_IT_LC). Furthermore, LC participants argued how both the competence of the physician and trust were crucial for a good physician-patient relationship: *"I must feel supported, I trust them, there must be trust"* (PA7_IT_LC). Besides physicians, DM participants highly valued the knowledge and skills from convenience nurses. In addition, one CVD participant spoke about how a good relationship with the pharmacist helped in getting the cheapest medical product with the same active ingredient. Besides the involvement of healthcare professionals, LC and DM participants spoke about their family supporting them in both accepting their disease and directing the choices they make: *"I couldn't accept it, when my family called me to ask about it (...) now I am coping well with it, I have accepted it, we have to go on, I know my strength comes from my family"* (PA2_IT_LC). Some DM participants added that sharing experiences through meetings with other DM patients and caregivers provide them psychological support.

Diagnosis. DM participants pointed towards the difficulty of getting DM diagnosed, and attributed this difficulty to the fact that DM has a wide range of multi-systemic symptoms: *"Nobody puts two and two together and makes DM (...) after the diagnosis, it all makes sense, it falls into place, but before then – "* (PA1_UK_DM).

Information on treatment. Participants from all disease areas stressed the importance of having (tailored) information on their treatment, including the different existing treatment options and treatment side effects. CVD and LC participants underlined that their physician should be the one providing them with sufficient information on their treatment: *"I would say that doctors need to inform patients better (...) he told me, 'we won't do chemotherapy, as they all belong to the same strain we will do immunotherapy', and he told me like that, without saying anything, nothing at all"* (PA4_IT_LC).

Healthcare system. Participants of all disease areas mentioned different aspects and points of critique towards the healthcare system and its actors. RO participants talked about a *"burdened"* healthcare system (PA2_RO_CVD), that causes them problems such as long waiting times, high prices of medical products, medical product shortages and a low disability allowance: *"I think the system should be reformed, because we are given a prescription and we cannot find the medicine in question"* (PA1_RO_CVD). RO participants further also criticized the competences of the healthcare ministry: *"In the Ministry of Health, there are people who have no idea what medicines are given"* (PA3_RO_CVD). LC and DM participants worried about a lack of treatment options: *"What can I have after (...) ? I am asking pharmaceutical companies to tell me that, if (...) doesn't work, I can try this or that"* (PA3_IT_LC). Further, besides an absence of cure, DM participants discussed the topic of off-label use of medical products and had diverging views on whether or not it should be made available on prescription. One DM participant worried about their limited share in healthcare spending due to the rarity of the disease and the cost of their treatment: *"The spend on epilepsy is something like 10,000 times more than all the muscular dystrophy put together because (a) the number of people and (b) the cost of the treatment and of the total spend of all neurology, we are the tiny pimple on top of the camel's back. So our voice as a financial spend is so small, it is frightening"*

(CA1_UK_DM). CVD, RA and DM participants highlighted the importance of getting their opinions and preferences across towards regulators and medical product developers: *“To listen to us, what opinions we have and if, I have told you my opinion about my injections and I think that this should reach them”* (PA2_SE_RA). In this context, RA participants spoke about how preferences are quicker taken into account for the development of medical products sold over the counter: *“There are really good products but they are not on prescription (...) That is, here there is a development of preferences for a commercial market that goes straight past us”* (PA3_SE_RA).

4.1.2 Healthcare aspects that matter to caregivers

DM caregivers explained the emotional burden of taking care of DM participants and mentioned emotions such as anxiety, frustration, anger and the insecurity of new symptoms that might surface: *“I think the worst thing about the condition is learning all the time about new things that can affect their potential, (...) So you are constantly being knocked.”* (PA1_UK_DM) Similarly, some DM caregivers claimed a need for psychological support: *“You need a one-to-one or family psychological support is what I am saying.”* (CA1_UK_DM) Besides the emotional burden, some DM caregivers argued that taking care of DM participants also limited them in performing their daily activities: *“If I can do something with those hands, that they are not turned out, so that they are not holding a cup like that and [name], if I say to him, “Can you carry that?” because I carry everything, I am the beast of burden in our house.”* (CA2_UK_DM)

4.1.3 Designing and conducting preference studies

During the FGDs, participants across disease areas and countries discussed their views on the design and conduct of preference studies. More specifically, they expressed their opinions on whose preferences should be measured and on method and instrument design (Figure 3).

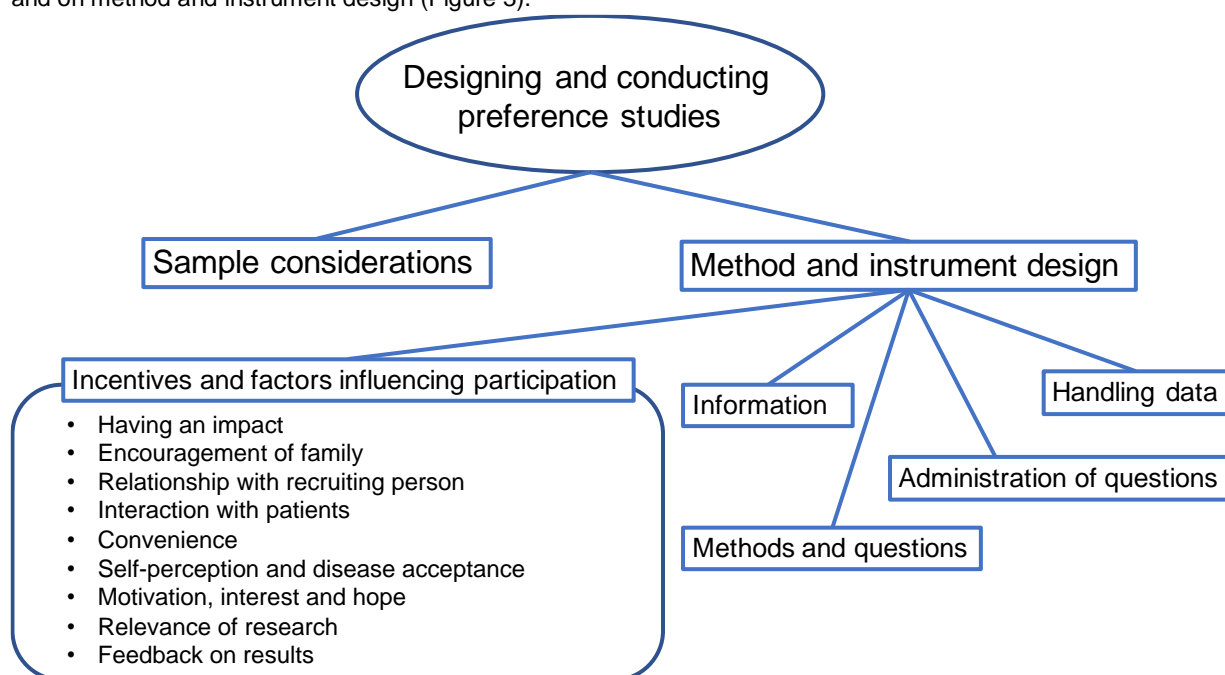


Figure 3. Themes identified related to the design and conduct of preference studies can be divided into sample considerations and method and instrument design.

Sample considerations

When talking about the type of participants that should be involved in preference studies, CVD and RA patients agreed that different types of patients should be involved and patients should not be excluded based on factors such as age, education or profession: *“It should not be any difference. Everybody can participate and answer, decide and give their opinion”* (PA2_SE_RA). Similar opinions were expressed regarding the level of disease and treatment experience; LC and RA patients argued that different levels of treatment and disease experience should be included: *“I think we should invite someone who feels less fine compared to us, who are here speaking calmly*

with a clear head” (PA6_IT_LC). One RA patient suggested that the patient sample should correspond to the patient population, and one DM patient thought that the sample depends on the treatment target population. CVD and DM participants suggested to include family that can talk on behalf of the patient they are taking care of. Specifically, among DM participants, there was the general view that including caregivers might be helpful, particularly for severely affected DM patients who have impaired cognitive function and where asking about their preferences could result in inaccurate information: *“because you have put them under pressure... you make them uncomfortable so you have not got the right response”* (CA1_UK_DM). One LC patient suggested to administer the questions to physicians, *“as they direct our choices in the first place”* (PA3_IT_LC).

Method and instrument design

Participants discussed the method and instrument design of patient preference studies, including factors influencing their participation, what kind of information they would like to receive when participating in a preference study, what methods and question design they would like, how the questions should be administered and finally how preference data should be handled.

Factors influencing participation in preference studies

Having an impact. Patients from all disease areas underlined that they would participate in preference studies to have an impact. LC patients mentioned that they would like to participate in studies when they know if and what impact their contribution will have: *“Knowing this, what the survey is for, what its purpose is, otherwise it is demotivating.”* (PA1_IT_LC) Different levels of impact were mentioned as incentives for participating. Patients from all disease areas mentioned the impact on their own health as an important incentive for participating: *“To be honest mine is a selfish opinion because if new things come up I hope I’ll have the possibility to try them.”* (PA6_LC_IT) Besides for their own health, having an impact on others’ health -including their own families’ health- was another important incentive mentioned by participants across disease areas: *“My motivation is my youngest grandson, his prognosis is, you know, if he lasts to 20 then he is lucky.”* (PA1_DM_UK) Doing something useful and helping research overall was mentioned as another important incentive and more specifically an impact on: quality and prices of medical products (CVD) and medical product development overall (e.g. new treatments (DM, RA) and new packages (RA)).

Encouragement of caregivers. LC and DM participants underlined how important the support and encouragement of family is to stimulate patients to participate in studies. DM participants in particular, stressed that oftentimes patients need to be motivated or even pushed by family member to attend meetings and studies of any kind: *“I am only here because of my carer and wife, [name of wife], who hasn’t got DM1 and she said, ‘You are going to this thing.’”* (PA1_DM_UK)

Relationship with recruiting person. LC and RA patients explained that the level of trust and relation they have with the person that asks them to participate influences their willingness to participate. More specifically, receiving this question from their treating physician, whom they trust, motivates them to participate: *“To encourage participation I believe also patients’ trust in their oncologist is important, because when they phoned me I trusted them so I was willing to participate.”* (PA5_LC_IT)

Interaction with patients. LC and DM participants mentioned that they are motivated to participate because of the possibility of sharing information, comparing experiences and just to go out and meet people: *“So if I have to say why I would encourage someone else to attend, it is because you meet other patients and you realize you are not alone.”* (PA3_LC_IT) However, this view was not supported by some DM participants, who argued that DM patients often do not want to attend big meetings (see below: self-perception and disease acceptance).

Self-perception and disease acceptance. According to DM participants however, young DM patients are often self-conscious about their illness and do not want to attend big meetings where severely affected DM patients are present, as it confronts them with their disease: *“Young people, sort of teen onwards, they are very self-conscious. They are very aware that they have got an issue and with my two, they don’t like discussing it and don’t want to be in an environment with other people, particularly wheelchairs and things, it is just a turn off for them.”* (CA1_DM_UK) Similarly, some LC participants mentioned that a lack of disease acceptance might hinder participating: *“There are people who hide their disease, they receive the treatment but don’t say it.”* (PA7_LC_IT)

Motivation, interest and hope. While LC and CVD participants mentioned they would participate out of interest: *“to become aware of the types of treatment available, to acquire knowledge, information”* (PA5_LC_IT), DM participants specifically spoke about hope for better as a major driver for them to participate: *“You can dress it up, but it is all about hope.”* (CA2_DM_UK) They also confirmed the opposite, namely that some DM patients lack interest and motivation and therefore would not participate: *“This really lights my fire and I am keen to do anything but then you’ve got people like my daughter, it doesn’t matter what you say to her (...) you could say, ‘There is a thousand pounds if you come along’ and that wouldn’t motivate her at all.”* (PA1_DM_UK) (see also below: financial compensation).

Financial compensation. Diverging views were expressed about whether or not financial compensations would incentivize patients to participate in preference studies; while some CVD participants argued that financial compensations are not needed, because they have a personal interest and “gain” from participating in preference studies, and because of the convenience of participating in preference studies situated in hospitals: *“But this is not something you should get paid for, because you don’t make any effort.”* (PA2_CVD_RO), one RA participant argued that financial compensations should take place if the preference study interferes with work and daily activities: *“I think that if people are paid, because everyone is working and is busy and... I think that it is something like this, that is, that one gets a benefit from it personally.”* (PA1_RA_SE)

Relevance of research. LC and RA mentioned they are happy to participate in studies regarding useful and relevant research: *“Actually, it was questions that I did not felt had relevance. A questionnaire regarding drug preferences I think I would be more engaged in.”* (PA2_RA_SE)

Feedback on results. DM participants argued that receiving information on the study results would make it worthwhile for them to participate: *“It would be nice to know, get some global feedback and individual feedback because it comes back to this apathy that for me, you start to think, “Oh, it is not worth it.”* (PA1_DM_UK) Further, this information ideally comes in the form of a short summary: *“I don’t want a massive amount. A few short summaries is what I would be looking for rather than the detail.”* (CA2_DM_UK)

Convenience. Participants from all disease areas mentioned different aspects impacting their participation in preference studies related to the convenience of the study. According RA and DM patients, the time investment of participation should be kept at a minimal level and hence, questionnaires should be as short as possible. One RA patient added that longer questionnaires, interfering with work life, should be financially compensated. Physical constraints (such as sleepiness and digestive problems), a long travel distance and an inconvenient time during the day were barriers to participating mentioned by DM patients: *“It is a physical constraint and that is not got to do with her willingness or not to participate, it is just the physical side, this continuing fatigue.”* (PA1_UK_DM) Some DM, CVD and LC patients suggested to organize preference studies in a hospital setting, as this would allow them to combine their participation and hospital stays or visits: *“We did not give up a profession, a meal, a study, an activity of sorts to come here, we stay with you for 7 days or 10 days, for as long as we are hospitalised.”* (PA2_RO_CVD) Some DM participants added that besides hospitals being *“the easiest place for them to go to”* (CA1_UK_DM), they are also familiar to DM patients.

Attractiveness. DM participants spoke about how some young DM patients dislike big events where they are confronted with their illness. In order to increase the attractiveness and hence, the participation of young DM patients into the preference study, some DM participants suggested to de-formalize the preference study: *“If you could de-formalise it (...) something like a barbeque or a party (...) music, they all love music.”* (CA2_UK_DM)

Information need in patient preference studies

LC and RA patients claimed a need for information of different kinds when participating in preference studies. More specifically, LC patients would value information on the purpose and topic of the study. One RA patient explained that in order to feel comfortable in participating, information about ethical review should be given. LC and RA participants described that in order to evaluate options in a preference study, they would like to receive treatment-related information, and more specifically, information about the side effects, expected effects and dosage form: *“First of all providing information, because if you hand me a questionnaire without explaining what I should write about, and I don’t know what the topic is, what am I going to write? Instead, if you inform me, this may happen, these may be the side effects, I can make a choice”* (PA4_IT_LC).

Instrument and question design

LC and RA patients discussed the advantages and disadvantages of questionnaires and qualitative methods such as interviews and FGDs. While one LC participant advocated using questionnaires as *“one can take the time to think about it, you don’t need to give an answer just for the sake of it”* (PA4_IT_LC), another LC patient preferred using interviews as they allow information to be obtained about the individual differences among patients in preferences: *“An individual interview would delve into the thoughts of a specific patient (...) questionnaire is a mass statistical tool, and the results are also quite standardized”* (PA6_IT_LC). RA patients argued that the methodology should be convenient, and suggested this could be done by having questionnaires that involve little writing, are not too long, and can be completed from home and at a time of their choice. Both RA and DM patients were positive about the idea of group discussions, as it allows them to discuss things *“outside the framework”* (PA1_SE_RA) and *“because people say something and then they trigger something in yourself”* (CA1_UK_DM). DM participants underlined the importance of organizing this discussion among a small number of participants, since DM patients often dislike bigger meetings as they do not like seeing people with the same suffering. RA and DM participants discussed the advantages and disadvantages of using disease-specific versus broader questions. While some RA and DM patients thought that questions should be specific to their illness, others spoke about the difficulty of having specific questions when the disease affects multiple organs. Moreover, one DM patient suggested that patients and caregivers could help in design and conduct of patient preference studies to adapt the questions to patients’ understanding: *“but people like us can then decide how are you going to get the information and how are you going to distribute the information?”* (PA1_UK_DM).

Administration of questions

Participants across disease areas had different ideas surrounding the way the questions should be administered to them. While CVD patients suggested this could be done best via electronic means (e.g. telephone based), some DM participants spoke about how electronic means are not always an option: *“My children don’t use the computer”* (CA1_UK_DM). CVD and LC patients agreed that a hospital based administration would be convenient and that physicians should be involved in the administration of questions: *“Maybe a personal interview with the doctor or the doctors could be the most suitable tool”* (PA6_IT_LC). Some LC and DM patients suggested eliciting preferences via the organization of local meetings for DM patients and their caregivers (‘support groups’): *“If you were to say, ‘Can I come to a support group meeting?’ and spend 20 minutes introducing what you are all about and then another hour getting people to chit chat, you might get it”* (CA1_UK_DM).

Handling preference study information

Participants discussed how patient and preference information coming forth from preference studies should be handled.

Data responsibility. LC participants thought that the hospital they are affiliated with should be responsible for what happens with their preference and personal information: *“[Hospital] is our data protection authority, more or less”* (P5_IT_LC) and explained that this was because of their trust in the hospital. RO CVD participants discussed that their information could be handled by the Ministry of Health or the National Insurance House. However, they also doubted the competences of the employees working for the Ministry of Health: *“But they are not appointed based on their medical competencies”* (PA2_RO_CVD) [...] *“More likely based on their economic competencies”* (PA6_RO_CVD) [...] *“Those who know how to count money for them get appointed”* (PA4_RO_CVD). RA and DM

patients underlined the importance of treating their information in a confidential way and some RA patients argued that a fear of not handling their information confidentially might even discourage them from taking part: *“Many people might also be worried a little bit about what we talked about a lot in the beginning: how the information is stored. Many people might be negative to... I don’t want to participate in something, I do not want to put my name on something or so, I imagine”* (PA3_SE_RA). DM patients explained that confidentiality would be best assured via the anonymization of their information. Importantly however, some spoke about the balance between confidentiality and *“moving things forward”* (PA1_UK_DM): anonymizing preference information should not inhibit the possibility of feeding back the results to patients nor should it stand in the way of the development of medical products that might ultimately benefit them: *“Equally, any contribution I make or that anybody else makes that my hold the key, not me, but something might just resonate that holds the key to moving things forward. I’d hate to think that because it is all anonymous, nobody knows how to move forward”* (PA1_UK_DM).

Data access and sharing. Participants from all disease areas agreed it would be beneficial to share information coming forth from preference studies among relevant stakeholders: *“Anyway of course this information needs to be used, it has to be shared with the relevant pharmaceutical company and university, and also with parallel research projects.”* (PA6_IT_LC) DM patients added the criterion of anonymizing their data before any use or sharing can take place. Moreover, although DM participants advocated the use of their preferences by industry for the development of medical products, they were against the use of this data for marketing purposes within pharmaceutical companies and targeted commercials: *“The pharmaceutical companies have got to have access to it but (...) it is within the pharmaceutical company to make certain that those procedures are in place to stop the research data getting out to the marketing side of things.”* (CA2_UK_DM) One DM participant was specifically against about sharing this data with insurance companies and social services.

4.2 Results from industry focus group discussions

Participant demographics of the industry FGD are presented in Table 2. The themes and sub-themes identified in the industry FGD are graphically presented in Figure 4 and described at length below.

Table 2 Participant demographics of the industry FGD

Stakeholder (N)	Geographical area	Expertise areas	Number of participants (n)
Industry (N=7)	Europe	Research & Development	2
		Regulatory Affairs	2
		Market Access	1
		Patient Affairs	2

Abbreviations: N, total number of participants.

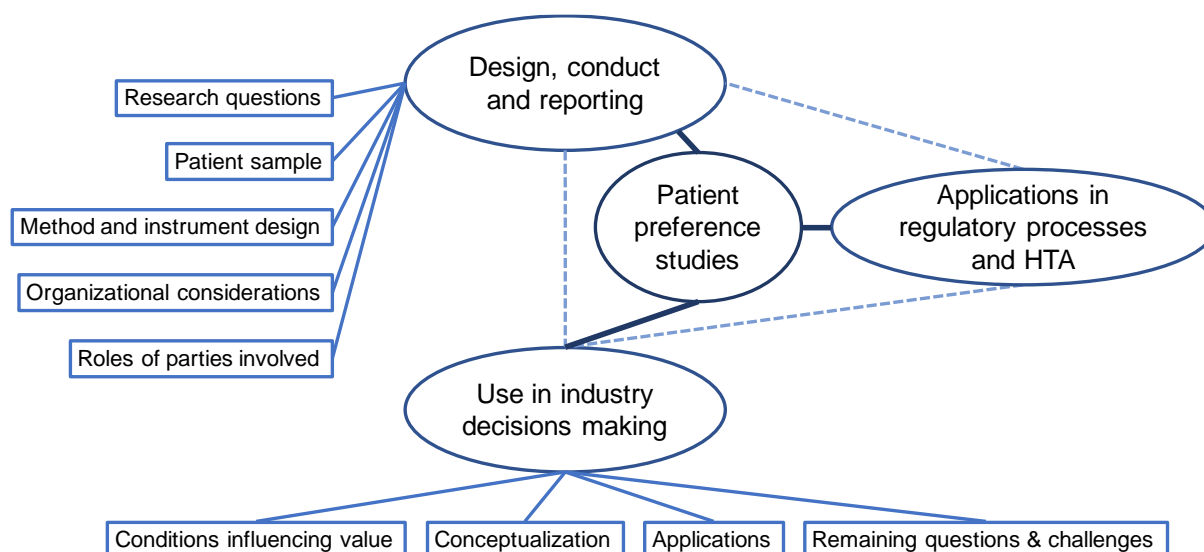


Figure 4. Themes identified in the industry FGD. Dotted line: indication of inter-relation between themes.

4.2.1 Designing, conducting and reporting patient preference studies

In the following part topics are explained, highlighted by industry representatives to consider in designing, conducting and reporting on patient preference studies.

Research questions

Industry representatives stated that patient preference studies showing how patients make trade-offs between benefits and risks, and between benefits and convenience could be valuable in decision making. Regarding these trade-offs one industry representative explained that it is important to know the risks and administration frequency that patients will tolerate, *“what your patient is prepared to put up with”* (IN7_EU). Besides trade-offs, industry representatives wanted patient preference studies to be informative on the impact of the treatment regimen on the patient and their family, including time investment and need to travel to hospitals versus self-administration at home.

