



*Teaser This study can inform different stakeholders on how to conduct, assess, and use patient preference studies and on when to include patient preference studies in development plans.*

# Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review

**Eline van Overbeeke<sup>1,‡</sup>, Chiara Whichello<sup>2,‡</sup>,  
Rosanne Janssens<sup>1</sup>, Jorien Veldwijk<sup>2</sup>, Irina Cleemput<sup>3</sup>,  
Steven Simoens<sup>1</sup>, Juhaeri Juhaeri<sup>4</sup>, Bennett Levitan<sup>5</sup>,  
Jürgen Kübler<sup>6</sup>, Esther de Bekker-Grob<sup>2</sup> and Isabelle Huys<sup>1</sup>**

<sup>1</sup> Clinical Pharmacology and Pharmacotherapy, University of Leuven, Herestraat 49 Box 521, 3000 Leuven, Belgium

<sup>2</sup> Erasmus School of Health Policy & Management (ESHPM) and Erasmus Choice Modelling Centre (ECMC), Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

<sup>3</sup> Belgian Health Care Knowledge Centre (KCE), Kruidtuinlaan 55, 1000 Brussels, Belgium

<sup>4</sup> Sanofi, 55 Corporate Drive, Bridgewater, NJ 08807, USA

<sup>5</sup> Janssen Research & Development, 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560, USA

<sup>6</sup> Quantitative Scientific Consulting, Europabadstr. 8, 35041 Marburg, Germany

**Industry, regulators, health technology assessment (HTA) bodies, and payers are exploring the use of patient preferences in their decision-making processes. In general, experience in conducting and assessing patient preference studies is limited. Here, we performed a systematic literature search and review to identify factors and situations influencing the value of patient preference studies, as well as applications throughout the medical product lifecycle. Factors and situations identified in 113 publications related to the organization, design, and conduct of studies, and to communication and use of results. Although current use of patient preferences is limited, we identified possible applications in discovery, clinical development, marketing authorization, HTA, and postmarketing phases.**

## Introduction

The importance of incorporating patient needs and perspectives into decision making throughout the lifecycles of drugs and medical devices, for the purpose of this study collectively called the medical product lifecycle (MPLC), is receiving increasing recognition [1–4]. Recognition of the value of patients' perspectives has led to a shift in drug development and assessments, from only looking at clinical outcomes to taking into account the judgements of patients on how these outcomes affect their lives. This shift originates from the notion that patients should be at the

Corresponding author. van Overbeeke, E. ([eline.vanoverbeeke@kuleuven.be](mailto:eline.vanoverbeeke@kuleuven.be))

<sup>‡</sup> Joint first authors.

**Eline van Overbeeke** is a PhD student at the University of Leuven (Belgium), and has worked on the Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project of the Innovative Medicines Initiative (IMI) since October 2016. Before her PhD, she was awarded her Masters in biomedical sciences at the University of Leuven and gained experience in medical affairs in the pharmaceutical industry. Eline considers it important that the voice of patients is listened to throughout the medical product lifecycle and focuses her current work on how to improve the implementation of patient preferences in assessments throughout this lifecycle.



**Chiara Whichello** is a PhD student at Erasmus University Rotterdam, and is currently also working on the IMI PREFER project. Chiara was awarded both an MSc in global health and an MA in anthropology & sociology from the University of Glasgow. Her current research interests include the appraisal of patient preference elicitation and exploration methods and the advancement of patient-focused drug development.



**Isabelle Huys** is the deputy coordinator of the PREFER project from the IMI PREFER project. She has a PhD in pharmaceutical sciences from the University of Leuven (Belgium) and carried out postdoctoral research at their Law Faculty on patents and biomedical inventions. Since 2010, she has been a full-time professor in regulatory sciences at the Faculty of Pharmaceutical Sciences and a member of the Center for IT & Intellectual Property IT law (CiTiP). She has also been an advisor for European projects, intellectual property officer and regional development officer in the R&D Department of the University of Leuven.



## GLOSSARY

**Attribute** feature of the product under investigation (e.g. price) [126]

**External validity** the degree to which it is warranted to generalize results to other contexts

**Internal validity** the extent to which a causal conclusion based on a study is warranted. Such warrant is constituted by the extent to which a study minimizes systemic error (or 'bias')

**Level** value of the attribute (e.g., US\$10) [126]

**Patient preferences (patient preference information)** qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions [4]

**Preference elicitation method** quantitative methods collecting quantifiable data that can be reported through statistical inferences or analysis

**Preference exploration method** qualitative methods that collect descriptive data through participant or phenomenon observation, examining the subjective experiences and decisions made by participants

**Preference-sensitive situation** preference-sensitive decisions are those in which there are multiple diagnostic or treatment options, and the decision which option to pursue depends upon the particular preferences of the decision-maker [3]

center of the MPLC, because they are the ones not only gaining the benefits, but also being exposed to the risks [5].

One option to better understand the patient perspective is through exploring and eliciting **patient preferences** (see [Glossary](#)). The US Food and Drug Administration (FDA) refers to patient preferences by defining patient preference information as 'qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other **attributes** that differ among alternative health interventions' [4]. Patient preferences can be obtained through the use of different exploration (qualitative) and elicitation (quantitative) methods [6]. **Preference exploration methods** can be defined as qualitative methods that collect descriptive data through participant or phenomenon observation, and examining the subjective experiences and decisions made by participants. Examples of preference exploration methods include semi-structured interviews and focus groups. **Preference elicitation methods** can be defined as quantitative methods collecting quantifiable data that can be reported through statistical inferences or analysis. Examples of preference elicitation methods include discrete choice experiments (DCE), analytical hierarchy process (AHP), and standard gamble. Although methods can be classified as exploration or elicitation methods, they can also be classified as structured-weighting, health-state utility, stated-preference, or revealed-preference methods, as described in the Medical Device Innovation Consortium (MDIC) Patient Centered Benefit-Risk Project report [3,7].

Stakeholders, including the pharmaceutical and medical device industry, regulatory authorities, HTA bodies, payers, clinicians, academia, and patient organizations, generally agree that there is value in using patient preferences to inform assessments and

decision making [1,3,4,8–13]. In addition, patients themselves have expressed interest in decision-making processes [14]. Patient preferences are found to provide additional information on medical products, such as insights into the relative importance of clinical outcomes and safety issues, and to help in transparent communication regarding the incorporation of patient views in regulatory decision making [1,3,15,16]. Moreover, they can lead to more relevant, well-informed, transparent, publically trusted, and patient-centric decisions [3,13,17,18]. In HTA specifically, patient preferences are believed to provide a health condition perspective and to improve the usefulness, appropriateness, and acceptability of the assessments [2,8,19,20]. Also, consideration of patient preferences in clinical trial design can lead to a lower burden for patients participating in the trial, and could result in improved recruitment, retention, and compliance of patients. Moreover, it could lead to more real-world clinical outcomes if preferences of patients are considered during the establishment of treatment arms [4,21–25].

European and US industry, regulators, HTA bodies, and payers are currently exploring the use of patient preferences in their processes and decision making. However, in general, these stakeholders have limited experience in conducting and assessing these studies. Moreover, they are generally not familiar with factors influencing the value of these studies, the situations in which these studies are most valuable, and possible applications of patient preferences in their processes and decision making [26–28].