Patient sample considerations

In patient preference studies the patient sample should be representative of the target population according to industry representatives. The target population could be defined as the patients *“who are going to make treatment decisions”* or *“the average person that’s going to be offered that therapy by a doctor in years to come”*, *“including those who decide not to take the medicine”* (IN7_EU). However, there was some discussion on how the patient population of which the patient sample should be representative depends on the situation or research question. *“That means they’re dependent on the situation then of what you’re expecting from the patient. That, of course, will be quite different and as a consequence the patient, [inaudible], characteristics will have to be adapted to the question and to the situation that you are confronted with”* (IN3_EU). Situations where patients make a choice for themselves were distinguished from situations where patients inform decisions impacting others. Regarding early stages of drug development, opinions differed on the need to include expert patients and one industry representative said that *“future patients to be enrolled in the clinical trial”* (IN1_EU) should be included. In early development of products for use in different countries, an industry representative suggested that the sample should be representative of different cultures and countries. The industry representative highlighted the importance of including different cultures and countries by stating *“I could imagine that [patient preferences] could be dramatically different depending on the culture or country. So, at this early stage, I think diversity in patients would be important”* (IN5_EU). At a later stage in development *“the patients who then face the decision”* (IN2_EU) would become important. The need for a representative sample would depend on the choice of method; for quantitative studies representativeness would be more important than for qualitative studies.

Industry representatives recognized the possible difficulty of realising the ideal sample. To ensure representativeness of the patient sample, industry representatives suggested taking the heterogeneity of the patient population into account through ensuring diversity within the sample around a set of criteria or characteristics. Others mentioned that diversity could be reached through stratified sampling or other sampling schemes. Industry representatives discussed the different patient characteristics that should be taken into account in designing the patient sample. It was suggested that the patient sample should ideally cover different backgrounds, cultures, ethnicities, continents, countries, regions, age groups, levels of education, and severities of disease. A comment was made on how to include the preferences of a common group of patients *“that actually want to defer the decision back on to the doctor”* (IN7_EU). The industry representative suggested assessing whether in the disease area or for the treatment option patients are dependent on doctors, since this might differ per situation. As previously touched upon, there was discussion between industry representatives on the inclusion of expert patients versus *“average”* (IN3_EU, IN6_EU, IN7_EU) patients. Expert patients were described as patients having knowledge on drug development, development issues and on the disease. Industry representatives advocating the inclusion of average patients only, explained that expert patients should not be included in the sample since *“That won’t be representative of the wider population”* (IN1_EU). Industry representatives advocating the inclusion of expert patients, reasoned that decision making of informed patients would be more relevant to inform decision making than average patients.

Method and instrument design

Industry representatives discussed question design and patient education during patient preference studies. While one industry representative stated *“There’s no reason why you can’t educate a patient to understand the questions that are being asked”* (IN4_EU), others disagreed and found it important that questions are simple and adapted to the patients, and not the patient sample to the method. Industry representatives agreed that it is important to provide patients with information on the study including background information and information on how the results would inform development, reimbursement or prescription, and sufficient information on the questions to enable patients to make a decision. Industry representatives highlighted that attention should be given to the manner in which information is communicated, and questions are asked to patients. Overall, industry representatives indicated that the importance of rigor, validity and robustness of the study design to increase the level of acceptance and use of results by regulators and HTA bodies and payers.

Organizational considerations

Industry representatives discussed the importance of including patient preference studies in the development plan. One industry representative indicated that including patient preferences in the development plan might extend the duration of the development phase and that the company might say *“We don’t have any time to do that”* (IN6_EU). Early planning of patient preference studies and integration in the development plan was key to industry representatives to allow for submission of these studies to regulators, HTA bodies and payers. One industry representative stated *“So you have to go back to the beginning because you can’t add it in at the end when you get into submissions, so you have to have planned for it earlier”* (IN1_EU). Another industry representative added that preference data presented to HTA bodies and payers should be collected along clinical development or in an earlier phase.

Stakeholder roles in patient preference studies

Industry representatives suggested that expert patients could have a role in formulating questions to make sure that questions are understandable. In addition, an industry representative suggested that the study design of patient preference studies should be agreed upon beforehand with regulators to ensure a rigorous design acceptable to regulators to be used in their decision making.

4.2.2 Use of patient preferences in industry decision making

The next part describes what industry representatives thought about using patient preferences in industry decision making, including their value, the methods to measure them and the potential application of patient preferences in industry processes.

Value and importance of patient preferences in industry decision making

Industry representatives agreed that patient preferences are valuable in decision making: *“So I think that we are pretty much agreed that there is value there”* (IN2_EU). An industry representative stated that patient preferences could *“drive development”, “influence decisions”, “develop decisions” and results in “better decisions”* (IN7_EU). An industry representative stated that when results of patient preference studies indicate patients accepting a product profile, these results would be regarded by all as confirmation of a *“winner”* (IN7_EU) product. The industry representative added that when results of patient preference studies would indicate patients do not accept a product profile it is likely that an attempt would be made to change the product profile or that the development of that product would stop. However, the industry representative also mentioned that because of the perception of patient preference studies not to be robust, negative patient preference results might not change the minds of some people.

Industry representatives were asked how most pharmaceutical companies would handle unexpected results from patient preference studies. Industry representatives discussed the case of phase 2 clinical trial results showing an innovative drug having high benefits but also high risks, and the patient preference study in phase 3 indicating patients to not accept these risks. Industry representatives thought the unexpected results would not be ignored and discussed ways to address these results. A suggestion was made to first explore the reason for this negative feedback to assess if there is a real problem in tolerability of risk or a mild problem like mild injection site reaction.

Industry representatives reasoned that the product profile would have to be compared to available products to assess the commercial future of the product. The importance of mitigating the safety risk was emphasised. Risk mitigation strategies included taking new measurements in new trials, testing alternative dosages, selecting different patients, and reducing risk through education or black box warnings⁹. If in phase 3, the results of phase 2 were replicated and risk mitigation would be impossible, industry representatives thought that the risk would be a heavy concern for regulatory authorities and payers, and therefore also for the company, and could make the company decide to *“abandon the program”* (IN7_EU). One industry representative stated that if risk mitigation is unsuccessful, this would not necessarily mean that the company changes its plans *“based purely on patient preference”* (IN4_EU), but that patient preferences would become an approvability question of regulators. Industry representatives discussed, but did not reach a consensus, on whether or not results of patient preference studies showing unexpected negative results would be communicated to evaluators and the public. While some industry representatives thought the results would become available to evaluators by inclusion in the submission to regulators and to the public *“in one way or another”* (IN6_EU), others thought this would only be the case if the company decides to file for marketing authorization. The latter industry representatives expressed that it is uncertain that unexpected negative results would be communicated since they did not know *“whether companies regard patient preference studies as clinical trials with an obligation to publish or market research, which there’s no tendency to publish”* (IN7_EU).

While industry representatives recognized that the patient is their customer and their preferences are important, they mentioned that needs and perspectives of other stakeholders also have to be taken into account. Industry representatives highlighted the importance of also taking into account the perspective of caregivers, especially in paediatric programs, and the perspective of health care professionals. Besides meeting the needs of health care professionals and caregivers, industry representatives expressed that they still have to meet regulatory, pricing and reimbursement requirements and expectations. One industry representative stated: *“I think we conceptualise it as important but secondary to the regulatory requirements”* and added *“our prime objective is to get a license, to get an approval, and if patient preferences is positive in achieving those objectives, then we’ll embrace it but if patients start to tell us to do something that we think is at odds to what the regulators might want, then I think we still regard the regulators as our customer”* (IN7_EU). Industry representatives discussed situations in which patient preferences would become more important than in other situations. These situations included:

Special disease areas and patient populations: Disease areas and populations including rare diseases and new disease areas *“where we don’t quite know what we’re doing”* (IN7_EU), paediatric populations because of challenges in clinical trials, chronic diseases and oncology because of the time patients have to live with the disease. However, one industry representative stated that he found patient preferences equally important in acute diseases. Another industry representative also stated that there is no major value of patient preferences in common diseases that are well known and studied for years.

- Unfamiliarity or uncertainties of regulators: Patient preferences could become more important than those of regulators when regulatory requirements are *“old fashioned or even limited”* (IN3_EU) because of unfamiliarity with the topic, when there are uncertainties with regards to clinical endpoints. One industry representative added that in the case of strict regulatory pathways or *“routine”* (IN7_EU) clinical studies and disease areas there is no added value of patient preferences.
- Special side effects: Unexpected side effects or safety issues.
- Symptom relief: One industry representative stated that because of the existence of a lot of drugs that impact symptom relief and not life span, and since symptom relief is something that can be perceived in a different way among patients, it is helpful to understand what patients value. Patient preferences could drive development in this area. Another industry representative expressed that it is also important to understand, in context of adherence to disease modifying drugs, how patients perceive taking drugs not having a direct impact on symptoms.
- Limited prolongation of life: One industry representative reasoned that life prolongation of two or three months *“might be considered by HTA bodies or payers as not so impressive”* (IN3_EU), but that patients can perceive this in a different way.

⁹ A black box warning is the strictest warning put in the labelling of prescription drugs or drug products by the Food and Drug Administration (FDA) when there is reasonable evidence of an association of a serious hazard with the drug.

Current conceptualization of patient preferences for industry decision making

Industry representatives discussed through which methods or measures preferences of patient are currently captured. Industry representatives agreed that currently companies mostly look for qualitative patient input, but that quantitative patient preference studies could provide more scientific evidence. In addition, they agreed to the statement made that the method can *“vary also according to the life cycle of the product”* (IN5_EU). Moreover, it was discussed that in early stages of development qualitative methods might be more appropriate to get some initial insights and to see if the product could fulfil any high unmet needs. Quantitative patient preference studies are currently rarely performed at this early stage but are performed in the context of market research, as indicated by the following quote: *“more really at a late phase when there is really product already on the market”* (IN6_EU).

Industry representatives also discussed other current measures and how they represent patient preferences. Quality of life was found to be important, also for some HTA/payer bodies, and perceived as indicating patient relevance. Patient relevant outcomes were not regarded as patient preferences, but also as being patient-centric. However, industry representatives mentioned that the validity and suitability for purpose of patient relevant outcomes is often questioned.

Position of patient preferences in industry decision making

Patient preference studies are rarely conducted outside marketing and not in a consistent way, according to the industry representatives. Patient preferences are new to the industry, but there is willingness, interest and aspiration to *“integrate the patient or the patient preference all along the life cycle”* (IN6_EU) and *“industry is still on the journey of trying to integrate patient preference throughout the life cycle”* (IN1_EU). One industry representative mentioned that patient preferences could be integrated more systematically in the future since there is a *“new requirement under the ICH guideline about including patient preference in our overall clinical overview”* (IN1_EU). Industry representatives agreed on the importance of having a *“process”* (IN7_EU), *“structure”* (IN3_EU), *“framework”* (IN1_EU, IN3_EU) or *“good practices”* (IN1_EU) for measuring and using patient preferences. The availability of such good practices would lead to more robust results and easier integration of patient preference studies in the development plan. Industry representatives further discussed the different potential applications of patient preferences along industry processes. These applications included:

- Understanding disease burden: To know what the disease means to the patient.
- Understanding what patients want: To understand what patients value, need, want and don't want regarding treatment options. To provide information on *“what problem they would like us to fix”* (IN7_EU) and the importance of outcomes to patients, impact on symptoms and survival.
- Scientific advice: To have patients, or a mix of patients and patient experts, involved in the discussion.
- Clinical trial design: To inform clinical trial design by understanding the impact of treatment on patients, which can be especially valuable in young paediatric populations, and could increase recruitment and retention of patients. More specifically, patient preferences can be used to choose and define (primary) endpoints and patient reported outcomes, and ameliorate presentation and content of patient information and consent forms.
- Formulation and dosage choice: To inform formulation and dosage choice, especially when there is a choice between formulations with different efficacies.
- Benefit-risk assessment: To assess if the delivered benefit is meaningful to patients. New ICH requirement asks to indicate *“where we have weighted patient preferences in our overall determination of benefit-risk as part of the submission package”* (IN1_EU), leading to the inclusion of patient preferences in the clinical overview.
- Subgroup identification: To know the types or classification of patients, identify subgroups where the relevance of the benefit could be more important and to show *“one size doesn't fit all”* (IN6_EU). On industry representative suggested that subgroup identification could possibly influence regulators in covering subgroups, that are often left out, in the label with limited evidence
- Labelling: To include patient preferences in labelling to reflect what is important to patients and to prevent from jumping too quickly to black box warnings and taking medicines off the market. One industry representative mentioned *“getting that into the label so that you can claim it and promote it”*.
- Submission to regulators, HTA bodies and payers: To include in submissions to support the evidence and value proposition in the dossier and to allow for discussion.

Remaining questions and challenges

The majority of the remaining questions dealt with how to measure and use patient preferences and to address the challenges arising along this process. One industry representative was not sure how to incorporate patient preference studies into the development plan, to allow for continuous collection of patient preferences instead of collection at specific points when a decision need to be made and to prevent perception of patient preference studies to be an add-on to phase 3 clinical trials. Having labelling reflect patient preferences to *“claim it and promote it”* was seen as a major challenge. Another industry representative was concerned about, and had experience with, the possibility of patient preferences pointing towards a wrong decision.

Industry representatives felt that investigation is needed on which patients to reach out to, and mentioned that interaction with patients is further complicated by conflict of interest. One industry representative had concerns about how to include the preferences of, according to the industry representative, a common group of patients *“that actually want to defer the decision back on to the doctor”* and how in these studies people might be forced to make a decision while they might actually *“just want to be advised”* (IN7_EU).

A cultural barrier toward the systematic use of patient preferences was identified by industry representatives. An industry representative mentioned that in industry there is *“a huge cultural view that we know how to develop medicines”* (IN7_EU). Industry representatives discussed that some people believe patient preferences should not be used in decision making, because they feel these studies are not credible or robust enough, do not have the weight of *“proper science”* (IN7_EU), or feel that they do not want patients influencing what they think they know best. In addition, industry representatives were not sure whether all authorities will accept and value patient preferences. They also mentioned that if robustness of the study design could be demonstrated, that this would *“help in increasing the level of acceptability”* (IN5_EU).

One industry representative indicated the need for a communication strategy towards the community on how the pharmaceutical industry is trying to embrace patient involvement and patient preferences. The industry representative explained that such communication could also lead to informing patients about opportunities to get involved.

4.3.2 Use of patient preferences outside industry decision making

In this last part of results from the industry FGD, information is given on what industry representatives said about using patient preferences by regulators and HTA bodies.

Industry representatives stated that results of patient preference studies could be used at the time of discussion with evaluators on the criticality of side effects for the benefit-risk profile when there may be a difference of opinion. Industry representatives were not sure how patient preferences would be used by regulators in their regulatory framework. On decision making by HTA bodies an industry representative highlighted that for some HTA bodies other evidence such as quality of life with progression-free survival remain very important and make a difference in their decision making.

4.3 Results from regulatory focus group discussions

Participant demographics of the regulatory FGDs are presented in Table 3. Two FGDs were conducted, one with EU and one with US regulators. The themes and sub-themes identified in the regulatory FGDs are graphically presented in Figure 5 and described at length below.

Table 3 Participant demographics of the regulatory FGDs

Stakeholder (N)	Geographical area	Expertise areas	Number of participants* (n)
EU regulators (N=5)	EU	Medicinal products	3
		Advanced therapies	1
		Orphan medicinal products	2
		Patient engagement	1
USA regulators (N=6)	US	Drugs	2
		Biologics	2
		Medical devices	2

Abbreviations: EU, Europe; N, total number of participants; US, United States of America.

* One EU regulator had expertise in three of the four expertise areas listed in the table.

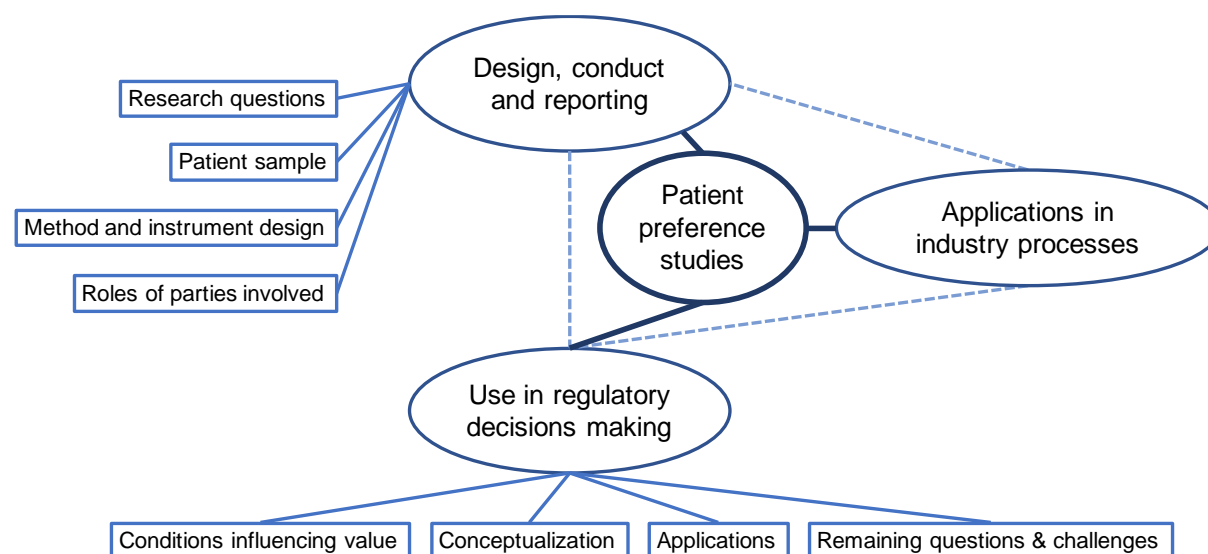


Figure 5. Themes and subthemes identified in regulatory FGDs. Dotted line: indication of inter-relation between themes.

4.3.1 Designing, conducting and reporting patient preference studies

In the following part topics are explained, highlighted by regulators to consider in designing, conducting and reporting on patient preference studies.

Research questions

EU regulators wanted patient preference studies to answer questions on how the formulation and route of administration impact preferences, as well as how patients trade-off benefits and risks, “*what risks are you [patients] willing to accept versus a certain amount of benefit*” (RE2_EU), which outcomes patients prefer, and how characteristics of patients and disease experience influence preferences. In addition to these clinical research questions, EU regulators also would like patient preference studies to answer the methodological research question of how results from different methods in the same population compare. While US regulators did not mention methodological research questions important to investigate in patient preference studies, they talked about clinical research questions that they were interested in including research questions on clinical endpoints that matter to patients, the burden of the disease and risk tolerance of patients. In addition, US regulators said that the research question and disease area determines the design and conduct of the study.

Patient sample considerations

EU regulators discussed the importance of representativeness of the sample to the population and how non-representativeness could lead to non-acceptance of the data by regulators. One EU regulator mentioned that while representativeness is not always assessed or important for direct patient input from patients, there is another standard for patient preference studies. US regulators also spoke about the importance of representativeness in generalising the results to the whole patient population and making sure that no subgroups are missed: “*If the sample is not representative it is hard to make predictions for the whole population because it might be missing important types of patients in your sample and therefore when you try to make inferences for the whole population, the inferences will be wrong*” (RE3_US). An EU regulator gave an example where a patient preference study was not accepted because of lack of representativeness.

EU and US regulators talked about the definition of a representative sample. EU regulators agreed that the target patient population and their acceptance of the product should be identified during development, and that representativeness in patient preference studies should be pursued “*so that they don’t come into regulatory hurdles at the stage of assessment*” (RE3_EU). According to EU regulators, the definition of the target population to which the patient sample should be representative depends on the “*claimed indication*” (RE1_EU), “*patient populations to*

be treated” (RE1_EU) and the “research questions” (RE5_EU). US regulators also spoke about targeting the “population of interest” (RE6_US) with relation to the claimed indication. One US regulator added that the sample should cover a broader population than in clinical trials.

To ensure representativeness of the patient sample, EU regulators believed that a structured approach is necessary. An estimation should be made of the necessary sample size to achieve representativeness. In addition, US regulators discussed the importance of setting up a research question and disease area specific sampling strategy, early in the design phase of a patient preference study. Early setup of a sampling strategy was found important to “try to attack the cause of the representativeness”, since “trying to crack some of these deficiencies or lack of representativeness after you have completed the study can be pretty more challenging” (RE1_US). In the context of rare diseases EU regulators expressed that it cannot be expected to reach representativeness as in common diseases but that agreements should be made on the approach of selecting the patient sample: “Obviously, if you are looking at a rare disease you can’t expect to have so many patients but if you are not looking at a rare disease, for example, a more common one, then, you know, there has to be some kind of agreement or some common approach as to what kind of numbers within the different parameters that we have already highlighted are considered representative of, you know, kind of general patient population” (RE2_EU). In addition to sample size calculation, EU and US regulators expressed that available epidemiological data should be investigated to assess sample and preference heterogeneity: “to see how heterogeneous a population is in the very first place” (RE4_EU) and “to understand the sort of heterogeneity of preferences within the population because you may need to adjust your sampling to capture those different perspectives” (RE4_US). On using epidemiological data to adapt the sampling strategy one US regulator stated that it is difficult to ensure representativeness: “You can try and then once you get the sample you can compare the co-variate values of that sample with the whole population and see if they more or less match and then you will see how representative your sample is of the population but to assure you, you know, maybe do the best you can” (RE3_US). One EU regulator stated that behavioural aspects and biases of patients should be taken into account, and that potential biases should be reported to regulators. Another EU regulator suggested investigating a few different samples, “the more different, the better” (RE4_EU), and assessing the difference in preferences between samples.

EU and US regulators agreed that characteristics of participants have to be taken into account in defining the participant sample: “you have to sample all the co-variants that correlate with the characteristics you want to study” and “depending on the conditions and on the context in which you were analysing the condition you have to define the co-variants and influence about it and then make sure that you have representativeness of all levels with all these co-variants in the study” (RE3_US). EU and US regulators discussed the different patient characteristics that should be taken into account in designing the patient sample. It was suggested that the patient sample should cover different ages, genders, socio-economic demographics including levels of education, racial demographics, geographical areas, treatment experiences, different stages of diseases including newly diagnosed or “naïve” (RE2_EU) patients, and durations of the patients having the disease since preference might change over time. If it is the aim to provide a European perspective, EU regulators indicated the need to include patients from different countries, or to assess whether preferences between countries might differ. US regulators also stated that based on these characteristics it has to be assessed if the sample is representative of “whatever population we’re looking to generalise to” (RE4_US). EU regulators again expressed that covering these characteristics is less important in direct patient input, where knowledge on disease and communication skills become more important.

In addition to reflection on sampling strategy and characteristics of patients that need to be taken into account, EU and US regulators emphasized the need to reflect on possible differences between patients from different recruitment sources. The recruitment sources that were discussed included, the internet, general practitioners, patient organizations, registries and ongoing healthcare initiatives. An US regulator expressed his concern on how recruitment via patient organizations could lead to an unrepresentative sample: “if a patient advocacy group decided to do a patient preference study, then they are going to collect patients who are more wealthy, who can attend that meeting, those who are sort of more invested, potentially, pharmaceutical companies” while “The ones that didn’t die, whereas the patients who are sort of... have very short life spans or who die rapidly, perhaps no access to drugs, who can’t fly to Switzerland or wherever to go to the meeting may not be represented” (RE2_US).

Method and instrument design

EU and US regulators found it important that the right methodology is chosen to answer the specific question. EU and US regulators also stated that the methodology might depend on the population and that it should be assessed whether patients understand the questions and attributes or not. If patients are not able to understand the questions, another methodology should be used. One EU regulator emphasized the importance of choosing the right methodology for paediatric populations: *“I think you just have to maybe gather the preferences in a slightly different way”* (RE2_EU). US regulators discussed that the design phase of a patient preference study is the phase in which bias can be introduced like during the development of attributes. US regulators mentioned that performing a qualitative study prior to a quantitative study is very important in developing an optimal design for the quantitative study: *“good qualitative research is going to be incredibly important in order to get to any good design of quantitative preference study”* (RE2_EU).

Stakeholder roles in patient preference studies

EU regulators agreed that different parties including, industry, regulators, academics or research groups can conduct patient preference studies. Regarding patient preference studies to inform regulatory decision making the sponsor, industry, was seen as the most likely party to conduct the study. However, EU regulators emphasized the need for robust studies and involvement of multiple stakeholders in the design and conduct of the study to prevent questions from being biased. US regulators said that they do not give advice on who should conduct the study or not and that submitted patient preference studies will be critically reviewed to assess the quality of the study and potential biases. US regulators stated that if the design of the study is good, that it does not matter who conducts the study. A EU regulator added *“I can imagine also in the industry if they are in the middle of designing a study they will strongly focus on... probably they will be more focused on the favourable effects of their own compound and probably it will not be addressed as it should be addressed”* (RE2_EU). According to EU regulators, the *“sponsor should initiate”* (RE1_EU) the study. EU and US regulators discussed how the following parties could be involved in design and conduct:

- Regulators (EU and US regulators): industry should act proactively to enable early discussion on necessity to conduct a patient preference study and their potential design, in EU through scientific advice, to limit occurrence of biases.
- HTA bodies (EU regulators): since the studies can also be of interest to them.
- Physicians (EU regulators): it might be important to involve physicians, in particular to plan recruitment.
- Patient organizations (EU and US regulators): could conduct the study instead of sponsor, or patient organizations or patients should at least be involved in the design of the study to ensure inclusion of the patient perspective in the study and also to plan recruitment.
- Academics (EU regulators): because of methodological expertise.

4.3.2 Use of patient preferences in regulatory decision making

The next part describes what regulators thought about using patient preferences in regulatory decision making, including their value, the methods to measure them and the potential application of patient preferences in regulatory processes.

Value of patient preferences in regulatory decision making

According to EU regulators, patient preferences are always valuable in decision making. An EU regulator stated *“At the end of the day, any patient preferences are going to be valuable at any kind of regulatory assessment, whether this is pre-, during or even doing post-authorisation studies”* (RE2_EU). US regulators also recognized the value of patient preferences in regulatory decision making: *“Patient preferences can be humbling. I like the humble factor. I mean you always come out on the other end saying, ‘Wow, I didn’t even know to think about it that way’. So, it is extremely valuable”* (RE4_US). Moreover, EU regulators expressed that *“it is always necessary to take patient preferences into account”* (RE2_EU). EU regulators argued that patient preferences are important to take into account since preferences and judgements of assessors might be different, probably more risk adverse, from patients. However, one EU regulator mentioned that patient preferences might not have a big impact if they are conflicting with the judgement of the assessor, but could lead to discussion. EU regulators expressed that there are very limited submissions of patient preference studies and that it is unclear if the submitted studies were included

in assessments and if they had an impact. On the impact of patient preferences in decision making, US regulators stated that all factors within the benefit-risk framework are to be considered for drug, biologics and medical devices. However, no strict weights for these factors like safety and effectiveness, and thus also patient preferences, are defined: *“they are all factors to be considered but, you know, we didn’t get to the weight part yet”* (RE3_US). In the US, currently patient preferences are considered to be an important factor for medical devices, and are increasingly being considered for drugs and biologics. While patient preferences are increasingly taken into account, US regulators also explained that safety and effectiveness remain more important than patient preferences: *“if a drug or a device or anything is unsafe, you know, patient preference sort of takes a back seat”* (RE2_US) and *“you deal with safety first and then go on to give effectiveness a little bit more air time but ultimately at the end of the day if there is no benefit to the treatment, patient preferences are not going to matter in one way or another”* (RE5_US).

While EU regulators recognized that patient preferences are important, they mentioned that perspectives of other stakeholders also have to be taken into account. The importance of also taking into account the perspective of caregivers, especially in some paediatric populations *“where you may have to gather preferences from carers”* (RE5_EU) while EU regulators also stated that they had experience with input from young patients also being informative, and the perspective of health care professionals was expressed: *“You shouldn’t leave out this stakeholder because at the end they will communicate with patients”* (RE1_EU). Also, US regulators spoke about preferences of health care professionals and how these can be different from patient preferences since patients might value outcomes that health care professionals do not.

EU regulators recognized the importance of reflecting on whether or not patient preference studies are valuable or necessary per situation, especially since they are resource intensive *“we have to take into account that conducting this kind of patient preference studies is quite huge in terms of resource, et cetera”* (RE2_EU). US regulators stated that they will work on a report describing preference sensitive areas. EU and US regulators discussed situations in which patient preferences would become more or less important than in other situations. These situations included:

- Special disease areas and patient populations (EU and US regulators): Patient preferences were found to be very valuable in paediatric populations, rare diseases and areas of unmet medical need where limited other information might be available, and diseases with a range of disease stages and manifestations.
 - Rare diseases (EU and US regulators): EU and US regulators both highlighted the importance of input from patients since doctors often have little expertise in those diseases. An EU regulator added *“in the orphan procedures when we have claims of major contribution to patient care, patient preference may be the main information that we are looking at for making our regulatory decisions, whether to grant or maintain an orphan designation”* (RE5_EU).
 - Paediatric populations (EU and US regulators): To understand how treatments would be managed in paediatric, sometimes rare disease, populations. However, frameworks had to be developed to allow interaction with people under 18. Since these frameworks now are put in place in Europe an EU regulator mentioned *“We do have that now and so I think this is definitely something that is going to be increasing very much in the near future now that we have these principles for involving young people”* (RE2_EU). While EU regulators explained that paediatric patient preference studies could be used for the same purposes as other patient preference studies, a specific role for patient preference studies in paediatric populations was expressed to be in identifying preferred formulation and route of administration.
 - Areas of unmet medical need (EU and US regulators): Both EU and US regulators highlighted the importance of taking into account preferences of patients in areas of unmet medical need since limited information is available to regulators.
 - Diseases with a range of disease stages and manifestations (EU and US regulators): *“it might be called one disease but it’s really, potentially it’s a lot of different [inaudible], different heterogeneity of how that could be manifest in different people, where patient preference helps you understand all the subgroups and there are different benefit-risk profiles based on patient experiences”* (RE6_US). This situation was found to be a possible cause of split views between regulators: *“one team member will think of a young patient at an early disease stage and another will think of an older patient at a later disease stage and that is where the different views and possibly the split opinions come from”* (RE4_EU).
- Availability of other treatments (EU regulators): In some disease areas where a lot of other treatments are available patient preferences were found to be not very valuable.

- Suspected preference heterogeneity and subgroups (EU regulators): Preference heterogeneity could lead to valuable identification of subgroups, but was also found to complicate assessments.
- Type of treatment (EU and US regulators): In case of novel technologies, novel benefits, *“unusual adverse effects”* (RE4_EU), highly toxic treatments like in oncology, precision medicine and treatments that preclude other treatments. An US regulator elaborated on the importance of patient preferences in treatments that preclude other treatments, stating: *“Let us say to have a device implanted sometimes if you get a better treatment in the future, you cannot, you know, extract that device for a better device. So, in that case you might want to ask the patient if they want their treatment now rather than wait for maybe having a better treatment in the future. It is the same with genetic therapy”* (RE3_US). Another US regulator elaborated on the importance of patient preferences in identifying *“the right patient”* in precision medicine, stating *“if you look at twins, identical twins. They both have the same disease. They are both offered the same treatment. The treatment, essentially, is going to react the same way with both of them but because of their different preferences one may choose it, one may not”* (RE1_US).
- Borderline versus clear-cut benefit-risk decisions (EU regulators): Patient preferences were found to be more valuable in borderline than in clear-cut benefit-risk decisions, especially since committee members might not reach consensus on the decision.
- Uncertainties to regulators (US regulators): Overall, patient preferences were seen as valuable in case there is uncertainty about the benefit-risk trade-off, when regulators are not familiar with a new type of treatment or in preference sensitive cases where *“some people like some benefits, some people like other benefits”* (RE3_US).

Current conceptualization of patient preferences for regulatory decision making

Regulators discussed methods and approaches currently used to capture preferences of patient. Currently direct patient input is systematically sought in EU and US regulatory processes through participation of patients, patient representatives or small patient groups in meetings, to see if claims align with preferences of patients, or by written consultation or document review. An US representative stated that having patients that are representative of the actual population is important, since in some previous meetings direct patient input resulted in the gathering of biased information since applicants were *“cherry-picking”* (RE3_US) and in some cases applicants were paying patients to share their experiences with the treatment. On the participation of patient representatives in meetings, EU regulators stated that these representatives do not only bring their own views to the meetings but also those of other patients.

EU regulators found direct patient input very valuable and informative in shaping decisions and discussed how quantitative patient preference studies cannot replace direct patient input. One EU regulator mentioned *“The use of these quantitative patient preferences. I think they no way can replace having the two or three patients at a given time where you can have more of an in-depth discussion and they can highlight issues and you can question back and forth”* (RE2_EU). While EU regulators found direct patient input important, concerns were expressed on the representativeness of direct patient input and one EU regulator stated *“of course having just a few patients at a given time you cannot say that they are representing the whole patient population or whatever but what they can do is highlight their views or they highlight issues or things from that patient perspective that perhaps hadn’t been considered before”* (RE2_EU). On the value of direct patient input another EU regulator added *“so far, the decisions we have made, helped by their position, haven’t been challenged by others [other patients]”* (RE3_EU).

In contrast to direct patient input, quantitative patient preference studies are not systematically taken into account in Europe since they are not often submitted. However, EU regulators mentioned that in the context of major contribution to patient care and orphan designation quantitative patient preference studies are provided or requested due to lack of other evidence available. The lack of submissions was emphasised by one EU regulator stating *“if you are talking more on the quantitative, larger samples, elicitation, for instance that is only being done as mentioned in the pilot studies”* (RE2_EU). While quantitative patient preference studies are not often taken to account in EU regulatory decision making, US regulators stated patient preferences studies are regularly submitted: *“in our regulatory decision making we are seeing quite a few preference studies”* (RE6_US), and named multiple examples of decision making on drugs, biologics and devices where patient preferences were taken into account.

Position of patient preferences in regulatory decision making

EU regulators agreed that currently patient preferences elicited in patient preference studies are not systematically taken into account. However, patient preferences can be taken into account or requested on a case-by-case basis and EU regulators reiterated the importance of assessing if patient preference studies could be of added value in the specific situation. One EU regulator added to the discussion *“as much as possible we do consider the patient preferences”* (RE3_EU). In contrast to EU regulators, US regulators stated patient preferences studies are regularly submitted, named multiple examples of decision making where patient preferences were taken into account and explained that patient preferences are increasingly becoming an important factor within the benefit-risk framework mostly for medical devices. While US regulators indicated that patient preference studies are increasingly being submitted and considered in applications, they also stated very clear that submission of patient preference studies is voluntary. EU and US regulators further discussed the potential integration of patient preferences along regulatory processes. These processes included:

- Understanding the disease (US regulators): Regulators found patient preferences able to improve their understanding of the disease.
- Benefit-risk assessment (EU and US regulators): EU and US regulators explained that patient preferences could become part of the different sections of the benefit-risk discussions and could influence the final decision: *“if we are trying to make an assessment we will look at that information, whatever information we may have to suggest what do patients really think”* (RE1_US). Multiple EU regulators believed benefit-risk assessment to be the only process through which patient preferences can have an influence on the final decision, as stated by one of the EU regulators *“Quite frankly, I think it can be only in the benefit-risk. That is where the regulators will make the decision”* (RE4_EU).
- Meaning of benefit-risk profile to patients (US regulators): Patient preferences can be used to understand what patients think about certain benefit-risk profiles.
- Maximum acceptable risk assessment (US regulators): Patient preferences can be used to assess *“The clinically meaningful benefit for a patient, so maximum acceptable risk to a patient”* (RE4_US).
- Weighing of endpoints (EU regulators): An EU regulator mentioned that patient preferences could be used to explore how important different endpoints are to patients.
- Subgroup identification (EU and US regulators): Patient preferences could be used to identify and understand subpopulations. If it would appear that this subpopulation would be more willing to accept the risk to receive the benefits than the majority, according to EU regulators, the product could get approved for the whole population to give patients and prescribers the choice. The subpopulation willing to take the risk would then have the chance of receiving that treatment, and the other patients could refuse the treatment.
- Assessment of major contribution to patient care (EU regulators): Major contribution to patient care was defined as an *“advantage based on a major contribution, so an advantage for a patient. So, it has nothing to do with efficacy and safety”* (RE5_EU). EU regulators are currently requesting to perform patient preference studies if major contribution to patient care is claimed. In the context of major contribution to patient care of orphan drugs an EU regulator stated *“patient preference may be the main information that we are looking at for making our regulatory decisions”* and added *“major contribution to the patient care that accounts for a very small part of the orphan designations that are granted and maintained and not in all cases there is the need of having a patient preference”* (RE5_EU).
- Post-authorisation assessments (EU regulators): EU regulators recognised the value patient preferences could have in post-authorisation assessments.
- Indication expansion (US regulators): Patient preferences were found to influence post-marketing indication expansion, and an example was given in which post-marketing patient preference data was submitted and indication expansion was approved.

Remaining questions and challenges

As indicated above EU regulators emphasized the importance of assessing the necessity of conducting patient preference studies per case or situation. On the difficulty of identifying situations of borderline benefit-risk profiles in advance one EU regulator stated *“I do realise that is going to be difficult to know in advance which one will be that. Therefore, it will probably be difficult to get clear guidance where you really need to do those studies, where you have to provide data in advance”* (RE4_EU).

Other challenges mentioned by EU regulators were: *“to know exactly what is the right number of patients to participate at any given time for it to be representative”* (RE2_EU) and how to be sure that patients understood the questions since regulators do not assess the cognitive burden of the instruments. EU regulators also mentioned that they were not sure how patient preferences could be implemented in evaluations, and about the weight they would have in decision making. Other remaining questions of EU regulators were on how results from different methods in the same population compare, how to distinguish acceptable risk taking from desperation of patients, and what an acceptable percentage of patients accepting the treatment would be and *“how do we translate that in regulatory decisions?”* (RE4_EU).

US regulators only raised the questions on when and how to use what method. US regulators explained that a catalogue of methods was created by US regulators, but that they do not have a lot of experience with the methods: *“we have a catalogue of methods that you are probably familiar with, but, you know, we don’t have a lot of experience with any one method, so we are learning. You know, we don’t know what are the big problems or some of them, you know, what can go wrong. We are open and we are even open to new methods”* (RE4_US).

4.3.3 Use of patient preferences outside regulatory decision making

In this last part on results from regulatory FGDs, information is given on what regulators said about using patient preferences by industry.

EU regulators expressed that *“you can think about patient preference studies almost in every part of the life cycle of the drug”* (RE1_EU). EU and US regulators discussed the following applications of patient preferences outside regulatory decision making:

- Identification of endpoints (EU and US regulators): It was found important that industry considers patient preferences in identifying endpoints for clinical trials: *“to help determine whether the outcomes are important to patients”* or even *“to get a better understanding of a super outcome”* (RE6_US).
- Understanding alternative treatments (US regulators): Patient preferences were found to be informative in assessing what treatment (medicinal products, surgery and devices) options exist for patients.
- Product profile validation (US regulators): To assess in the post-marketing phase if the product fulfils the target product profile including patients’ needs, and to assess factors influencing adherence.
- Informing new product development (US regulators): Patient preferences were seen as a source of information that could inform development of new products, especially for medical devices where development is *“a lot faster”* (RE6_US).

4.4 Results from HTA/payer focus group discussions

Participant demographics of the HTA/payer FGD are presented in Table 4. The themes and sub-themes identified in the HTA/payer FGD discussion are graphically presented in Figure 6 and described at length below.

Stakeholder (N)	Geographical area	Number of participants (n)
HTA/payer (N=4)	Belgium	1
	Germany	1
	UK	1
	Canada	1

Abbreviations: HTA, Health Technology Assessment; N, total number of participants.

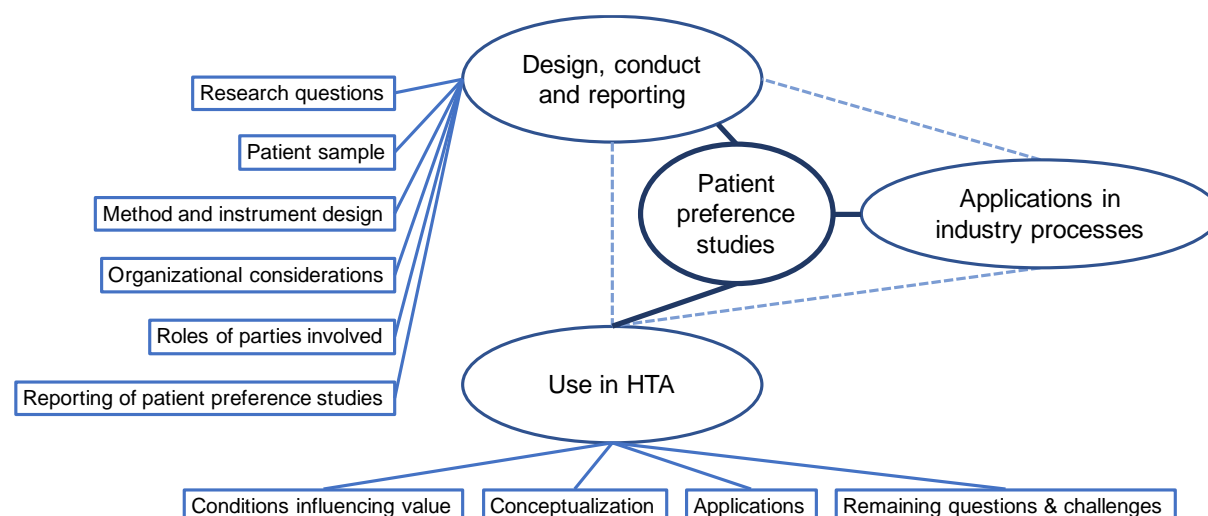


Figure 6. Themes and subthemes identified in the HTA/payer FGD. Dotted line: indication of inter-relation between themes.

4.4.1 Designing, conducting and reporting patient preference studies

In the following part topics are explained, highlighted by HTA/payer representatives to consider in designing, conducting and reporting on patient preference studies.

Research questions

HTA/payer representatives would like patient preference studies to show the outcomes important to patients to assess whether treatments provide these outcomes: *“type of research question that they should answer for me is what kind of treatments which attribute with which outcomes are considered more important for patients than others? In order to allow us to assess whether the treatment that is [inaudible] really works on these outcomes that are considered most important for patients”* (HTA1_EU).

Sample considerations

HTA/payer representatives indicated that the representativeness of the patient sample to the target population is very important. HTA/payer representatives defined the target population to be all patients *“eligible”* (HTA1_EU) or *“authorized”* (HTA3_EU) for the treatment, or *“the expected population in which the treatments will be used”* (HTA2_EU).

On manners to ensure representativeness of the patient sample, HTA/payer representatives highlighted the importance of matching the patient sample to epidemiological data: *“I guess you would have to provide epidemiological data to see what patients there are and that the same numbers are represented in your preference study”* (HTA3_EU). HTA/payer representatives recognized that matching the patient sample to epidemiological data is difficult since *“the data available is always going to be incomplete and imperfect”* and stated that it should be *“a balance between methodological rigour and pragmatism”* (HTA2_EU). One HTA/payer representative suggested that if country-specific information on the population is missing, it is likely that the sample will have to be based on data from other countries. In addition, HTA/payer representatives expressed that characteristics determining preferences should be taken into account and that *“all types of patients”* (HTA1_EU) should be included. HTA/payer representatives mentioned that the patient sample might need to cover different age classes, social economic classes and experiences, before and after, with the respective treatment. Moreover, one HTA/payer representative stated that possible preference heterogeneity should be taken into account. Also, another HTA/payer representative stated that the sample should not only include patients from the clinical trials of that product if the target population is different from the clinical trial sample.

HTA/payer representatives touched upon some cases, including dementia and Alzheimer’s disease, where it is not

possible to elicit patient preferences or where eliciting patient preferences might lead to useless data, and caregiver preferences might be an alternative: *“in some cases it's just not possible to ask patients directly for their preferences and a proxy would be the only alternative”* (HTA1_EU). HTA/payer representatives emphasized that if caregiver preferences are going to be submitted to them, that it should be justified why caregiver preferences were sought and not patient preferences. In addition, one HTA/payer representative mentioned that caregiver preferences would not lead to HTA/payer bodies not accepting the data: *“I think the proxy does have to be justified but shouldn't be a reason for exclusion”* (HTA4_CAN). In contrast, another HTA/payer representative stated that in Germany caregiver preference studies would most likely not be accepted.

Methodology

HTA/payer representatives recognized that certain preference elicitation methods, *“while very rigorous”* (HTA4_CAN), come with a high cognitive burden for patients and found it very important that the method used can be understood by patients, and that there is no large drop-out. Patients should not be excluded from a patient preference study because they do not understand the questions. Instead, HTA/payer representatives argued that the method should be adapted to the patients: *“I think, again, it comes down to, for example, the patient population and other factors that would influence the way you would then design that study”* (HTA2_EU); *“The questionnaire, it's difficult for too many patients so maybe it's not a good questionnaire”* (HTA1_EU).

Organizational considerations

HTA/payer representatives discussed about the resources needed to conduct patient preference studies. The HTA/payer representatives believed these studies to be costly and long in duration, especially in the case of smaller patient populations where recruitment might be more difficult: *“I think often these things are quite expensive and they can take quite a long time in order to recruit, particularly if you have a patient population that's relatively small in number”* (HTA2_EU).

Stakeholder roles in patient preference studies

On roles of stakeholders in designing and conducting patient preference studies, HTA/payer representatives mentioned HTA/payer bodies cannot fund these studies and that *“we're never going to be see[ing] these conducted by HTA bodies”* (HTA4_CAN). HTA/payer representatives expected industry to fund and conduct the studies, but emphasized that industry should assess the appropriateness of conducting such a study per case. Charities were also mentioned as a source of funding. HTA/payer representatives stated that while industry could fund patient preference studies, there might be value in having other independent parties like academics and patient organizations conducting these studies, to account for possible biases from industry. The idea of having multiple parties involved was found to be *“appealing”* (HTA2_EU). Patient preference studies could be conducted in *“public-private partnerships”* (HTA4_CAN) including companies, patient organizations, regulators and HTA/payer bodies, or could be conducted by multiple companies that *“could challenge each other”* (HTA4_CAN). However, HTA/payer representatives mentioned that it is challenging for HTA/payer bodies to be involved in projects because of conflict of interest and because it is *“out of their comfort zone”* (HTA4_CAN), their comfort zone being to critique and appraise. One participant stated that HTA bodies could be involved through scientific advice: *“there's certainly a place for this within scientific advice and I think that would be potentially a dialogue between industry and the HTA bodies to sort of say: Well, this is what we want to do, this is the kind of data we want to collect and this is the method that we think is appropriate for doing that. Now, what are your requirements in terms of, you know, we don't want to spend all this money and all this time to present data to you that you throw out immediately because it hasn't satisfied some requirement”* (HTA2_EU).

On ownership of patient preference data, HTA/payer representatives argued that these data should remain in the public domain and should not be owned by a single company since patient preferences are not treatment specific. Moreover, HTA/payer representatives believed this could avoid duplication of efforts and research fatigue within patient populations.

In contrast to patient preference studies, HTA/payer representatives stated that they would prefer to keep the gathering of qualitative input within the HTA agencies, *“to get a better feel”* (HTA3_EU), or coordinating by these or other agencies.

Reporting patient preference studies to evaluators

HTA/payer representatives emphasized that if patient preference studies would be submitted to them, the objective of the study and how this could facilitate, improve or complicate decision making should be clear. In addition, the selection of the patient or caregiver sample should be justified.

4.4.2 Use of patient preferences in HTA decisions

The next part describes what HTA/payer representatives think about using patient preferences in HTA, including their value, the methods to measure them and the potential application of patient preferences in HTA processes.

Value of patient preferences in HTA

HTA/payer representatives explained that the HTA community find patient preferences to be important: *“there's a very strong recognition of the importance of patient preferences”* (HTA2_CAN). In addition, there is a willingness to incorporate patient preferences in assessments. However, HTA/payer representatives were not sure how important patient preferences could be in HTA since current frameworks do not give weights to the different criteria and are holistic. One HTA/payer representative mentioned that in the future it might be possible to incorporate all aspects in a multi criteria decision analysis. HTA/payer representatives talked about the hierarchy of evidence. While effectiveness was stated to be perceived as the most important criteria, HTA/payer representatives found it difficult, and maybe wrong, to place all types of evidence in a hierarchy. However, one HTA/payer representative expressed that quantitative patient preference studies might be placed over qualitative data, but should be considered together: *“I think in terms of hierarchy of evidence for the patient side, you might place these studies over and above qualitative data but obviously in the way that they sort of complement each other rather than being taken in isolation”* (HTA2_EU). When patient preference studies would be submitted, HTA/payer representatives stated that they would always be considered. Nevertheless, they also expressed that they were unsure if patient preference studies will be submitted often in the future and whether they should always be required.

There was a discussion on the cases for which patient preference studies would be an added value or where it would be difficult to take them into account. While some HTA/payer representatives stated that patient preference studies and qualitative data would be important in all assessments, others stated that it is important to assess when these studies are appropriate since in some cases it might make assessments more complex: *“just to do it uniformly may not be the best approach, just because in some cases it may muddy the waters, it may sort of give you conflicting evidence. It may make decision makers more confused and so it's, again, it's practically weighing up when it's appropriate and when it's not so appropriate to have these preference data”* (HTA2_EU). Cases were discussed where patient preference studies would have the most influence on the assessment, and were summarized as *“when it makes decision making easier or when it gives a better-quality decision making”* (HTA2_EU):

- Availability of other treatments: *“I think that in general when you have a comparative treatment available already and you have a new treatment that modified certain aspects of patients' life then it's important to have information on patient preferences about these domains that will be impacted by treatment”* (HTA1_EU).
- Suspected preference heterogeneity and subgroups: When it is possible that there are subgroups for which the treatment might have a specific value.
- Borderline versus clear-cut benefit-risk decisions: *“In the patients where it's not very clear where you have kind of borderline incremental cost effectiveness ratio, you could use the additional information from the patient preference study”* (HTA1_EU).
- Treatments with minor modifications in quality of life: To understand the value of minor modifications in quality of life, since these are difficult to understand by evaluators.
- Complexity of the treatment: When it not sure that the patient will recover with the treatment.
- Formulation and route of administration influencing adherence: It was found important to assess patient preferences when through measuring these a preferred formulation could be identified reducing non-adherence.
- Prolongation of life treatments affecting quality of life: It is important to know patient preferences on impact on quality of life in case of live saving treatments: *“If they don't get the treatment, they die immediately,*

then it's probably less important to know their preference for life expectancy. Unless of course, this extended quality of life is ten years of additional life years goes with a very bad quality of life" (HTA1_EU).

- Screening programmes: It would be important to know preferences of patients on screening programmes since these might not have an impact on treatment and outcomes.

Current conceptualization of patient preferences in HTA

HTA/payer representatives discussed through which methods and approaches preferences of patient are currently captured. Currently qualitative patient input is, sometimes systematically, sought by HTA bodies through involvement in projects or requesting feedback on decisions and guidelines. HTA/payer representatives stated that they were content with the way qualitative patient input is currently sought and used and stated *"It's also a way of engagement with our stakeholders"* (HTA4_CAN). Qualitative patient input was considered to always have a place in HTA and impossible to replace with quantitative patient preference studies. However, HTA/payer representatives expressed that both could be used in harmony. HTA/payer representatives also acknowledged the limitations of qualitative patient input, being non-representative and unable to explore preference heterogeneity.

The importance and use of QALYs was explained to be different in the different healthcare systems. HTA/payer representatives stated that QALYs and QoL do not cover the patient experience sufficiently and that additional measures are sometimes necessary: *"We see them through assessments, through scientific advising currently, you know, it's not sufficient"* (HTA4_CAN). Also, HTA/payer representatives expressed concerns toward adding more information into the QALY, since that would lead to confusion.

HTA/payer representatives highlighted that there is a place within HTA to take into account quantitative patient preferences: *"I think there's certainly scope and I think this is being increasingly recognised"* (HTA2_EU); *"if there are methods to quantify it and our method can be used in our assessments we would be happy to incorporate them in the future"* (HTA3_EU). The HTA/payer representatives thought quantitative patient preferences could lead to more insight *"into some of the specifics around how preferences work in terms of shaping behaviours and shaping value constructs"* (HTA2_EU). One HTA/payer representative emphasized the importance of keeping patient preferences on outcomes separate from cost information. A concern was expressed on how using both patient preferences and QALYs could lead to double counting: *"I think there is a concern [...] that you might sort of double count in some sense with your patient preference data with what's already included in the QALY"* (HTA2_EU). HTA/payer representatives reiterated the added value of combining quantitative and qualitative evidence in assessments.

Position of patient preferences in HTA

HTA/payer representatives discussed how patient preferences would always be considered when submitted, but explained that their use in assessments would be done on a *"case-by-case basis"* (HTA3_EU). HTA/payer representatives emphasized that use of patient preference studies has to be practical and has to fit within their timelines. In addition, HTA/payer representatives expressed concerns on how patient preferences could complicate decision making and could be confusing: *"I think you also have the aspect of adding to people's workload and potentially adding to complexity and decisions in cases where it's not really warranted"* (HTA2_EU). Because of the cost of patient preference studies, HTA/payer representatives thought they would not be provided in all circumstances, and reiterated on the importance of assessing in which cases these data will support decision making: *"I think it's understanding more about when these data will actually help their decision-making, make it easier, give them better quality data that doesn't already exist or complement other data"* (HTA2_EU). HTA/payer representatives mentioned that patient preference studies should be kept separate from other processes and assessments in HTA, but that it could be combined with qualitative evidence. However, one HTA/payer representative mentioned the difficulty of evaluating patient preferences separately since these can provide information on the importance of the effectiveness to patients.

HTA/payer representatives further discussed the different potential applications of patient preferences along HTA processes. These applications included:

- Scientific advice: To assess if activities in *"development labs"* (HTA4_CAN) are justified.
- Identification of endpoints: To assess which endpoints to consider in assessments.
- Weighing of endpoints: To weigh *"efficacy versus safety"* (HTA3_EU) and *"weigh the end points according to the preferences expressed in preference studies"* (HTA1_EU).

- Subgroup identification: To understand to what subgroups *“the treatment might have particular value within a much larger patient population”* (HTA2_EU), and to understand what the uptake would be in that subgroup.
- Effectiveness and general assessment: To use patient preferences in effectiveness assessments to understand the importance of the effectiveness to patients, leading to inclusion of the results in the general assessment of the intervention.
- Cost effectiveness: HTA/payer representatives thought patient preferences could be included in cost-effectiveness assessments, but were unsure of the mechanism to enable this. Suggestions included: use patient preferences to give a weight to QALYs, predict real-world adherence and cost-effectiveness.

To allow for assessment of patient preference studies, HTA/payer representatives thought a tool to assess the quality and appropriateness of patient preference studies could be valuable, but acknowledged that assessing quality might be context dependent making it difficult to create such a tool: *“it would be great to get to a place where you had a best practice checklist but I'd have my suspicions that it may be not be that straightforward and actually that it may be quite context dependent and there may be a quite a few variables to consider”* (HTA2_EU). The form of the tool was discussed and HTA/payer representatives thought the tool could take the form of a best practice checklist or decision tree and should be validated. The tool should allow for, according to HTA/payer representatives, assessment of appropriateness of the sample and methods, validity, consistency and quality of data.

Remaining questions

The majority of the remaining questions were on what the best methods are to measure patient preferences, how patient preference studies should be designed to inform HTA, the cases in which patient preferences should be included in assessments, and how they could be integrated into HTA: *“I don't know whether we've thought about how we would actually use something like that.”* (HTA4_CAN). In addition, one HTA/payer representative raised the question as to what extent patient preferences are valid over time: *“there is a question, once you've conducted a preference study, how valid are those preferences across over time. You know, even within that sample, preferences may change over time”* (HTA2_EU).

4.4.3 Applications of patient preferences outside HTA

In this last part of results from the HTA FGD, information is given on what HTA/payer representatives said about using patient preferences by industry.

HTA/payer representatives found it interesting how patient preferences can be used in early development to inform *“go, no-go type decisions made by companies”*.

5. Topics table integrating results from literature, interviews and focus group discussions

In the results of the literature review and interviews, several topics reappear, either: 1) across different decision-making contexts (for literature results) 2) across different stakeholder groups (for interview or FGD results) 3) as a concern, need, expectation or desire (for literature and interview results). Therefore, these topics were reorganized into **five overarching themes**: 1) topics related to the **‘Awareness & attitudes among stakeholders’** 2) topics related to the **‘Methods and design for patient preference studies’** 3) topics related to **‘Practical issues’** and 4) topics related to **‘Handling patient preference information’** (see table 9). This table aims to give a general overview of the integrated results from the four different sub-tasks of task 2.1. More context such as references and explanatory quotes to these topics can be found in the results section of the literature review or interviews above.

1. Topics/issues ~ Awareness & attitudes among stakeholders	For INT/FGD: stakeholder group	For LIT: decision-making context	Needs/ Expectations/ Concerns/ Other	Source (LIT/INT/FGD)
Positive attitude towards concept of PP	AC, HTA, REG, IN	IDM, MA, HTA	Other	LIT, INT, FGD
Awareness & understanding among stakeholders about concept of PP	AC, HTA	NA	Needs	INT
Education/training opportunities for stakeholders	AC, HTA, REG	NA	Concerns, needs	INT
Terminology & taxonomy of PP research	AC	HTA	Needs	INT, LIT
Acceptance/cultural change	AC, HTA, IN, PO	NA	Concerns, needs	INT, FGD
Demonstrating added value of including PP in development	REG	MA	Needs	INT, LIT
Experience & familiarity with PP & methods among sponsors, researchers, decision-makers	HTA, REG	MA, HTA	Concerns, needs	INT, LIT, FGD
2. Topics/issues ~ METHODS and DESIGN for studying PP	For INT/FGD: stakeholder group	For LIT: decision-making context	Needs/Expectations/ Concerns/Other	Source (LIT/INT)
Patient knowledge & patient education	AC, IN, PA/CA, PH, REG, HTA, PO	IDM, MA, HTA	Reason for doubting PP, concerns, needs	INT, LIT, FGD
Samples & representativeness (type of sample, sample size, societal preferences vs patient preferences, representativeness of sample, patient heterogeneity)	AC, PO, REG, IN, HTA	MA, HTA	Reason for doubting PP, concerns, needs	INT, LIT, FGD

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Stability of PP & influences on PP (emotional, subjective aspects, heuristics, time)	AC, PH, REG, HTA	MA	Reason for doubting PP, concerns	INT, LIT, FGD
Transferability of PP	NA	HTA	Concerns	LIT
Scientifically strong/robust methods	REG, AC, HTA	NA	Reason for doubting PP, concerns, needs	INT, LIT, FGD
Validation and validity of PP methods & results	AC, HTA, REG, IN	MA, HTA	Concerns, needs	INT, LIT, FGD
Reproducibility of PP method & results	AC, HTA, PH	MA	Concerns, needs	INT, LIT
Generalizability of PP method & results	AC, REG	HTA	Reason for doubting PP, concerns, needs	INT, LIT
Best practices	AC, IN, HTA	MA, HTA	Needs, concerns	INT, LIT, FGD
Regulatory rules/guidance on how to measure PP (e.g. selection of method, sample, time point in MPLC)	AC, IN	MA, HTA	Concerns, needs	INT, LIT, FGD
Standardization of collecting PP	HTA, IN, PH, AC	NA	Concerns, needs	INT, FGD
Quality criteria/checklist of PP studies	HTA	NA	Needs, other	INT, FGD
Avoiding influences on study design leading to bias (e.g. question framing)	REG, AC, HTA, PA/CA, PH	MA, HTA	Concerns, needs	INT, LIT, FGD
Choosing endpoints & levels	AC	HTA	Concerns	INT, LIT
Uncertainty about comparability of results between methods	AC, REG	MA, HTA	Concerns	LIT, INT, FGD
Reliability of method	HTA	NA	Concerns	INT, LIT
Cognitive burden of method	PA, HTA	MA, HTA	Concerns	INT, LIT, HTA
Communication towards patients of quantitative aspects in PP study	NA	MA	Concerns	LIT
Quality of PP study results	In	HTA	Concerns	INT, LIT
Wording & complexity of questions	PO, REG, HTA	HTA	Concerns	INT, LIT, FGD
Including relevant stakeholders in design (e.g. patients, decision-makers)	PO, IN, REG, HTA	Industry, MA	Concerns, needs	INT, LIT, FGD
Necessity of PP study	NA	MA	Other	LIT
Responsible stakeholder for collecting PP	REG	MA	Concerns, other	LIT, FGD
Point in time in MPLC to collect PP	NA	MA	Concerns, needs	LIT
Type of PP needed for decision (e.g. PP for health-related aspects or broader)	NA	HTA	Concerns	LIT
Focus of preference study & research questions preference studies should answer	PA, CA, IN, REG	NA	NA	FGD

Complementarity between qualitative and quantitative research in preference studies	REG	NA	NA	LIT, FGD
Importance considering heterogeneity in preferences	REG, HTA	NA	NA	FGD
Sample considerations: importance of introducing heterogeneity in the sample	PA, CA, IN, REG, HTA	NA	NA	FGD
Sample considerations: using epidemiological data	HTA, REG	NA	NA	FGD
Information need when participating in preference study	PA, CA	NA	NA	FGD
Preferred methodology for asking questions on preferences	PA, CA, IN	NA	NA	FGD
Preferred way of handling preference study information	PA, CA	NA	NA	FGD
3. Topics/issues ~ Practical issues	For INT/FGD: stakeholder group	For LIT: decision-making context	Needs/Expectations/Concerns/Other	Source (LIT/INT)
Barriers to approaching patients	IN, PO	NA	Concerns, needs	INT
Reflecting on recruitment source of patients	REG	NA	Needs	FGD
Risk of obtaining unrepresentative sample if recruitment via PO	REG	NA	Concern	FGD
Incentivizing patients to participate in PP study	PO	NA	Needs	INT
Factors influencing patient participation	PA, CA	NA	Other	FGD
Money, logistics and collaboration to conduct PP	PH, REG, HTA	NA	Needs	INT, FGD
Early planning of preference study	IN	IDM, MA, HTA	Needs	LIT, FGD
Early set-up of sample strategy	REG	NA	NA	FGD
4. Topics/issues ~ Handling PP information	For INT/FGD: stakeholder group	For LIT: decision-making context	Needs/Expectations/Concerns/Other	Source (LIT/INT)
Data disclosure to patients	PA/CA	NA	Needs	INT
Ownership of PP study results should remain in public domain	HTA			FGD
Method for submitting PP to decision-makers	NA	MA	Concerns	LIT
Transparent reporting of PP study	AC, HTA	HTA	Concerns	INT, LIT, FGD
Transparent reporting of potential sample biases towards regulators	REG	NA	NA	FGD
Transparent reporting of sample strategy	HTA	NA	NA	FGD
Avoiding misuse of PP data to overcome other aspects of technology	AC, REG	NA	Concerns	INT

Dealing with unexpected results	IN	MA	Concerns, needs	INT, LIT, FGD
Confidentiality of PP study results	PA/CA, PO	NA	Concerns	INT
5. Topics/issues ~ Using PP IN decision-making	For INT/FGD: stakeholder group	For LIT: decision-making context	Needs/Expectations/Concerns/Other	Source (LIT/INT)
Uncertainty about how to use/integrate preferences in development/regulatory/HTA decisions	IN, REG, HTA	NA	Other	FGD
Complementarity between direct patient input and use of PP from studies in decision-making	HTA, REG	MA, HTA	Other	LIT, INT, FGD
Uncertainty about acceptance & use of PP by decision-makers	IN	MA	Concerns	LIT, FGD
Legal/regulatory/policy/other framework for integrating PP	AC, REG, HTA, PO	NA	Needs	INT, FGD
Impact/weight of PP in decision/vs other decision criteria	IN, PH, AC, REG, HTA	HTA, REG	Reason for doubting PP, concerns	INT, LIT, FGD
Relevance of PP for decision in view of other factors	REG, IN, HTA	MA, HTA	Other	INT, LIT, FGD
Feasible way of including PP in current (regulatory) framework (incl. resources)	REG, HTA	MA, HTA	Reason for doubting PP, needs, concerns	INT, LIT
Applicability of PP data to MA decision	REG	NA	Needs	INT
Avoiding disparity between disease areas with strong & weak PO	HTA	NA	Concerns	INT
PP rendering decision process more complex	HTA	NA	Reason for doubting PP	INT, FGD
Using PP together with QALY for reimbursement would lead to double counting	HTA	NA	Concern	FGD
Final impact of PP on decision-making	AC, HTA, IN, PA, PH, REG	NA	Expectations	INT, FGD

Table 9. 1st column: topic mentioned in literature review or interviews, 2nd column: stakeholder that indicated the topic during the interview or focus group discussion, 3rd column: decision-making context where topic is mentioned in literature results 4th column= nature of the topic, 5th column= source of the topic. PP= patient preferences; INT= interviews; FGD= focus group discussions; LIT= literature review; AC= academics; IN= industry representatives; PA= patients; CA= caregivers; HTA= HTA/reimbursement (representatives); PH= physicians; REG= regulators; IDM= industry decision-making; MA= marketing authorization; NA= not applicable.

Limitations

It is important to acknowledge the limitations of the studies conducted within task 2.1. Below, the limitations per sub-study conducted within task 2.1 are discussed.

Exploratory interviews

As regards the exploratory interviews, sampling occurred through a purposive sampling technique; we invited interviewees based upon whether or not we thought they could contribute to answering our research questions. However, potential interviewees were also selected based upon convenience; namely on whether or not they could attend the PREFER meeting. This sampling strategy might have resulted in a biased sample, as interviewees from outside the PREFER consortium were not eligible. Next, the interview guide of the exploratory interviews contained several questions that appeared to be too complex for interviewees. Similarly, although we adopted a semi-structured interview approach, often the interview protocol was not tailored enough to the interviewee's field of expertise. This became apparent when discussing all stages of the MPLC; most participants were not able to offer information about each stage of the life cycle as their experience was often limited to one particular stage. We addressed these problems in the subsequent round of semi-structured interviews: 1) the sampling strategy was modified in order to include stakeholders from outside the PREFER project and we selected interviewees based upon selection criteria to allow for a heterogeneous sample, 2) questions that were too complex were removed from the interview guide, 3) the subsequent interviews allowed for a more flexible interviewing approach as we highlighted in the interview guide those specific questions that could be skipped for interviewees that indicated they were not familiar with preference methods.

Literature review

The literature review was also subject to limitations. First, the review was based upon published literature only. This might have coloured the views that are described in the literature review, as only published views could be described (publication bias). Second, as a preliminary scoping exercise revealed a lack of qualitative research articles on stakeholder perspectives, we needed to broaden our scope to allow different types of literature such as project reports, perspective articles and reviews. This expansion led to the inclusion of different types of literature, which might be viewed as a limitation since we wanted to investigate stakeholder views, which are primarily investigated via qualitative research. However, we felt that this expansion contributed to the richness of our review results, given the novelty of the research field and the diversity of information it enabled us to capture. Third, grey literature was mainly obtained via PREFER members, which might be a biased population. However, we felt that we needed to make as much as possible use of the expertise within the consortium and we included other grey literature via hand searching and snowballing. Further, because of the size of our consortium and the amount of literature that was forwarded we believe that we successfully included the most important additional literature. Fourth, our exclusion criteria led to the exclusion of: 1) literature focussed only on preferences within the individual treatment decision-making, 2) non-English literature and 3) literature from outside the US/EU. Although this exclusion might have resulted in a biased pool of included literature, it is difficult to assess the exact impact of this exclusion and we felt these exclusion criteria were needed to have literature specific enough to answer our review questions. Fourth, the second step of our selection protocol, namely the application of the in- and exclusion criteria to the full text, was applied by only one researcher (RJ). However, we felt that it was necessary to take this approach due to time restrictions limiting the possibility of reviewing full texts by two persons. Fifth, we included literature if they described the use of a preference method or the use of preferences resulting from the application of a preference method without defining beforehand "preference method". It remains unknown whether this criterion led to the exclusion of relevant literature, given the novelty of the preference research field and the inconsistency in terminology related to preference research in literature. A final limitation related to the literature review might be that the studies were not formally appraised through the use of existing quality appraisal techniques because we did not find a technique to appraise all the different types of literature included, from single studies to systematic reviews and guidelines.

Semi-structured interviews

For the semi-structured interviews, we used a Google form to invite PREFER members to suggest potential interviewees, which might have resulted in a biased sample. However, the suggested interviewees were afterwards screened against the inclusion criteria and suggested interviewees from within the PREFER consortium were excluded. Moreover, we actively reached out to potential interviewees from outside the PREFER consortium. Second, the traditional limitations of opting for phone interviews instead of face-to-face interviews apply for the phone interviews we conducted: 1) the reduction of social cues and spontaneity: as we were unable to see the interviewee, body language could not be used as an extra source of information and interviewees might have been less spontaneous in their reactions, 2) the reduction of standardization of the interview environment: phone interviews limited our control over the interviewee's environment: e.g. industry interviewees might have been located in the vision field of their co-workers/managers during the interview (*). Despite these limitations, we feel phone interviews were justified in our case since we wanted to interview geographically dispersed people and we wanted to make the interview as convenient as possible for people with limited time and/or mobility (*). Third, there were eight different interviewers, with likely different interviewing styles. However, we felt that having 8 different interviewers was necessary to have some of the interviews conducted in the native language of the interviewee and in order to have the 142 interviews conducted within a reasonable amount of time. We tried to counteract the possible variability in interviewing styles by setting-up an interviewing protocol describing specific instructions on how the interview should be conducted. A last important limitation relates to terminology; interviewees had a variety of definitions in mind when talking about 'patient preferences', which might have coloured our results. Furthermore, because we wanted to allow for a heterogeneous sample, we chose not to exclude potential interviewees with a lower familiarity and/or expertise with patient preferences and methods, which might have contributed to differences in definitions of 'preferences' interviewees were referring to when talking about preferences throughout the interview. We paid attention to this by: i) providing a definition¹⁰ in the beginning of the interview to denote patient preferences in a more precise way and ii) indicating in the results the different types of definitions interviewees spontaneously had in mind.

Focus group discussions

As for the FGDs, although it is often advocated to have as much as possible a homogenous group, the inclusion criteria for the participants of the patient FGDs did not include criteria related to the time of diagnosis nor to their age, which might have led to an increased variability in participants. Moreover, different recruitment strategies were used in the different countries: participants from Italy, Romania and Sweden were recruited via the treating physician, whereas participants from the UK were recruited via the patient organization 'MDUK'. Also, the number of patients and the ratio of patients versus caregivers differed in the different patient FGDs (e.g. the Romanian FGD consisted out of ten patients and no caregivers and the UK patient FGD consisted out of two patients and two caregivers). Similarly, the FGDs took place in different settings (e.g. the Romanian FGD took place in the hospital where the selected patients were hospitalized, whereas the UK FGD took place in a hotel). However, we felt this flexibility was needed as different patient populations require different approaches; e.g. for the UK FGD it was critical to have caregivers present in view of the severity of the disease whereas for the Romanian FGD, the FGD could easily be conducted with only patients as they were physically capable of being present. Next, there were some limitations specific to the Romanian and Italian FGD. For the Romanian FGD, there was a miscommunication about the starting hour of the FGD, resulting in the fact that the participants had been waiting prior to the FGD for the moderating team to arrive. However, we felt that this did not detract significantly from the richness of the FGD. For the Italian FGD, there was one participant that arrived after the start of the FGD. However, at this time only the introduction was given and the first topic was introduced. Finally, with respect to the FGDs conducted with industry, HTA and regulatory representatives, we chose to conduct these FGDs through a conference call with only sound and no visuals, for which the above-mentioned limitations and justifications apply (*).

¹⁰ *Academics, regulators, HTA/reimbursement representatives and industry interviewees were presented with the following definition: "The relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions. In other words, patient preferences are the basis of how patients choose a particular treatment over others. To make a choice, patients make trade-offs between a treatment's characteristics, weighing its advantages and disadvantages collectively."*

Conclusion

Patient preferences can serve to inform various stakeholders in many ways, however more awareness, acceptance and education regarding the concept, measurement and its implementation is needed throughout the various steps in the medical product life cycle. The lack of standardization and consensus on methodological aspects of methods to measure patient preferences needs special attention in follow-up research.

Appendix

Appendix 1: Search queries

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((opinion[tiab] OR opinions[tiab] OR belief[tiab] OR beliefs[tiab] OR believes[tiab] OR view[tiab] OR views[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR attitude[tiab] OR attitudes[tiab] OR assumption[tiab] OR assumptions[tiab] OR judgment[tiab] OR judgments[tiab] OR "point of view"[tiab] OR "points of view"[tiab] OR perspective[tiab] OR perspectives[tiab] OR desire[tiab] OR desires[tiab] OR expectations[tiab] OR expectation[tiab] OR prediction[tiab] OR predictions[tiab] OR outlook[tiab] OR prospect[tiab] OR prospects[tiab] OR expectancy[tiab] OR expectancies[tiab] OR concern[tiab] OR concerns[tiab] OR doubt[tiab] OR doubts[tiab] OR requirement[tiab] OR requirements[tiab] OR necessity[tiab] OR precondition[tiab] OR prerequisite[tiab] OR condition[tiab] OR demand[tiab] OR demands[tiab] OR needs[tiab] OR need[tiab] OR consideration[tiab] OR considerations[tiab] OR problem[tiab] OR problems[tiab] OR issue[tiab] OR issues[tiab] OR recommendation[tiab] OR guideline[tiab] OR 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Embase

opinion:ti,ab OR opinions:ti,ab OR belief:ti,ab OR beliefs:ti,ab OR believes:ti,ab OR view:ti,ab OR views:ti,ab OR viewpoint:ti,ab OR viewpoints:ti,ab OR attitude:ti,ab OR attitudes:ti,ab OR assumption:ti,ab OR assumptions:ti,ab OR judgment:ti,ab OR judgments:ti,ab OR 'point of view':ti,ab OR 'points of view':ti,ab OR perspective:ti,ab OR perspectives:ti,ab OR desire:ti,ab OR desires:ti,ab OR expectations:ti,ab OR expectation:ti,ab OR prediction:ti,ab OR predictions:ti,ab OR outlook:ti,ab OR prospect:ti,ab OR prospects:ti,ab OR expectancy:ti,ab OR expectancies:ti,ab OR concern:ti,ab OR concerns:ti,ab OR doubt:ti,ab OR doubts:ti,ab OR requirement:ti,ab OR requirements:ti,ab OR necessity:ti,ab OR precondition:ti,ab OR prerequisite:ti,ab OR condition:ti,ab OR demand:ti,ab OR demands:ti,ab OR needs:ti,ab OR need:ti,ab OR consideration:ti,ab OR considerations:ti,ab OR problem:ti,ab OR problems:ti,ab OR issue:ti,ab OR issues:ti,ab OR recommendation:ti,ab OR guideline:ti,ab OR recommendations:ti,ab OR guidelines:ti,ab OR assessment:ti,ab OR assessments:ti,ab OR criteria:ti,ab OR criterias:ti,ab OR criterion:ti,ab OR 'decision making':ti,ab OR 'decision-making':ti,ab OR 'decision point':ti,ab AND (patient:ti,ab OR patients:ti,ab OR 'patient advisory':ti,ab OR 'patient advocacy':ti,ab OR 'patient advocate':ti,ab OR 'patient advocacy'/de OR 'patient association':ti,ab OR 'patient associations':ti,ab OR 'patient organization':ti,ab OR 'patient organisation':ti,ab OR 'patient organizations':ti,ab OR 'patient organisations':ti,ab OR 'health technology assessment body':ti,ab OR 'health technology assessment institution':ti,ab OR 'hta body':ti,ab OR 'hta institution':ti,ab OR 'reimbursement body':ti,ab OR 'national reimbursement body':ti,ab OR 'national reimbursement institution':ti,ab OR 'reimbursement institution':ti,ab OR 'reimbursement agency':ti,ab OR regulatory:ti,ab OR 'ministry of health':ti,ab OR 'regulatory body':ti,ab OR 'regulatory bodies':ti,ab OR 'regulator':ti,ab OR ema:ti,ab OR

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((opinion or opinions or belief or beliefs or believes or view or views or viewpoint or viewpoints or attitude or attitudes or assumption or assumptions or judgment or judgments or "point of view" or "points of view" or perspective or perspectives or desire or desires or expectations or expectation or prediction or predictions or outlook or prospect or prospects or expectancy or expectancies or concern or concerns or doubt or doubts or requirement or requirements or necessity or precondition or prerequisite or condition or demand or demands or needs or need or consideration or considerations or problem or problems or issue or issues or recommendation or guideline or recommendations or guidelines or assessment or assessments or criteria or criterias or criterion or "decision making" or "decision-making" or "decision point").ab,ti. and ((patient or patients or "patient advisory" or "patient advocacy" or "patient advocate" or "patient association" or "patient associations" or "patient organization" or "patient organisation" or "patient organizations" or "patient organisations" or "health technology assessment body" or "health technology assessment institution" or "HTA body" or "HTA institution" or "reimbursement body" or "national reimbursement body" or "national reimbursement institution" or "reimbursement institution" or "reimbursement agency" or regulatory or "ministry of health" or "regulatory body" or "regulatory bodies" or "regulator" or EMA or "European Medicines Agency" or FDA or "Food and Drug Administration" or "policy maker" or "Health Planning Organization" or "Health Planning Organizations" or "Health Planning Organisation" or "Health Planning Organisations" or "drug industry" or "Medical device industry" or "pharmaceutical industry" or "pharmaceutical company" or "pharmaceutical companies" or "pharmaceutical sector").ab,ti. or pharmaceutical industry/ or physician.ab,ti. or physicians.ab,ti. or clinician.ab,ti. or clinicians.ab,ti. or "health care professional".ab,ti. or "health care professionals".ab,ti. or "healthcare professional".ab,ti. or "healthcare professionals".ab,ti. or "health care provider".ab,ti. or "health care providers".ab,ti. or "healthcare provider".ab,ti. or "healthcare providers".ab,ti. or doctor.ab,ti. or doctors.ab,ti. or caregiver.ab,ti. or caregivers.ab,ti. or caretaker.ab,ti. or caretakers.ab,ti. or academic.ab,ti. or academics.ab,ti. or academician.ab,ti. or academicians.ab,ti. or researcher.ab,ti. or researchers.ab,ti.) and ("patients preference" or "patients preferences" or "preference of patients" or "preferences of patients" or "patient preference" or "patient preferences" or "preference of a patient" or "preference of the patient" or "preferences of a patient" or "preferences of the patient").ab,ti. and (("elicitation methods" or method or methodology or empirical or "qualitative method" or qualitative or "quantitative method" or quantitative or technique or techniques or Methodology).ab,ti. or methodology/ or Measuring.ab,ti. or measurement.ab,ti. or measurements.ab,ti. or assessment.ab,ti. or assessments.ab,ti. or inclusion.ab,ti. or including.ab,ti. or include.ab,ti. or incorporate.ab,ti. or incorporating.ab,ti. or incorporation.ab,ti. or involving.ab,ti. or involvement.ab,ti. or involve.ab,ti.) and ("life cycle of a drug" or "life cycle of a medical device" or "medical device life cycle" or "lifecycle of a drug" or "lifecycle of a medical device" or "medical device lifecycle" or "drug life cycle" or "drug lifecycle" or "drug development" or "medical device development" or "development of drugs" or "development of a drug" or "development of medical devices" or "development of a medical device" or "benefit and risk" or "risk and benefit" or benefit-risk or risk-benefit or reimbursement or "drug research" or "medical device research" or "clinical trials" or "clinical trial" or "health technology assessment" or "health technology assessments").ab,ti.) not ("shared decision making" or "shared decision-making" or monitoring or biomarker or biomarkers).ab,ti. AND english.lg. AND ("2011" or "2012" or "2013" or "2014" or "2015" or "2016").yr.

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OR criterias OR criterion OR "decision making" OR "decision-making" OR "decision point") OR ab(opinion OR opinions OR belief OR beliefs OR believes OR view OR views OR viewpoint OR viewpoints OR attitude OR attitudes OR assumption OR assumptions OR judgment OR judgments OR "point of view" OR "points of view" OR perspective OR perspectives OR desire OR desires OR expectations OR expectation OR prediction OR predictions OR outlook OR prospect OR prospects OR expectancy OR expectancies OR concern OR concerns OR doubt OR doubts OR requirement OR requirements OR necessity OR precondition OR prerequisite OR condition OR demand OR demands OR needs OR need OR consideration OR considerations OR problem OR problems OR issue OR issues OR recommendation OR guideline OR recommendations OR guidelines OR assessment OR assessments OR criteria OR criterias OR criterion OR "decision making" OR "decision-making" OR "decision point")) AND (ti(patient OR patients OR "patient advisory" OR "patient advocacy" 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Guidelines International Network

"patient preferences"

Appendix 2: Deductive coding tree

1. General considerations

- Desires
 - Value of patient preferences in all stages of the medical product life cycle
 - One patient preference method to inform both benefit-risk and cost-benefit assessments
- Expectations
- Concerns
- Requirements
 - Interaction between stakeholders

2. Industry processes and decision-making

- Desires
 - Value of patient preferences in industry processes and decision-making
- Expectations
- Concerns
 - Methodological and operational concerns
 - Sample characteristics
 - Recruitment
 - Feasibility
- Requirements
 - Methodological and operational requirements
 - Type of patient preference method
 - Feasibility
 - Type of patient preference information
 - Reliability, validity and generalizability
 - Sample characteristics

3. Benefit-risk assessment (BRA)

- Desires
 - Value of patient preferences in BRA
- Expectations
- Concerns
 - Methodological and operational concerns
 - Sample characteristics
 - Recruitment
 - Feasibility
 - Interpretation and uptake of PP
 - Aligning patient preference information with clinical trial results
- Requirements
 - Methodological and operational requirements
 - Type of patient preference method
 - Feasibility
 - Type of patient preference information
 - Reliability, validity and generalizability
 - Sample characteristics

4. Health technology assessment (HTA)

- Desires
 - Value of patient preferences in HTA
- Expectations
- Concerns
 - Methodological and operational concerns
 - Sample characteristics
 - Recruitment
 - Feasibility
 - Interpretation and uptake of PP
 - Aligning patient preference information with other data
- Requirements
 - Methodological and operational requirements
 - Type of patient preference method
 - Feasibility
 - Type of patient preference information
 - Reliability, validity and generalizability
 - Generic versus disease-specific information
 - Sample characteristics

Appendix 3: Online form sent to PREFER members for interviewee proposals

IMI PREFER: Suggest an interviewee

*** Registration form below ***

Dear PREFER member,

As you know our project IMI PREFER will develop knowledge about the implementation of patient preferences according to the needs and opinions of different stakeholders. IMI PREFER intends to develop candidate guidelines and standards for industry, regulators and payers for the collection and use of this information. For more information on the IMI PREFER project please visit our website: <http://imi-prefer.eu/>.

Through a series of interviews, data will be collected that will help understand the needs, desires, expectations and requirements of different stakeholders about the assessment and use of patient preference information. Also, the interviews will reveal in which processes of drug and medical device development, patient preferences are already used and which conditions and contextual factors influence this usage.

The interviews will be conducted with the different stakeholders: patient advisory groups, Health Technology Assessment bodies, regulatory bodies, industry experts, physicians, patients, caregivers and academics in 8 different countries: Sweden, Italy, Romania, the United Kingdom, the United States, the Netherlands, France, and Germany. The interviews will be conducted between January and April 2017. Each interview will take about an hour, and can be conducted face to face, by phone or Skype, as preferred by the interviewee.

If you, as a PREFER member, are/know a person who should be interviewed because of his/her knowledge or position, who belongs to one of the stakeholder groups, and is a resident of one of the countries mentioned above please fill out the registration form below. The deadline to suggest interviewees is the 30th of January 2017.

If you would like to register/suggest multiple interviewees, please fill out this form separately for each suggested interviewee. You can already open this form again in another window by clicking on this link: <https://goo.gl/forms/bqUs5dw0xtFze1B73>. Do not forget to click on the 'submit' button for every form that you fill in.

A selection will be made of the proposed interviewees based on purposive sampling.

Thank you in advance!

On behalf of the PREFER project team,
Prof. Dr. Isabelle Huys

Ethics details of the study:

Title of the study: Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) 2.1 + 2.2

Sponsor of the study: The European Commission, the Innovative Medicines Initiative

Medical Ethics Committee: Medical Ethics Committee of UZ KU Leuven

Head of research: Prof. Huys Isabelle, KU Leuven, Clinical Pharmacology and Pharmacotherapy,

O&N II Herestraat 49 - Box 521, 3000 Leuven, Belgium

E-mail: isabelle.huys@kuleuven.be Tel.: +32 16 33 04 09

* Required

Your details

Your name *

Your answer

Would you like to register yourself as an interviewee or would you like to suggest an interviewee? *

- ☐ I want to register myself as an interviewee
- ☐ I want to suggest an interviewee

The interviewee's contact information

- If you would like to register yourself as an interviewee please fill in your contact information

- If you want to suggest an interviewee please fill in the contact information of this person

Name *

Country *

- ☐ France
- ☐ Germany
- ☐ Italy
- ☐ the Netherlands
- ☐ Romania
- ☐ Sweden
- ☐ United Kingdom
- ☐ United States
- ☐ Other: _____

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Class of stakeholder group *

- ☐ Academia
- ☐ Caregivers
- ☐ Industry (pharmaceutical / medical device)
- ☐ Health Technology Assessment body
- ☐ Patient advocacy group
- ☐ Patients
- ☐ Physicians
- ☐ Regulatory body
- ☐ Reimbursement agency

Organization *

Your answer

Current role *

Your answer

Fields of expertise *

Your answer

What is the value of interviewing this person for the PREFER project? *

Your answer

Email *

Your answer

Phone number

Your answer

Comments

Your answer

The provided information will not be used for any other purposes than contacting the interviewee for an interview. To register the interviewee in our database please agree with the terms. *

- ☐ I agree with the terms. The IMI PREFER consortium can use the information that I provided here in this registration form to contact the interviewee.

Please submit the form below

SUBMIT

Never submit passwords through Google Forms.

Appendix 4: Inclusion criteria for interviewees

For all stakeholders: think about a mix of males and females whenever possible

1) Regulatory Authorities:

Within each main country at least one interviewee with knowledge in medical device regulation (n=4).

MAIN COUNTRIES

SWEDEN

N=2 Representatives of Swedish Medical Products Agency with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=2 Swedish nationals with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

2) ROMANIA

N=2 Representatives of Romanian National Agency for Medicines and Medical Devices with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=2 Romanian nationals with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

ITALY

N=2 Representatives of Italian Medicines Agency (AIFA) with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=2 Italian nationals with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

UK

N=2 Representatives of Medicines & Healthcare Products Regulatory Agency with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=2 UK nationals with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

VALIDATION COUNTRIES

THE NETHERLANDS

N=1 Representative of Medicines Evaluation Board (CBG) with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=1 Dutch national with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

GERMANY

N=1 Representative of Federal Institute for Drugs and Medical Devices (BfArM) - with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=1 German national with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

FRANCE

N=1 Representative of French National Agency of Medicine and Health Products Safety (ANSM) with i) a formal role in healthcare products regulation process AND ii) experience in regulatory affairs as well as knowledge of national regulations

N=1 French national with a role or official position within EMA OR ii) collaborations and/or interactions with European regulatory agencies for the Evaluation of Medicinal Products AND ii) knowledge of European legislation

US

N=1 Representative of US Food and Drug Administration (FDA) FDA from the Center for Drug Evaluation and Research (CDER)

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or the Center for Biologics Evaluation and Research (CBER)

N=1 Representative of US Food and Drug Administration (FDA) from the Center for Devices and Radiological Health (CDRH).

2) HTA/reimbursement

Additionally over the countries: ensure the inclusion of bodies with differing scope and budget responsibilities

MAIN COUNTRIES

SWEDEN

N=4 Representatives of i) a Swedish Health Technology Assessment Organization or a Swedish reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

ROMANIA

N=4 Representatives of i) a Romanian Health Technology Assessment Organization or a reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

ITALY

N=4 Representatives of i) an Italian Health Technology Assessment Organization or a Italian reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

UK

N=4 Representatives of i) an UK Health Technology Assessment Organization or a reimbursement agency OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

VALIDATION COUNTRIES

THE NETHERLANDS

N=2 Representatives of i) a Dutch Health Technology Assessment Organization or a reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

GERMANY

N=2 Representatives of i) a German Health Technology Assessment Organization or a reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

FRANCE

N=2 Representatives of i) a French Health Technology Assessment Organization or a reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

US

N=2 Representatives of i) an American Health Technology Assessment Organization or a reimbursement agency; OR ii) who are involved in the evaluation of a health technology OR in the prescription drugs and health care reimbursement decision-making procedures.

3) Patient, caregivers and Patient Organisation:

MAIN COUNTRIES

SWEDEN

Target disease: Rheumatoid Arthritis

N=1 Swedish representative of one of the main (Swedish) Rheumatoid Arthritis patient organisations

N=1 Patient over 18 newly diagnosed with RA (within 6 months)

N=1 Patient over 18 on at least one synthetic DMARD

N=1 Patient over 18 on at least one biological DMARD

ROMANIA

Target disease: Cardiovascular Diseases

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N=1 Romanian representative of one of the main (Romanian) Cardiovascular diseases patient organisations

N=1 Patient i) aged ≥ 18; ii) recent (<6months) cardiovascular event

N=1 Patient i) aged ≥ 18; ii) diagnosed with a cardiovascular disease; iii) more than 2 years post-event

N=1 Patient i) aged ≥ 18; ii) diagnosed with a cardiovascular disease; iii) more than 5 years post-event

ITALY

Target disease: lung cancer

N=1 Italian representative of one of the main (Italian) cancer patient organisations

N=1 Patient i) aged ≥ 18; ii) diagnosed with lung cancer within 3 months; and iii) in treatment

N=1 Patient i) aged ≥ 18; ii) diagnosed with lung cancer within 1 year; and iii) in treatment

N=1 Patient i) aged ≥ 18; ii) diagnosed with lung cancer iii) more than 5 years post-diagnosis; and iv) out of treatment

UK

Target disease: muscular dystrophy

N=1 UK representative of one of the main (UK) muscular dystrophy patient organisations

N=1 Patient newly diagnosed (<6months) with muscular dystrophy; i) aged ≥ 18 OR ii) caregiver if patient is younger than 18 or cognitive impaired

N=2 Patient diagnosed with muscular dystrophy; i) aged ≥ 18 OR ii) caregiver if patient is younger than 18 or cognitive impaired

VALIDATION COUNTRIES

THE NETHERLANDS

Target disease: muscular dystrophy

N=1 Dutch representative of one of the main (Dutch) muscular dystrophy patient organisations

N=1 Patient diagnosed with muscular dystrophy; i) aged ≥ 18 OR ii) caregiver if patient is younger than 18 or cognitive impaired

GERMANY

Target disease: Rheumatoid Arthritis

N=1 German representative of one of the main (German) Rheumatoid Arthritis patient advocacy organisations

N=1 Patient over 18 on at least one biological DMARD

FRANCE

Target disease: lung cancer

N=1 French representative of one of the main (French) cancer patient organisations

N=1 Patient i) aged ≥ 18; ii) diagnosed with lung cancer iii) more than 5 years post-diagnosis; and iv) out of treatment

US

Target disease: Cardiovascular diseases

N=1 US representative of one of the main Cardiovascular diseases patient organisations (in the USA)

N=1 Patient i) aged ≥ 18; ii) diagnosed with a cardiovascular disease; iii) more than 2 years post-event

4) Physicians

Additionally over the countries: ensure the inclusion of both physicians of university and local hospitals

MAIN COUNTRIES

SWEDEN

Target disease: Rheumatoid Arthritis

N=4 Rheumatologists OR primary care provider OR physicians working with Rheumatoid Arthritis patients OR physicians as part of a medical team caring for Rheumatoid Arthritis patients in Sweden

ROMANIA

Target disease: Cardiovascular Diseases

N=4 Cardiologists OR Cardiothoracic surgeons OR Primary care providers OR physicians working with CVD patients OR physicians as part of a medical team caring for CVD patients in Romania

ITALY

Target disease: lung cancer

N=4 Oncologists OR Surgeon OR Primary care providers OR physicians OR working with lung cancer patients OR physicians as part of a medical team caring for lung cancer patients in Italy

UK

Target disease: muscular dystrophy

N=4 Specialists (cardiologists; neurologists; orthopaedists; physiatrists; pulmonologists) OR primary care provider working with

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Neuromuscular Dystrophy patients OR physicians as part of medical team caring for Neuromuscular Dystrophy patients in the UK

VALIDATION COUNTRIES

THE NETHERLANDS

Target disease: muscular dystrophy

N=2 Specialists (cardiologists; neurologists; orthopaedists; physiatrists; pulmonologists) OR primary care provider working with Neuromuscular Dystrophy patients OR physicians as part of medical team caring for Neuromuscular Dystrophy patients in the Netherlands

GERMANY

Target disease: Rheumatoid Arthritis

N=2 Rheumatologists OR primary care provider OR physicians working with Rheumatoid Arthritis patients OR physicians part of a medical team caring for Rheumatoid Arthritis patients in Germany

FRANCE

Target disease: lung cancer

N=2 Oncologists OR surgeon OR Primary care providers OR physicians OR working with lung cancer patients OR physicians as part of a medical team caring for lung cancer patients in France

US

Target disease: Cardiovascular diseases

N=2 Cardiologists OR Cardiothoracic surgeons OR Primary care providers OR physicians working with CVD patients OR physicians as part of a medical team caring for CVD patients in the US

5) Academics

MAIN COUNTRIES

SWEDEN

N=4 persons working in a Swedish academic/research institution with knowledge/experience in patient involvement methods OR patient preference methods

ROMANIA

N=4 persons working in a Romanian academic/research institution with knowledge/experience in patient involvement OR patient preference methods

ITALY

N=4 persons working in an Italian academic/research institution with knowledge/experience in patient involvement OR patient preference methods

UK

N=4 persons working in an English academic/research institution with knowledge/experience in patient involvement OR patient preference methods

VALIDATION COUNTRIES

THE NETHERLANDS

N=2 persons working in a Dutch academic/research institution with knowledge/experience in patient involvement OR patient preference methods

GERMANY

N=2 persons working in a German academic/research institution with knowledge/experience in patient involvement OR patient preference methods

FRANCE

N=2 persons working in a French academic/research institution with knowledge/experience in patient involvement OR patient preference methods

US

N=2 persons working in a North American academic/research institution with knowledge/experience in patient involvement OR patient preference methods

6) Industry Representatives (incl. consultants for industry):

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Additionally over the countries: ensure the inclusion of both smaller and larger companies

MAIN COUNTRIES

SWEDEN (N=4)

n=2/3 persons whose activities are focussed on pharmaceuticals

n=1/2 persons whose activities are focussed on medical devices

ROMANIA (N=4)

n=2/3 persons whose activities are focussed on pharmaceuticals

n=1/2 persons whose activities are focussed on medical devices

ITALY (N=4)

n=2/3 persons whose activities are focussed on pharmaceuticals

n=1/2 persons whose activities are focussed on medical devices

UK (N=4)

n=2/3 persons whose activities are focussed on pharmaceuticals

n=1/2 persons whose activities are focussed on medical devices

VALIDATION COUNTRIES

THE NETHERLANDS (N=2)

n=1/2 persons whose activities are focussed on pharmaceuticals

n=0/1 persons whose activities are focussed on medical devices

GERMANY (N=2)

n=1/2 persons whose activities are focussed on pharmaceuticals

n=0/1 persons whose activities are focussed on medical devices

FRANCE (N=2)

n=1/2 persons whose activities are focussed on pharmaceuticals

n=0/1 persons whose activities are focussed on medical devices

US (N=2)

n=1/2 persons whose activities are focussed on pharmaceuticals

n=0/1 persons whose activities are focussed on medical devices

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Appendix 5: Invitations for semi-structured interview

1. Invitation for HTA body representatives, reimbursement agency representatives, regulators, industry representatives, academics

Subject line of the e-mail:

Invitation to participate in an interview about patient preferences in the medicinal product and medical device lifecycle

Attachment:

Applicable information sheet in PDF

Body of the e-mail:

Title of the study: **Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) task 2.1 and 2.2**

Sponsor of the study: The European Commission, the Innovative Medicines Initiative

Ethics Committees:

- Belgium: Medical Ethics Committee of UZ KU Leuven/Research
- France: Commission Nationale de l'Informatique et des Libertés (CNIL)
- Germany: Ethik-Kommission der Friedrich-Alexander Universität
- Italy: Comitato Etico IEO
- the Netherlands: Medisch Ethische Toetsings Commissie Erasmus MC
- Romania: Comisia de Bioetica a Medicamentului si a Dispozitivelor Medicale (CNBMDM)
- Sweden: Regionala Etikprövningsnämnden Uppsala (EPN)
- United Kingdom: Newcastle University Ethics Committee
- United States: Western Institutional Review Board (WIRB)

Head of research: Prof. Huys Isabelle, KU Leuven, Clinical Pharmacology and Pharmacotherapy
O&N II Herestraat 49 – Box 521, 3000 Leuven, Belgium
E-mail : isabelle.huys@kuleuven.be ; Tel. : +32 16 33 04 09

Local investigator: [Contact details](#)

Dear Mr./Mrs./Miss + [last name](#),

Because of your expertise in [...](#), brought to our attention by [...](#), we would like to invite you to participate in an interview within a study that aims at strengthening patient-centric decision-making throughout the lifecycle of medicinal products and medical devices, to give insights from a [...](#) perspective. This research is part of a project, entitled 'Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle' (PREFER). PREFER is a five-year project funded by the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative between the *European Union* and the *European Federation of Pharmaceutical Industries and Associations* (EFPIA). PREFER will develop knowledge about the implementation of patient preferences according to the needs and opinions of different stakeholders: patients, patient organisations, regulatory agencies, health technology assessment (HTA) bodies, reimbursement agencies, academicians and physicians.

Through a series of interviews with these stakeholders, information will be collected to learn about patient preferences from a variety of perspectives. We regard you as a critical stakeholder, which is why you are receiving this invitation. The interview will be conducted at a location convenient for you, via telephone, or via skype. The interview will take approximately one hour, but we kindly ask you to schedule 1.5 hours of availability to compensate for any running over, or technical difficulties that might occur.

The interview will address the following topics: (1) your definition of patient preferences, (2) your idea on the current situation of patient preferences and methods in the life cycle of medical products and (3) your idea on the (future) role of patient preferences and methods in the life cycle of medical products.

Participation in this research is entirely voluntary. You do not have to take part and you can decide to withdraw at any point, without having to give a reason. You do not have to answer any questions during the interview that you do not feel comfortable answering. There is no cost associated with participating in this interview.

Please read the attached information sheet about the sub-study.

If you are interested and willing to participate in this interview, please reply to this e-mail. You will then be contacted to make further arrangements. For more information of the PREFER project visit the project website: www.imi-prefer.eu. Do not hesitate to contact us if anything is unclear.

Thank you in advance for your participation,

Kind regards,

E-mail signature of the person who sent the invitation

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2. Invitation for patients, patient representatives, caregivers, physicians

Subject line of the e-mail:

Invitation to participate in an interview about patient preferences in the medicinal product and medical device lifecycle

Attachment:

Applicable information sheet in PDF

Body of the e-mail:

Title of the study: **Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) task 2.1 and 2.2**

Sponsor of the study: The European Commission, the Innovative Medicines Initiative

Ethics Committees:

- Belgium: Medical Ethics Committee of UZ KU Leuven/Research
- France: Commission Nationale de l'Informatique et des Libertés (CNIL)
- Germany: Ethik-Kommission der Friedrich-Alexander Universität
- Italy: Comitato Etico IEO
- the Netherlands: Medisch Ethische Toetsings Commissie Erasmus MC
- Romania: Comisia de Bioetica a Medicamentului si a Dispozitivelor Medicale (CNBMDM)
- Sweden: Regionala Etikprövningsnämnden Uppsala (EPN)
- United Kingdom: Newcastle University Ethics Committee
- United States: Western Institutional Review Board (WIRB)

Head of research: Prof. Huys Isabelle, KU Leuven, Clinical Pharmacology and Pharmacotherapy
O&N II Herestraat 49 – Box 521, 3000 Leuven, Belgium
[E-mail : isabelle.huys@kuleuven.be](mailto:isabelle.huys@kuleuven.be) ; Tel. : +32 16 33 04 09

Local investigator: [Contact details](#)

Dear Mr./Mrs./Miss + [last name](#),

We would like to invite you to take part in an interview because of your experience as a [...](#), brought to our attention by [...](#), to get your views on how and when patients can and should influence the development of medicines. These interviews are part of a project entitled 'Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle' (PREFER).

Patients are included at every level of the PREFER project. You receive this invitation because your opinion is of particular importance since we regard you as a critical stakeholder. The interview will take about one hour and will be conducted at a location convenient for you, via telephone, or via skype. The interview will address the following topics: (1) your definition of patient preferences, (2) your idea on the current situation of patient preferences and methods in the life cycle of medicinal products and medical devices and (3) your idea on the (future) role of patient preferences and methods in the life cycle of medicinal products and medical devices.

Please read the attached information sheet about the sub-study, part of the PREFER project.

If you are interested and willing to participate in this interview, please reply to this e-mail. You will then be contacted to make further arrangements. You will find more information of the PREFER project on the project website: www.imi-prefer.eu. Do not hesitate to contact us if anything is unclear.

Your participation is highly appreciated.
Thank you in advance,

Kind regards,

[E-mail signature of the person who sent the invitation](#)

Appendix 6: Information forms for semi-structured interviews

1. Information for HTA body representatives, reimbursement agency representatives, regulators, industry representatives, academics

Title of the study:	Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) task 2.1 and 2.2
Sponsor of the study:	The European Commission, the Innovative Medicines Initiative
Ethics Committees:	<ul style="list-style-type: none"> Belgium: Medical Ethics Committee of UZ KU Leuven/Research France: Commission Nationale de l'Informatique et des Libertés (CNIL) Germany: Ethik-Kommission der Friedrich-Alexander Universität Italy: Comitato Etico IEO the Netherlands: Medisch Ethische Toetsings Commissie Erasmus MC Romania: Comisia de Bioetica a Medicamentului si a Dispozitivelor Medicale (CNBMDM) Sweden: Regionala Etikprövningsnämnden Uppsala (EPN) United Kingdom: Newcastle University Ethics Committee United States: Western Institutional Review Board (WIRB)
Head of research:	Prof. Huys Isabelle, KU Leuven, Clinical Pharmacology and Pharmacotherapy O&N II Herestraat 49 – Box 521, 3000 Leuven, Belgium E-mail : isabelle.huys@kuleuven.be ; Tel. : +32 16 33 04 09
Local investigator:	Contact details

Introduction

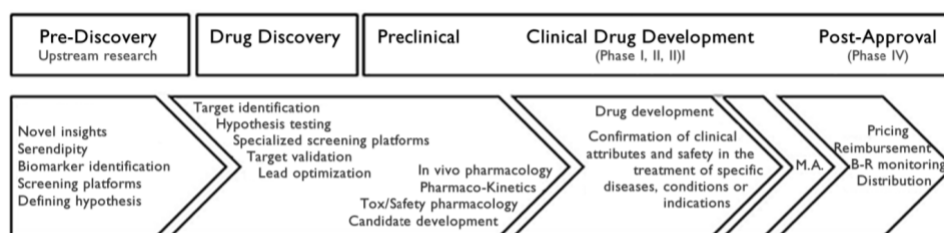
The Innovative Medicines Initiative (IMI) is Europe's largest public-private partnership aiming to speed the development of better and safer medicines for patients. IMI supports this aim through collaborative research projects and building networks of industrial and academic experts in order to boost European pharmaceutical innovation. In the IMI 2 Joint Undertaking, IMI has defined health priorities in its Strategic Research Agenda to ensure that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged (IMI 5th call for proposal, IMI2/INT/2015-01343,p.3).

There is increasing recognition of the importance of incorporating patient needs and perspectives into decision making and to provide more avenues for patient engagement. Patients have expressed interest in seeing the decision-making processes of the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) take patient considerations into even greater account, e.g., in appropriate design of pre- and post-approval studies and risk management plans. For benefit-risk assessments in particular, decisions should take into consideration patient preferences but also endpoints and outcomes that patients regard as relevant, preferred treatment options, impact of the disease, and trade-offs between favorable and unfavorable effects.

While stakeholders value patient preferences, a structured approach including a set of systematic methodologies and recommendations to include and engage patient preferences in the drug and device lifecycle is lacking. Therefore, this project (PREFER) was set up by IMI to accommodate the requirements of Regulatory Authorities as well as health technology assessment (HTA) bodies and reimbursement agencies.

Overall aim of the PREFER project

The main objective of PREFER is to strengthen patient-centric decision-making throughout the life cycle of medicinal products and medical devices (figure 1) by developing evidence-based recommendations to guide industry, Regulatory Authorities, and HTA bodies on how and when patient-preference studies should be performed and when the results can be used to support and inform decision-making.



M.A. = marketing authorisation

Fig 1 Medicinal product life cycle

Aim of this sub-study

This sub-study is carried out within the framework of the PREFER project. This study is designed to explore the opinions of different stakeholders, including patients, patient organisations, physicians, regulators, HTA bodies and payers. Data will be collected through a series of interviews that will help to understand the needs, desires, expectations and requirements of each class of stakeholder about the assessment and use of patient preference information. Also, the interviews will reveal in which processes of drug and medical device development, patient preferences are already used and which conditions and contextual factors influence this usage. Interviews will be carried out by different European institutions:

- University of Leuven (KUL), Belgium
- Uppsala University (UU), Sweden
- Erasmus University Rotterdam (EUR), the Netherlands
- European Institute of Oncology (IEO), Italy

Your participation in an interview

Participation in an interview is entirely voluntary. You do not have to take part and you can decide to withdraw at any point, without having to give a reason. You do not have to answer any questions during the interview that you do not feel comfortable answering. There is no cost associated with participating in this interview and you will not receive any compensation to take part. Your contribution will help us explore these issues, meaning that there are no wrong answers;

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we are interested in everything you have to say.

The interview will be audio recorded and transcribed (written down). All data will be encoded for those who take part in the study, which means each participant receives a unique code. The collected data will not contain your name and will be identifiable only by this code. Your personal information will be used in compliance with the appropriate confidentiality standards, with the laws on privacy and with the protection of personal data. No private details about you, including your name, work, address or other contact details will ever be published. The information will be stored securely and protected at the University of Leuven. The answers you give in the interview will be analysed together with others. If we use a quote from you in our reports and publications, you (as well as the company you work for) will not be identifiable. The results of the analysis will be published in project reports and scientific articles. The anonymized information could also be used for academic purposes at universities or research organisations that are partners in this project.

Funding and publication

This research is funded by the Innovative Medicines Initiative (IMI): Europe's largest public-private initiative between the European Union's Horizon 2020 program and the European pharmaceutical industry association EFPIA. Through IMI the European Union funds academic research that is matched by contributions 'in-kind' from the pharmaceutical industry in the form of personnel and other resources. The researchers and doctoral students conducting this study are not paid by companies. The results will be published in peer-reviewed English language journals following the Vancouver rules for authorship.

Ethical review and approval

All studies in the PREFER project are reviewed and approved by local research ethics committees. This study has been approved by the Ethics committees listed at the top of this information sheet. The task of these committees is monitoring the scientific relevance of the research and ensuring that participants' rights are protected.

More information can be found at the PREFER project website: www.imi-prefer.eu.

Thank you in advance for your participation!

The PREFER team

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2. Information for patients, patient representatives, caregivers, physicians

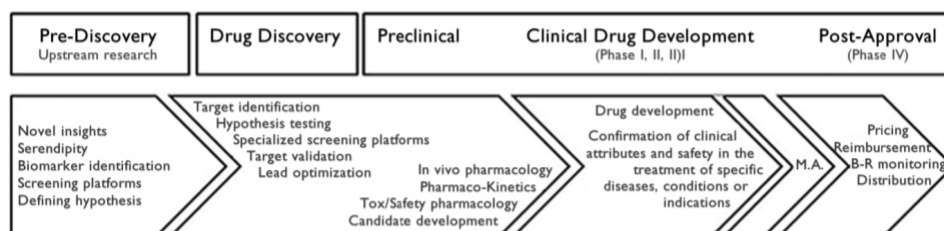
Title of the study:	Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) task 2.1 and 2.2
Sponsor of the study:	The European Commission, the Innovative Medicines Initiative
Ethics Committees:	<ul style="list-style-type: none"> Belgium: Medical Ethics Committee of UZ KU Leuven/Research France: Commission Nationale de l'Informatique et des Libertés (CNIL) Germany: Ethik-Kommission der Friedrich-Alexander Universität Italy: Comitato Etico IEO the Netherlands: Medisch Ethische Toetsings Commissie Erasmus MC Romania: Comisia de Bioetica a Medicamentului si a Dispozitivelor Medicale (CNBMDM) Sweden: Regionala Etikprövningsnämnden Uppsala (EPN) United Kingdom: Newcastle University Ethics Committee United States: Western Institutional Review Board (WIRB)
Head of research:	Prof. Huys Isabelle, KU Leuven, Clinical Pharmacology and Pharmacotherapy O&N II Herestraat 49 – Box 521, 3000 Leuven, Belgium E-mail : isabelle.huys@kuleuven.be ; Tel. : +32 16 33 04 09
Local investigator:	Contact details

Background

Patient-preference studies collect information about what groups of patients prefer, and why they would choose a particular drug or medical device over other available options. This information is important for many different stakeholders who make decisions on medical products. This includes companies that develop drugs (pharmaceutical industry), the authorities that approve drugs (the regulators) and the authorities that decide how much a drug will cost for patients (Health Technology Assessment bodies and reimbursement agencies).

About PREFER and its aim

At the moment, there is little guidance on how and when patient-preference studies should be incorporated into the drug life cycle (figure 1). The PREFER project will help to address this by developing evidence-based recommendations. These will advise industry, Regulatory Authorities, HTA bodies, reimbursement agencies, academia, and health care professionals on how and when patient-preference studies should be performed and how the results should be used to support and inform decision making.



M.A. = marketing authorisation

Fig 1 Medicinal product life cycle

About this particular sub-study

This particular sub-study is carried out in the context of the PREFER project. This study is designed to explore the opinions of different stakeholders, including patients, patient organisations, physicians, regulators, HTA bodies and industry on patient preference studies. Also, the interview will explore how patient preferences are currently used. Data will be collected through a series of interviews that will be carried out by different European institutions:

- University of Leuven (KUL), Belgium
- Uppsala University (UU), Sweden
- Erasmus University Rotterdam (EUR), the Netherlands
- European Institute of Oncology (IEO), Italy

What is this research for?

These interviews will help to understand the needs, desires, expectations and requirements of each class of stakeholder about the assessment and use of patient preference information, and about how patient preferences are currently taken into account. We include patient stakeholders at every level of the project. The result of these interviews will be the first step towards developing case studies to test different kinds of patient preference studies in different patient populations for different drugs. Those results in turn will advise the recommendations that will be written as part of the overall PREFER project.

What are we asking of you?

We are asking whether you are willing to participate in this interview for the sub-study of PREFER. If you confirm your participation, we will contact you to schedule the interview.

How to apply for study participation?

Please reply to the e-mail that you have received from one of the PREFER researchers. There is no cost associated with participating in this interview and you will not receive any compensation to take part.

Why are you asking me?

You have been chosen because you represent one of the stakeholders identified by PREFER. If you receive this letter, it means you are either a patient, a doctor, a caregiver, or that you work for a patient organisation.

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What happens if I say no?

Participation in this research is entirely voluntary. You do not have to take part if you do not want to. If you change your mind, you are free to leave the study any point, without having to give any reason. You do not have to answer any questions that you do not feel comfortable answering. You do not have to pay anything to take part.

What about my privacy?

The interview will be audio recorded and transcribed (written down). We will give you an identification number instead of using your name. No private details about you, like name, work, address or contact details will be published anywhere.

The information will be stored securely and protected at the University of Leuven. The information will only be viewed by approved researchers working on this project. The answers you give in the interview will be analysed together with others. Even if we quote you, you will not be identified. The results of the analysis will be published in reports and articles. The information we collect from you could also be used anonymously in education at universities or research organisations that are partners in this project.

Who is responsible for this study?

This research is part of the PREFER research project. The project is funded by the Innovative Medicines Initiative (IMI). You will find more information about the PREFER project on the project website: www.imi-prefer.eu.

Who checks that this is ethical?

All studies in the PREFER project are reviewed and approved by local research ethics committees. This study has been approved by the Ethics committees listed at the top of this information sheet. The task of these committees is monitoring the scientific relevance of the research and ensuring that participants' rights are protected.

More information on the PREFER project can be found on the project website: www.imi-prefer.eu.

Thank you in advance for your participation!

The PREFER team

Appendix 7: Consent form

Consent form – PREFER

Title of the study: **Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) task 2.1 and 2.2**

Sponsor of the study: The European Commission, the Innovative Medicines Initiative

Ethics Committees:

- Belgium: Medical Ethics Committee of UZ KU Leuven/Research
- France: [Commission Nationale de l'Informatique et des Libertés \(CNIL\)](#)
- Germany: Ethik-Kommission der Friedrich-Alexander Universität
- Italy: Comitato Etico IEO
- the Netherlands: Medisch Ethische Toetsings Commissie Erasmus MC
- Romania: Comisia de Bioetica a Medicamentului si a Dispozitivelor Medicale (CNBMDM)
- Sweden: Regionala Etikprövningsnämnden Uppsala (EPN)
- United Kingdom: Newcastle University Ethics Committee
- United States: Western Institutional Review Board (WIRB)

Head of research: Prof. Huys Isabelle, KU Leuven, Clinical Pharmacology and Pharmacotherapy
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Local investigator: [Contact details](#)

Filled in by the PARTICIPANT

Tick the boxes to agree with the terms:

- ☐ I have read the information concerning this project and I have had an opportunity to ask questions;
- ☐ I was given sufficient time to decide whether I am willing to participate in this project;
- ☐ I am aware that participating in this project is completely voluntary;
- ☐ I am aware that I can stop participating in this project at any time;
- ☐ I give permission for the collection of information about my insights and opinions concerning the inclusion of patient preferences into decision making during the drug life cycle. All collected information on my insights and opinions will be given a code and processed anonymously;
- ☐ I give permission that the anonymized data of this interview is shared within the involved parties of the PREFER project and that it can be used for publications in scientific journals;
- ☐ I have received the information sheet and I hereby confirm my voluntary participation in the project.

Name participant Signature participant Date

Filled in by the RESEARCHER

I have discussed the content of the invitation and the information with the above-mentioned person. I have asked for any additional questions and I have answered these.

Name researcher Signature researcher Date

Appendix 8: Interview guides

BLUE = instructions to the interviewer (not to be spoken out loud)

BOLD= eye-catcher to interviewer (important terms)

ITALICS= definition/quote

Introduction

0. Before interview: read briefing on how to conduct interviews on Project Place
- 1 Present yourself: say your name and that you are a researcher of the IMI PREFER project
- 2 Thank for participation in advance
- 3 Briefly explain the aim of the IMI PREFER project and interviews:
 - Project: to **strengthen patient-centric decision-making throughout the life cycle** of drugs and medical devices by **developing recommendations** to guide industry, Regulatory Authorities, and HTA bodies on how and when patient preference studies should be performed and the results can be used to inform decision-making
 - Interviews: to **explore the opinions** of different stakeholders about the assessment of patient preferences and use of patient preference information in the development and evaluation of drugs and medical devices. These stakeholders are patients, patient organization representatives, physicians, industry representatives, academics, regulators, HTA body representatives and reimbursement agency representatives
- 4 Put interviewee at ease:
 - No wrong answers
 - Digitally recorded
 - Confidential, anonymous
 - Interview will be approximately 45 minutes to 1 hour
 - Voluntary, do not have to answer anything they do not feel comfortable answering
 - They can stop the interview at any time, without having to give a reason
5. Give the informed consent form, if not signed yet
6. Put on audio recorder

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Guide 1: HTA body representatives - Reimbursement agency representatives - Regulators - Industry representatives - Academics

1. Can you tell me **a little bit** more about yourself and your background?
 - What is your **current role** in your organization?
2. The IMI PREFER project wants to determine **how** patient preferences can be measured for the development and evaluation of drugs and medical devices. How would you **define** the term 'patient preferences'?

For this interview, we are using the definition of patient preferences used in the FDA guidance for medical devices:

"The relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions"

In other words, patient preferences are the basis of how patients choose a particular treatment over others. To make a choice, patients make trade-offs between a treatment's characteristics, weighing its advantages and disadvantages collectively.

- What do you think about this definition of '**patient preferences**'?
- Does it differ at all from your own understanding of 'patient preferences'?

First, we have some questions about your thoughts on the **current situation** of measuring and using patient preferences.

3. How **familiar** are you with patient preference studies?
 - Do you have experience with designing or conducting patient preference studies?
4. **If interviewee has experience with patient preference methods or studies:** Which challenges did you encounter?
 - In the organization and management of patient preference studies?
 - In the design of patient preference studies?
 - During the conduct of patient preference studies?
 - In the use of the results?
5. **If interviewee has experience with patient preference methods or studies:** Do you consider these challenges to be factors that influence the utility of patient preference studies?
6. **If interviewee has experience with patient preference methods or studies:** Was heterogeneity of the **patient sample** a factor that influenced the utility of your patient preference study?
 - How did you deal with this?
7. Several **decisions** are made in the drug or medical device life cycle, such as industry decisions about product development, regulatory decisions about marketing authorization and decisions about pricing and reimbursement. To what extent do you think patient preferences are **currently** used for these decisions?
 - Which decisions in particular and why?
8. What are the **current procedures or protocols** to integrate patient preferences in these decisions?
 - In the evaluation of drugs and medical devices, how are patient preferences currently compared or combined with other clinical or non-clinical data?
9. Under what conditions, situations or circumstances are patient preferences **less important** and why?
 - Are there circumstances where using patient preferences is **counterproductive**? Why?
 - Under what conditions, situations or circumstances are patient preferences **extremely important** and why?
10. In this project, we focus on the drug and medical device life cycle, **starting from discovery to post-marketing surveillance**. Patient preference studies can be conducted in different stages.
 - To your knowledge, **at what point** in the drug and medical device life cycle are patient preference studies **currently** being conducted?
 - Do you know **who** is conducting patient preference studies?
 - Do you know what **methods** they are using?
11. Do you know of any other methods for measuring patient preferences?

We would like to ask you questions about what you would like to see happen for the possible role of patient preferences.

12. How important do you think it to measure and use patient preferences when making a drug or medical device, or do you think it is not important at all?
 - Why (not)?
13. We talked about the different decisions that are made in the drug or medical device life cycle. In which **decisions** do you believe patient preferences **should be** taken into account?
 - **Why** should they be taken into account **for this decision specifically**?
 - In addition to clinical evidence, what **information** could patient preferences add in **this decision specifically**?
 - In which **decisions** do you believe patient preferences **should not be** taken into account?
 - **Why** should they not be taken into account **for this decision specifically**?
14. Are there any **other** decisions made by your organisation, that you think should take patient preferences into account?
15. According to you, **when or at which stage in** the drug and medical device life cycle do you think patient preference studies **should be conducted** for informing the decisions we have talked about?
16. In order to use the results from a patient preference study for informing a specific decision, it has to be decided when to start the patient preference study. **How much time should be allocated before a decision point** in order to conduct the patient preference study and to incorporate the results from this study in the decision?

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17. We talked about the different decisions in the drug or medical device life cycle where patient preferences **should be** taken into account. According to you, **what is needed** to implement the use of patient preferences at those decisions?
 - What would help **your organization** to take patient preferences into account more **systematically for decision-making**?
 - What is **lacking** now?
 - Do you think a registry for patient preference studies is needed?
18. Do you think specific protocols or procedures are needed to **integrate** patient preferences into decision-making?
 - If so, what protocols are needed for **industry** decision-making?
 - If so, what protocols are needed for **marketing authorization** decision-making?
 - If so, what protocols are needed for **HTA**?
 - If so, what protocols are needed for **reimbursement** decision-making?
 - If so, what protocols are needed for (...) other decision-making?
19. When patient preference studies are designed, it has to be decided who will participate in patient preference studies. **Who** do you think should participate in patient preference studies?
 - To what extent should they have **experience with the disease**?
 - To what extent should they have **experience with treatment**?
 - What is your opinion of using caregivers like family or partners as proxies for patients in patient preference studies?
 - To what extent do you think that they **reflect** the patient's preferences?
20. We talked about some patient preference methods. What are your thoughts about the **usefulness** of each method that we have discussed?
 - Under what circumstances would you recommend using one **rather than other**?
 - Under what circumstances would you recommend using a **quantitative or a qualitative** approach?
21. To what extent does the **method** need to have high **validity** for you to want to **use or consider it for evaluation**? *If interviewee is unsure/asks about validity: "Validity means the extent to which a test or study measures what claims to measure. Internal validity refers to whether a finding that incorporates a causal relationship between two or more variables is sound. External validity refers to whether the results of a study can be generalised beyond the specific research context in which the study was conducted. Face validity is a concern with whether an indicator appears to reflect the content of the concept in question."*
22. What do you consider to be important indicators for **evaluating the quality of patient preference studies**?
 - How do these **differ** from quality indicators of **evidence from clinical trials**?
23. Do you have any concerns about **how** patient preferences **are measured**?
24. Do you have any concerns about **using** patient preferences in decision-making?
 - Do you have any concerns about using patient preferences specifically **by your organization**?
25. Is **heterogeneity** of the **patient sample** a concern when **conducting or assessing** patient preference studies?
26. Do you think anything will **happen or change** when patient preferences are used **more widely** in decision-making?
 - ... in **industry** decision-making?
 - ... in **marketing authorization** decision-making?
 - ... in **HTA**?
 - ... in **reimbursement** decision-making?
 - ... in other decision-making?

These were all the questions I had for you, but before we finish:

- Do you have anything you want to **add or emphasise**?
- Do you have any **questions for me**?

Put off audio recording

- Do you have a suggestion for **another interesting interviewee**?
- Would you feel comfortable being contacted again if we have any **follow-up questions**?

Thank you for your participation. If you have any other questions, comments, or want to get in touch with me, I will give you my contact details.

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Guide 2: Patients + Patient representatives + Caregivers + Physicians

1. Can you tell me a **little bit** more about yourself and your background?
 - **For patient representatives ONLY:** What is your **current role** in the patient organization?
2. The PREFER project wants to determine **how** the preferences of patients can be measured when making drugs or medical devices. What does the term 'patient preferences' mean to you?

For this interview, we are using the following definition of patient preferences:

Patient preferences reflect why patients choose a particular health treatment over other available options. This health treatment can be a drug or a medical device. A preference can be stated for a health treatment as a whole or for the advantages and disadvantages of one treatment. In order to make a choice or state a preference, patients need to weigh up the advantages and disadvantages and compare them to those of other health treatments.

- What do you think about this definition of '**patient preferences**'?
- Does it differ at all from your own understanding of 'patient preferences'?

Give glossary to interviewee: There are some terms that we will use here today that you might not use in everyday language, so if there's anything that you have not heard before, or aren't too sure about, we have a glossary for you. You can stop and read it at any time.

We have some questions about your thoughts on the current situation of measuring and using patient preferences.

3. How **familiar** are you with patient preference studies?
 - **If patient/caregiver:** Have you already taken part in a study on patient preferences?
 - **If physician/patient representative:** Do you have experience with designing a patient preference study?

Examples to give: A patient preference study asks patients about what they want from a flu vaccine (flu shot) by asking what matters most to them, such as how effective it is, how long it lasts, its side-effects, where patients can get it, or how much it costs. Some patients might say that the effectiveness of the vaccine is most important, while others think that a vaccine should have the lowest level of side-effects.

4. Drugs are made in different stages: first it is made in a laboratory, then the drug is tested in animals and then in humans (these are the clinical trials). Finally, based on the results from these studies, the government decides if the pharmaceutical company can sell the drug. Medical devices are approved in a different way, but have to respect similar requirements.

To your knowledge, **when** are patient preferences currently being measured? At what stage of developing a drug and bringing it to patients?

- Do you know **who** is measuring preferences?
- Do you know what **methods** are being used to measure preferences?

If interviewee get stuck: **Methods** mean how researchers ask patients for their preferences and then analyse the answers, such as by interview, questionnaire, or asking patients to pick between a series of choices...

5. **If interviewee has experience with patient preference methods or studies:** What were the study results used for? (e.g. in the development of drugs, marketing authorization decisions, reimbursement decisions if applicable, decisions about the price of a product)
6. **If interviewee has experience with patient preference methods or studies:** Which challenges did you encounter in:
 - In the organization and management of patient preference studies?
 - In the design of patient preference studies?
 - During the conduct of patient preference studies?
 - In the use of the results of patient preference studies?
7. **If interviewee has experience with patient preference methods or studies:** Did these challenges influence the usefulness of the patient preference study?
8. **If interviewee has experience with patient preference methods or studies:** Did the heterogeneity of the patient sample influence the usefulness of your patient preference study?
 - How did you deal with this?
9. **If interviewee has experience with patient preference methods or studies:** Under what conditions, situations or circumstances would you think that patient preferences are less important and why?
 - Are there circumstances where using patient preferences is counterproductive? Why?

We would like to ask you questions about what you would like to see happen if the role of patient preferences were to be increased.

10. Do you think it is important to measure and use patient preferences when making a drug or medical device?
 6. Why (not)?
11. As we mentioned before, drugs and medical devices are made in different stages.
 - According to you, **when or at which stage** in making a drug or medical device, do you believe patient preferences **should** be measured?
 - Several decisions need to be made when making a medical product. A decision point is a moment when a decision is made about whether a drug or medical device moves forward to the next stage in the drug lifecycle. Examples of decision points can be the decision made by companies to develop the product, decisions made by the government whether to put the product on the market, decisions about the price of a product, and (if applicable) whether it can be reimbursed. **In which of these decisions** do you believe patient preferences need to be taken into account?
12. In order to set up a patient preference study, first, it has to be decided who will participate in patient preference studies.
 7. **Who** do you think should participate in patient preference studies?
 - **How long** should they have been **experiencing the disease**?
 - To what extent should they have **experience with treatment**?
 - To what extent do you think that caregivers **reflect** the patient's preferences?
13. What else do you think is needed in a patient preference study in order to measure patient preferences?

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14. Do you have any concerns about **how** patient preferences are **measured**? `
15. Do you have any concerns about **companies using** information from patient preference studies?
[ex. This information could include a patient's personal preferences or medical history](#)
16. Do you have any concerns about **using** patient preferences at other decision points, ([ask if they remember taking about decision points](#)) such as helping the government decide **whether to put the product on the market**, deciding the **price** of a product, ([if applicable](#)) and whether it can be **reimbursed**?
17. [As a patient](#), **would you advise** companies and policy-makers to use patient preferences **more often** to make drugs or medical devices?
 - If so, why?
18. Do you think anything will **happen or change** when patient preferences are used **more often** in the development and evaluation of drugs or medical devices?

These were all the questions I had for you, but before we finish:

8. Do you have anything you want to **add** or **emphasise**?
9. Do you have any **questions for me**?
10. Do you have a suggestion for **another interesting interviewee**?
11. Would you feel comfortable being contacted again if we have any **follow up questions**?

Thank you for your participation. If you have any other questions, comments, or want to get in touch with me, I will give you my contact details.

Appendix 9: Procedure for analysis interviews: Framework Method Analysis

Core analyzing team: RJ and SR

Stage 1: Transcription

General explanation and important considerations, see: Gale et al. (1)

A good quality audio recording and, ideally, an at *verbatim* (word for word) transcription of the interview is needed. For Framework Method analysis, it is not necessarily important to include the conventions of dialogue transcriptions which can be difficult to read (e.g. pauses or two people talking simultaneously), because the content is what is of primary interest. Transcripts should have large margins and adequate line spacing for later coding and making notes. The process of transcription is a good opportunity to become immersed in the data. However, in some projects, the decision may be made that it is a better use of resources to outsource this task to a professional transcriber.

- Due to the high number of transcripts, we will outsource the transcription of our interviews.
- All interviews will be transcribed in their native language, and then translated, if necessary, to English.

Stage 2: Familiarization with the interview

General explanation and important considerations, see: Gale et al. (1)

Becoming familiar with the whole interview using the audio recording and/or transcript and any contextual or reflective notes that were recorded by the interviewer is a vital stage in interpretation. It can also be helpful to re-listen to all or parts of the audio recording. In multi-disciplinary or large research projects, those involved in analyzing the data may be different from those who conducted or transcribed the interviews, which makes this stage particularly important. One margin can be used to record any analytical notes, thoughts or impressions.

- This stage is particularly important in our case, because those involved in analysing a certain interview are not necessarily the same as the one conducting the interview.
- In our case, primarily the transcripts will be used for familiarization. If the analyser has difficulty in understanding the transcript, the analyser will re-listen to the audio file. If the analyser still does not understand a certain part of the transcript after re-listening the audio-file, he/she will ask the interviewer who conducted the interview for clarification about that part OR ask the other analyser that he/she listens to the audio file so that they can agree together about what was said in that certain part of the interview.
- SR and RJ will thoroughly read and re-read each transcript, and listen back to the audio-recorded interviews if necessary to become familiar with the whole data set.
- The margins of the transcripts will be used to write down analytical notes, thoughts or impressions (e.g. when interviewees expressed exceptionally strong or contrasting views to other interviewees). No feedback will be given towards interviewees about these notes.

Stage 3: Coding

General explanation and important considerations, see: Gale et al. (1)

After familiarization, the researcher carefully reads the transcript line by line, applying a paraphrase or label (a 'code') that describes what he has interpreted in the passage as important. In more inductive studies, at this stage 'open coding' takes place, i.e. coding anything that might be relevant from as many different perspectives as possible. Codes could refer to substantive things (e.g. particular behaviours, incidents or structures), values (e.g. those that inform or underpin certain statements, such as a belief in evidence-based medicine or in patient choice), emotions (e.g. sorrow, frustration, love) and more impressionistic/methodological elements (e.g. interviewee found something difficult to explain, interviewee became emotional, interviewer felt uncomfortable). In purely deductive studies, the codes may have been pre-defined (e.g. by an existing theory, or specific areas of interest to the project) so this stage may not be strictly necessary and you could just move straight onto indexing (stage 5: assigning text to codes), although it is generally helpful even if you are taking a broadly deductive approach to do some open coding on at least a few of the transcripts to ensure important aspects of the data are not missed. Coding aims to classify all of the data so that it can be compared systematically with other parts of the data set. At least two researchers (or at least one from each discipline or speciality in a multi-disciplinary research team) should independently code the first few transcripts, if feasible. Patients, public involvement representatives or clinicians can also be productively involved at this stage, because they can offer alternative viewpoints thus ensuring that one particular perspective does not dominate. It is vital in inductive coding to look out for the unexpected and not to just code in a literal, descriptive way so the involvement of people from different perspectives can aid greatly in this. As well as getting a holistic impression of what was said, coding line-by-line can often alert the researcher to consider that which may ordinarily remain invisible because it is not clearly expressed or does not 'fit' with the rest of the account. In this way the developing analysis is challenged: to reconcile and explain anomalies in the data can make the analysis

- We will take a combined approach to analysis: themes will be **both inductively** from the accounts (experiences and views) of research participants **and deductively** from specific pre-defined sets of interests to the project and thus the research questions and questions in the interview guide. We will use the following pre-defined coding list and hierarchy (coding tree):
 - Patient preferences definition
 - Value and limitations of using patient preferences (**desires**):
 - General value and limitations of patient preferences throughout life cycle
 - Value and limitations of using patient preferences for industry decision-making
 - Value and limitations of using patient preferences for regulatory BRA
 - Value and limitations of using patient preferences for HTA/reimbursement
 - What is needed to implement the use of patient preferences (**requirements**)?
 - General needs
 - Timing of patient preference studies to inform a specific decision
 - Timing of patient preference study for industry decision-making
 - Timing of patient preference study for regulatory BRA
 - Timing of patient preference study for HTA/reimbursement
 - Quality requirements
 - Sample characteristics
 - Type of method
 - Concerns
 - Concerns about measurement of patient preferences
 - Concerns about use of patient preferences in decision-making
 - Expectations
 - What do they expect will happen when patient preferences are used more systematically throughout the life cycle?
 - What do they expect will happen when patient preferences are used more systematically for industry decision-making?

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- What do they expect will happen when patient preferences are used more systematically for regulatory BRA?
- What do they expect will happen when patient preferences are used more systematically for HTA/reimbursement?
- To ensure important aspects of the data will not be missed, SR and RJ will also independently do **open-coding** on the first available 6 transcripts to check if all relevant themes are covered with the predefined coding tree. The 6 transcripts will be printed out and coded independently: meaning that each researcher will check if all themes are covered and if not, new codes will be assigned.
 - 1 patient/caregiver/ PO transcript
 - 1 physician transcript
 - 1 regulator transcript
 - 1 HTA transcript
 - 1 industry transcript
 - 1 academic transcript
- The two coding researchers, SR and RJ are from two different disciplines: psychology (SR) and biomedical sciences (RJ). Gale et al. argue that in this stage, it is valuable to involve other stakeholders to give alternative viewpoints, e.g. clinicians. In our case however, we found it sufficient and more pragmatic that coding was independently done by two researchers from different disciplines, without actively involving the stakeholders themselves. The reason for this is that involving other stakeholders might slow down the coding stage considerably, as well as leading to discussions, as this would require involving at least one representative from each of the interviewed stakeholder groups, to ensure that all perspectives are equally represented.
- The following example format will be used for open-coding. Coding labels (these could be the ones from the pre-existing framework or new ones) will be noted left from the transcript. Notes and ideas will be noted on the right side of the transcript:

Coding labels	Participant 31: General Practitioner S	Notes and ideas
Professional role	154 I think, sometimes, I think again <u>paediatrics has more in common</u> 155 <u>with General Practice than most specialties</u> , but obviously in General 156 <u>Practice you're looking at the whole person, not just the disease and</u>	Family centred care; holistic versus disease model; 1' vs. 2' care
Place & Space	157 obviously the good quality Paediatrician does that and <u>if you're</u> 158 <u>seeing people nearer to their home setting</u> , then you can see, you	Local = more holistic – families in their environment not doctors; more relaxed; shift in power?
Place & Space; Patient experience	159 know an <u>outpatient department is a bit remote</u> and I'm not saying 160 it's inhumane but <u>if you are in a setting you're comfortable in</u> , 161 <u>you're going to be more relaxed</u> , you might be <u>more honest and</u>	Experience differs according to setting – impact on consultation / outcomes? Construction of consultant as detached?
Primary-secondary care	162 <u>open and give better quality answers particularly if there are social</u> 163 <u>issues. It would be good for consultants to be, you know recognised</u> 164 <u>in a certain area</u> and I think they would appreciate that as well. So	Notes, technology, IT systems affect quality of care, risks
Quality of care	165 no I think, obviously <u>ways in which care could deteriorate are in</u> 166 <u>terms of records</u> because obviously if the consultant doesn't have	
Technology	167 the notes, that's a disaster, so I don't know what the <u>IT set up</u> would 168 be like, that would, you know obviously if the <u>consultant can access</u> 169 <u>notes remotely</u> whatever you're planning, that would be very, very 170 important.	

Source: Heath G, Cameron E, Cummins C, Greenfield S, Pattison H, Kelly D, Redwood S: Paediatric 'care closer to home': stake-holder views and barriers to implementation. *Health and Place* 2012, 18(5):1068–1073.

Stage 4: Developing a working analytical framework

General explanation and important considerations, see: Gale et al. (1)

After coding the first few transcripts, all researchers involved should meet to compare the labels they have applied and agree on a set of codes to apply to all subsequent transcripts. Codes can be grouped together into categories (using a tree diagram if helpful), which are then clearly defined. This forms a working analytical framework. It is likely that several iterations of the analytical framework will be required before no additional codes emerge. It is always worth having an 'other' code under each category to avoid ignoring data that does not fit; the analytical framework is never 'final' until the last transcript has been coded.

- After SR and RJ have each coded the same 6 transcripts, we will meet to discuss the labels we have assigned to each passage. We will discuss each coded section of each of the 6 transcripts in terms of why we have coded it and why we perceived it as meaningful to answer the research questions. After discussion, we will agree on a set of codes, each with a brief definition. This will form the initial analytical framework. The initial analytical framework will have an 'other' code underneath each category where data that does not fit will be placed in.
- SR and RJ will then independently code 6 more transcripts (1 patient/caregiver/patient advocate transcript, 1 physician transcript, 1 regulator transcript, 1 HTA transcript, 1 industry transcript and 1 academic transcript) using the initial framework, taking care to note any new codes or impressions that do not fit the existing set.
- We will then meet again and discuss the new codes and revise the initial framework to incorporate new and refined codes. At this point we will also decide if codes are related and we will decide if they can be grouped together -> secondary framework.
- The process of refining, applying, and refining the analytical framework will be repeated until no new codes are generated.
- The final framework will consist of codes and categories, each with a brief explanatory description of their meaning and examples of what ideas or elements might be summarized under that code. See example underneath:

CODE	DESCRIPTION
Working Practices	
Professional role	<i>Perception of own or other's roles, including empowerment, professional pride, GP commissioning, GPs with Special Interest (GPwSI)</i>
Relationship between primary and secondary care	<i>Barriers, gaps, advantages and drawbacks, working relationships</i>
Knowledge and skills transfer	<i>Education, information, explanations, teaching, training (student doctors, GPwSI)</i>

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Joined up working	<i>Instances of working together from two or more different disciplines, working across care sectors</i>
Changes in working practices	<i>Impact / outcome in terms of changes to working practice (e.g. Saturday clinics), changes to clinician workload, consultant travel</i>
Philosophy of Care	
Ideology of 'care closer to home' (CCTH)	<i>Attitude towards closer to home agenda and satellite clinic model</i>
Patient-centered approach	<i>Biopsychosocial & holistic approaches, opportunities for health promotion, patient choice</i>
Equivalence to hospital care	<i>Comparisons with the hospital, e.g. trying to match standards of care</i>
Equity in service provision	<i>Distribution of services, equity in access to services, postcode lottery, service distribution</i>

Source: Heath G, Cameron E, Cummins C, Greenfield S, Pattison H, Kelly D, Redwood S: Paediatric 'care closer to home': stake-holder views and barriers to implementation. *Health and Place* 2012, 18(5):1068–1073].

Stage 5: Applying the analytical framework

General explanation and important considerations, see: Gale et al. (1)

The working analytical framework is then applied by indexing subsequent transcripts using the existing categories and codes. Each code is usually assigned a number or abbreviation for easy identification (and so the full names of the codes do not have to be written out each time) and written directly onto the transcripts. Computer Assisted Qualitative Data Analysis Software (CAQDAS) is particularly useful at this stage because it can speed up the process and ensures that, at later stages, data is easily retrievable. It is worth noting that unlike software for statistical analyses, which actually carries out the calculations with the correct instruction, putting the data into a qualitative analysis software package does not analyze the data; it is simply an effective way of storing and organizing the data so that they are accessible for the analysis process.

- We will use NVivo for this stage: the final analytical framework (coding tree) will be uploaded in NVivo. The transcripts will be divided among SR and RJ, who will each code 1/2nd of the transcripts. SR and RJ will systematically go through each transcript and highlight passages of text, selecting and attaching an appropriate code from the final analytical framework (coding).

Stage 6: Charting the data into the framework matrix

General explanation and important considerations, see: Gale et al. (1)

Qualitative data are voluminous (an hour of interview can generate 15–30 pages of text) and being able to manage and summarize (reduce) data is a vital aspect of the analysis process. A spreadsheet is used to generate a matrix and the data are 'charted' into the matrix. Charting involves summarizing the data by category from each transcript. Good charting requires an ability to strike a balance between reducing the data on the one hand and retaining the original meanings and 'feel' of the interviewees' words on the other. The chart should include references to interesting or illustrative quotations. These can be tagged automatically if you are using CAQDAS to manage your data (N-Vivo version 9 onwards has the capability to generate framework matrices), or otherwise a capital 'Q', an (anonymized) transcript number, page and line reference will suffice. It is helpful in multi-disciplinary teams to compare and contrast styles of summarizing in the early stages of the analysis process to ensure consistency within the team. Any abbreviations used should be agreed

- We will use excel for charting/summarizing the data. First, we will export the coded text per code from NVivo to word documents, resulting in 1 word document per code (e.g. 1 word document for "value and limitations of using patient preferences for industry decision-making", see yellow in stage 3). We will make a separate matrix per category (e.g. 1 matrix for "value and limitations of using patient preferences", see green in stage 3) where the matrix describes all the codes that fall underneath that category of the final coding tree. We will use thematic matrices: one matrix will be comprised of one row per code and one column per case. The cases are the interviewees. In the columns, we will indicate the background of each case/interviewee: namely the stakeholder group and country we assigned them to. Row 1,2 and so on will be the different codes of our final analytical framework (see example below, codes are those of the predefined coding tree above and thus not final yet).
- We will divide the transcripts among 2 researchers: SR and RJ will each chart 1/2nd of the transcripts.
- We will include references to interesting or illustrative quotations in this table and indicate them as follows: Q, transcript number (anonymized), page and line reference.
- We will indicate verbatim text (quotes) by underlining it.
- Abbreviations will be agreed upon in the early phases of charting.
- Meetings during the early phases of charting will allow us to compare how we chart the data and to ensure consistency.
- Example of how a matrix might look like:

MATRIX 1 "Value and limitations of using patient preferences"			
	CASE 1 "regulator, Italy"	CASE 2 "HTA representative, Germany"	...
CODE 1 "General value and limitations of patient preferences throughout life cycle"			
CODE 2 "Value and limitations of using patient preferences for industry decision-making"			
CODE 3 "Value and limitations of using patient preferences for regulatory BRA"			
CODE 4 "Value and limitations of using patient preferences for HTA/reimbursement"			

Stage 7: Interpreting the data

General explanation and important considerations, see: Gale et al. (1)

It is useful throughout the research to have a separate note book or computer file to note down impressions, ideas and early interpretations of the data. It may be worth breaking off at any stage to explore an interesting idea, concept or potential theme by writing an analytic memo to then discuss with other members of the research team, including lay and clinical members. Gradually, characteristics of and differences between the data are identified, perhaps generating typologies, interrogating theoretical concepts (either prior concepts or ones emerging from the data) or mapping connections between categories to explore relationships and/or causality. If the data are rich enough, the findings generated through this process can go beyond description of particular cases to explanation of, for example, reasons for the emergence of a phenomena, predicting how an organisation or other social actor is likely to instigate or respond to a situation, or identifying areas that are not functioning well within an organisation or system. It is worth noting that this stage often takes longer than anticipated and that any project plan should ensure that sufficient time is allocated to meetings and individual researcher

- RJ and SR will interpret the data by reviewing the matrix and making connections within and between participant and categories. This process will be influenced by the research questions and by new codes generated inductively from the data. During the interpretation stage, we will try to go beyond descriptions of individual cases. Team meetings will help interpretation of data.

Appendix 10: Procedure for analysis focus group discussions: Thematic Analysis

Chosen method: Thematic analysis based upon "Qualitative Research Methods in Psychology" – Dennis Howitt (40)

Core analyzing team ("CAT"): Eline van Overbeeke (EvO) and Rosanne Janssens (RJ)

Major steps in thematic analysis:

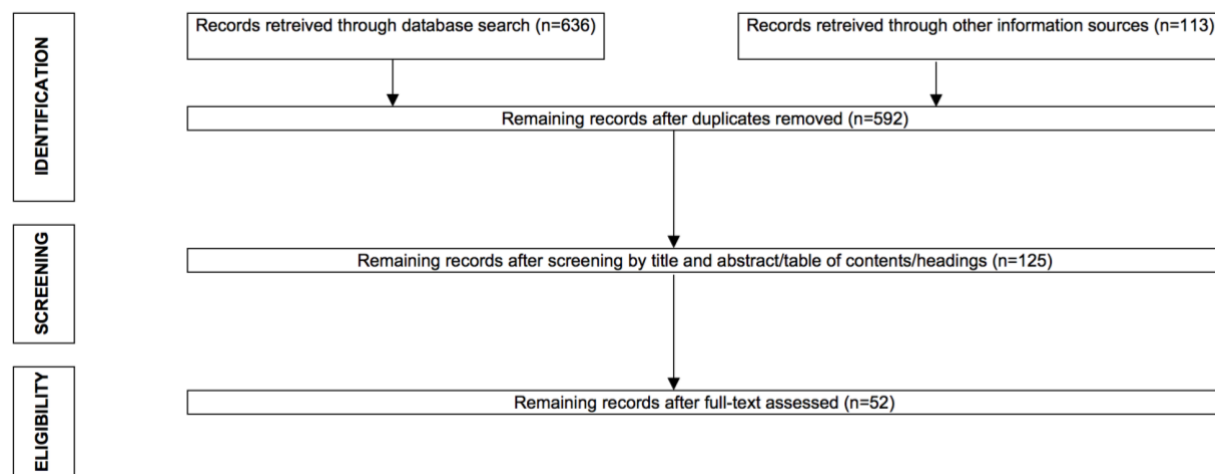
1. Data familiarization
2. Initial coding generation
3. Search of themes
4. Review of themes
5. Theme identification and labelling

Step-wise explanation:

1. Data familiarization
 - a. Howitt states that:
 - i. Data familiarization can take place via several methods and will differ according to the details of the study. Ways of familiarizing with the data are: i) being involved in the data collection stage, ii) doing the transcription, iii) playing the recordings repeatedly or iv) re-reading the transcripts;
 - ii. Start **think** about what is happening in the data during this stage. These early thoughts may suggest ways in which the data might be coded;
 - iii. Use **literal transcription** (since thematic analysis is about what was said rather than how it was said);
 - iv. Novice researchers to do all the **data collection** and **transcription themselves**;
 - b. Therefore, we will:
 - i. Become familiar with the data **by**:
 1. **Being present** during the FGD as moderator or assistant to the moderator. Because of practical limitations, 2 FGDs were moderated by an external partner, which make the steps below critical to become familiar with those FGDs. These external partners were actively involved during the set-up the research (e.g. during the set-up of the protocol and FGD questions) as we had several discussions with them to inform them and ask about their feedback about our focus group questions and protocol. Next, because of the amount of the FGDs (n=8) and the different languages used, we chose to outsource the transcription and translation of the FGDs to a professional transcription company (*TodayTranslations*).
 2. Thoroughly **reading** the transcript **several times**;
 - ii. Have the transcription done literally (at verbatim) by the transcription company;
 - iii. Have the transcripts checked for completeness and accuracy by moderator and/or assistants present during FGD;
 - iv. **Convene and discuss** in order to agree together about what was said in that particular part of the FGD, should there be difficulties in understanding the transcript. Should there be any remaining difficulties in understanding a certain part of the FGDs where neither one of EvO or RJ was present, we will **contact** the moderator and/or assistant present during that FGD to discuss and agree upon what was said.
2. Initial coding generation
 - a. Howitt states that:
 - i. This stage does not aim at identifying the themes that the research will generate; initial codes are nothing more than **labels** that will describe the content of 1 or 2 lines, they are **not sophisticated analyses** of the data. However, ideas as to what the themes might be can already occur (as during any stage of thematic analysis);
 - ii. There are **no "rules"** describing that initial coding has to be done line-by-line. Coding frequency depends on circumstances, if every line is not possible then every 2/3 lines is "all right";
 - iii. Best if these codes are based on an abstraction rather than something concrete, **the more conceptual (i.e. the less concrete, the more abstract) the codes, the better** the final themes;
 - iv. Researchers can choose:
 1. To work through the **entirety of data** or **a subset** of the data selected because it deals with a topic/matter of interest to the researcher;
 2. Between a **theory-led** or **data-led approach**;
 - v. During this stage, it may be appropriate to **re-name** codes that are covering the same meaning so they have the same wording;
 - vi. After the initial coding has been done, researchers should put together all of the transcript which has received a certain code. Reviewing all coded text of a certain code can reveal that:
 1. A coding **label** is not accurate/precise enough and needs to be **renamed**;
 2. **New codes** need to be formed as some of the data in a certain code "does not match";
 3. Certain codes need to be **combined** to one code as the coded text below two codes is too similar.
 - b. Therefore, we will:
 - i. Aim for 1 initial code **every 2/3 lines**;
 - ii. Use a **data-led** approach as described by Howitt, in which codes are primarily guided by careful analysis of what is in the data;
 - iii. **Independently code** the entirety of the data (n=8 FGDs), since there are two core analyzers;
 - iv. Convene after the independent coding of the data and perform steps vi.1, 2 and 3 together in order **to agree upon the final list of initial codes**
3. Search for themes based on initial codes
 - a. Howitt states that:
 - i. This stage involves **turning the initial codes into themes**, which requires a lot of analytic work on the part of the researchers;
 - ii. Searching for themes involves searching for **patterns** among the initial codes; as they will probably notice that some codes are more related than others;
 - iii. Themes are the result of **grouping and categorizing** codes, which does not preclude that some codes might turn out to be very important and result in this code being an actual theme;
 - iv. Some themes may be very obvious from the initial codes, whereas sometimes **methods of sorting** might help, e.g. by writing down all the initial codes on separate slips of paper and creating piles of related codes. NVivo or Word might be used in this stage.
 - b. Therefore, we will:
 - i. Each **independently search for themes** based upon the initial codes;
 - ii. Convene, discuss and **agree upon the themes** that we independently found.
4. Review of themes
 - a. Howitt states that:

- i. At this stage, there is **a set of tentative themes** which help to understand the data;
 - ii. In the case that these themes are not fully defined or refined at this stage, it is essential to **examine these themes against the original data**;
 - iii. Reviewing of themes involves organizing the data around the set of themes **just as previously the data was organized around the codes**;
 - iv. The possible scenarios of this stage are:
 1. **Modifying or abandoning the theme** if there is very little in the data supporting the theme;
 2. **Dividing or subdividing** the theme if the data in one theme actually imply two different themes or sub-themes;
 3. **Find a new theme** if some of the data you initially believed were part of the theme does not fit. If this is the case, a check for applicability of these themes to this data as well as the entire data set is advised.
 - b. Therefore, we will:
 - i. **Divide** the total number of transcripts among EvO and RJ;
 - ii. Separately **go back to each of the assigned transcript** and organize the text that was captured by the initial codes around our identified themes;
 - iii. Separately **critically revise** whether the theme should be abandoned, modified, (sub)divided or whether a new theme should be found;
 - iv. Any modification to our initial found themes will **trigger a discussion** between EvO and RJ and should this discussion lead to a modification of the initial list of themes, **a check** of the applicability of this modified list of themes to the entire data set will be done.
5. Theme definition and labelling
- a. Howitt states that:
 - i. Although it might be easy to give a label to a theme, it might be **more difficult to define exactly what a theme is**;
 - ii. It is important to be able to **conceptually distinguish** one theme from another;
 - iii. It is likely to continue **developing sub-themes** at this stage;
 - iv. It is important to **talk with other people** about your analysis at this stage and allow them to question you and throw in ideas of their own.
 - b. Therefore, we will:
 - i. Discuss and agree upon the final list of themes and sub-themes and our explanation to it. This will form the basis of the report (see 6.);
 - ii. **Discuss within our CAT as well as with other persons** how our themes differ from each other.
6. Report writing
- a. Howitt states that:
 - i. The explanation and description of the themes in the final report of thematic analysis involve the selection of appropriate illustrations taken from the material which is associated with the theme;
 - ii. Criteria that may be applied for this selection are:
 1. How 'typical' the material is of the data which belong to a particular theme;
 2. How 'fit' the material is in relation to the theme; some excerpts might illustrate particular features of the theme better than others;
 3. How 'eye-catching' the excerpt is; some data might be preferred to other excerpts as it is more vivid;
 4. Some might prefer using excerpts from just one of the participants to get into more detail about that particular case
 - iii. It is helpful to indicate in the report the basis for your excerpt selection
 - b. Therefore, we will:
 - i. Explain and describe in the final report the themes we identified;
 - ii. Use appropriate excerpts to illustrate these themes;
 - iii. Apply criteria ii.1, 2, 3 to select the excerpts we will use to describe the themes.

Appendix 11: Search flow



Appendix 12: Included literature

	Reference	Literature type	Stakeholder perspective	Decision-making context(s) described
1	FDA guidance (18)	Regulatory document	Regulatory agency	BRA
2	EMA report (7)	Regulatory document	Regulatory agency	BRA
3	KCE report (10)	HTA report	HTA	HTA/reimbursement
4	IQWiG report (61)	HTA report	HTA	HTA/reimbursement
5	Weernink MGM, 2014 (28)	Systematic review	Researcher	BRA + HTA/reimbursement
6	Gutknecht M, 2016 (50)	Systematic review	Researcher	BRA + HTA/reimbursement
7	Brooker AS, 2013 (76)	Systematic review	HTA	HTA/reimbursement
8	Irony T, 2016 (70)	Review	Regulator	BRA
9	Mühlbacher AC, 2013 (44)	Review	Researcher	BRA + HTA/reimbursement + ITD + CPG
10	Johnson FR, 2016 (30)	Review	Researcher	BRA
11	Martin-Fernandez J, 2014 (75)	Review	Researcher	HTA/reimbursement
12	Mühlbacher AC, 2016 (25)	Review	Researcher	BRA + HTA/reimbursement
13	Mühlbacher AC, 2015 (43)	Review	Researcher	BRA + HTA/reimbursement
14	Puhan MA, 2012 (80)	Review	Researcher	BRA
15	Stewart KD, 2016 (23)	Review	Researcher	IPDM
16	Evers P, 2016 (59)	Review	Patient advocate	IPDM + BRA + HTA/reimbursement
17	Marsh K, 2016 (34)	Review	Researcher	IPDM + BRA + HTA/reimbursement
18	Pisa G, 2015 (74)	Review	Researcher	BRA
19	Ho MP, 2016 (54)	Review	Regulator	IPDM + BRA
20	Mott DJ, 2016 (52)	Review	Researcher	BRA + HTA/reimbursement
21	Hauber B, 2013 (51)	Review	Researcher	BRA
22	Utens C, 2015 (2)	Original research	Researcher	HTA/reimbursement + CPG
23	Bridges JFP, 2014 (48)	Original research	Researcher	BRA
24	Chow RD, 2014 (56)	Original research	Researcher	IPDM
25	Danner M, 2011 (60)	Original research	Researcher	HTA/reimbursement
26	Ho MP, 2015 (68)	Original research	Researcher	BRA
27	Hollin IL, 2016 (65)	Original research	Researcher	BRA
28	Hummel MJM, 2012 (62)	Original research	Researcher	HTA/reimbursement
29	Ijzerman MJ, 2012 (78)	Original research	Researcher	HTA/reimbursement

30	Mol PG, 2015 (71)	Original research	Researcher	BRA
31	Postmus D, 2016 (29)	Original research	Researcher	BRA
32	Roy AN, 2015 (55)	Original research	Researcher	IPDM + HTA/reimbursement
33	Morel T, 2016 (58)	Original research	Researcher	BRA
34	Peay HL, 2014 (67)	Original research	Patient advocate	BRA
35	Avila M, 2015 (77)	Original research	Researcher	HTA/reimbursement
36	Medical Device Innovation Consortium (MDIC) report, 2015 (24)	Project report	MDIC	IPDM + BRA
37	PROTECT report 'Recommendations for Patient and Public Involvement in the assessment of benefit and risk of medicines', 2013 (49)	Project report	PROTECT	BRA
38	Biotechnology Innovation Organization and Parent Project Muscular Dystrophy report, 2016 (45)	Project report	Consultancy firm	BRA
39	EUPATI report, 2016 (79)	Project report	EUPATI	HTA/reimbursement
40	Avalere and Milken Institute report (41)	Project report	Avalere/FasterCures	ITD + BRA
41	PROTECT report 'Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines.' (66)	Project report	PROTECT	BRA
42	PROTECT report 'Review of methodologies for benefit and risk assessment of medication.' (73)	Project report	PROTECT	BRA
43	EMA workshop report (47)	Workshop report	Regulatory agency	BRA + HTA/reimbursement
44	FasterCures workshop report (57)	Workshop report	Patient advocate	ITD + BRA
45	DIA workshop report (53)	Workshop report	Industry representative	IPDM
46	Smith MY, 2016 (63)	Perspective article	Industry representative	IPDM
47	Dirksen CD, 2014 (42)	Perspective article	Researcher	HTA/reimbursement
48	Eichler HG, 2013 (64)	Perspective article	Regulator	BRA
49	Egbrink MO, 2014 (46)	Perspective article	Researcher	BRA + HTA/reimbursement
50	Eichler HG, 2012 (69)	Perspective article	Regulator	BRA
51	van Til JA, 2014 (72)	Perspective article	Researcher	BRA
52	Hunter NL, 2016 (81)	Perspective article	Regulator	BRA

Legend

BRA= benefit-risk assessment
HTA= health technology assessment
IPDM= industry processes and decision-making
CPG= clinical practice guideline development
ITD= individual treatment decision-making

Appendix 13: Boxes

Box 1. Definitions for preference sensitive decisions	References
When multiple treatment options exist and there is no option that is clearly superior for all patients AND the evidence supporting one option over others is considerably uncertain or variable AND/OR patients' views about the most important benefits and acceptable risks of a technology vary considerably within a population, or differ from those of healthcare professionals.	(18)
When a patient has multiple treatment options with at least one of the following characteristics: 1) No option is clearly superior over a plausible range of preferences 2) The evidence supporting one option over others is considerably uncertain	(24, 45)
When: 1) A product generates clear clinical benefits , but has a greater risk of events that are likely to concern regulators , such as potentially fatal side effects. 2) A product generates similar benefits to standard of care, but with a different safety profile.	(34)
When there are multiple diagnostic or treatment options , and the decision which option to pursue depends upon the particular preferences of the decision maker.	(24, 45)
When there is a high degree of uncertainty with regards to the treatment outcomes	(24, 65)
When treatment involves challenging trade-off (marginal benefit-risk or complex benefit-risk trade-offs)	(24, 70)
e.g. patient preference sensitive decision if the benefits as well as the risks of less invasive approaches are less than those of the more invasive options	(24)
e.g. patient preference sensitive decision if unclear whether benefits exceed risks	(24)
Box 2. Factors influencing the value of patient preferences in BRA and situations where using patient preferences are particularly useful	References
Factors relating to the unique perspective of patients with the disease : when personal experience is required to understand the disease	(24, 45)
Rarity of the diseases	(24, 45, 58, 65)
High uncertainty regarding treatment outcomes	(65)
Likelihood of differences in views between reviewers and patients because reviewers likely have limited clinical exposure to the disease	(24, 65)
Likelihood of significant differences between what would be expected by patients vs by others who do not experience the challenges of living with the disease	(24)
Decisions concerning end-of-life care or coping with debilitating chronic diseases	(24)
Decisions concerning serious, progressive disorders with limited treatment options, because regulators may be less able to imagine how patient might weigh benefits and risks	(45)
Decisions concerning subjective endpoints	(24, 45)
Decisions concerning quality of life	(24, 30)
Differences in opinions about risk tolerance between patients and other key stakeholders	(24, 45)
Factors relating to the novelty of the medical product	(24)
Lack familiarity of assessors/sponsors with the medical product	(24)
Decisions concerning unmet medical needs	(24, 30, 45)
Fundamental difference in treatment paradigms (e.g. device vs drug)	(24)
Treatment choice involves a change in lifestyle	(24, 70)
Device is used directly by the patient	(24, 30)
Existence of heterogeneity in patient preference	(24)
Occurrence of benefits early and harms much later or when harms occur early and benefits occur much later (e.g. a treatment to delay onset or worsening of a disease)	(24)
Box 3. The use of public preferences vs patient preferences	References
Reasons to use public preferences and not patient preferences	
Members of general public bear costs associated with health care decisions, they should have a say in resource allocation decisions	(42, 52)
Patients are biased and are assumed to act in their self-interest	(42, 52)
Patients value their own health state higher compared to the general public, because of adaption to ill-health	(42, 52)
Guidelines are focused on the use of public preferences (e.g. NICE guideline)	(52)
Some countries have a publicly funded health care (e.g. U.K.), which makes it hard to argue against public preferences	(52)
Reasons to use patient preferences and not public preferences	
Generic health state descriptions and vignettes lack important details	(42)
Healthy people tend to focus on the negative aspects of disease due to a 'focusing illusion' heuristic and ignore the positive aspects and the bigger picture of life	(42)

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Healthy respondents do not recognize and predict adaptation to ill-health and coping mechanisms that patients are likely to develop	(42)
Because there is no firm theoretical base for the use of public instead of patient preferences for construction of the QALY	(42)

The statements are grouped into a hierarchy. This hierarchy is indicated by grey shaded cells, (=1st level of the hierarchy), no shaded cells (=2nd level of the hierarchy), tab (=3rd level of the hierarchy).

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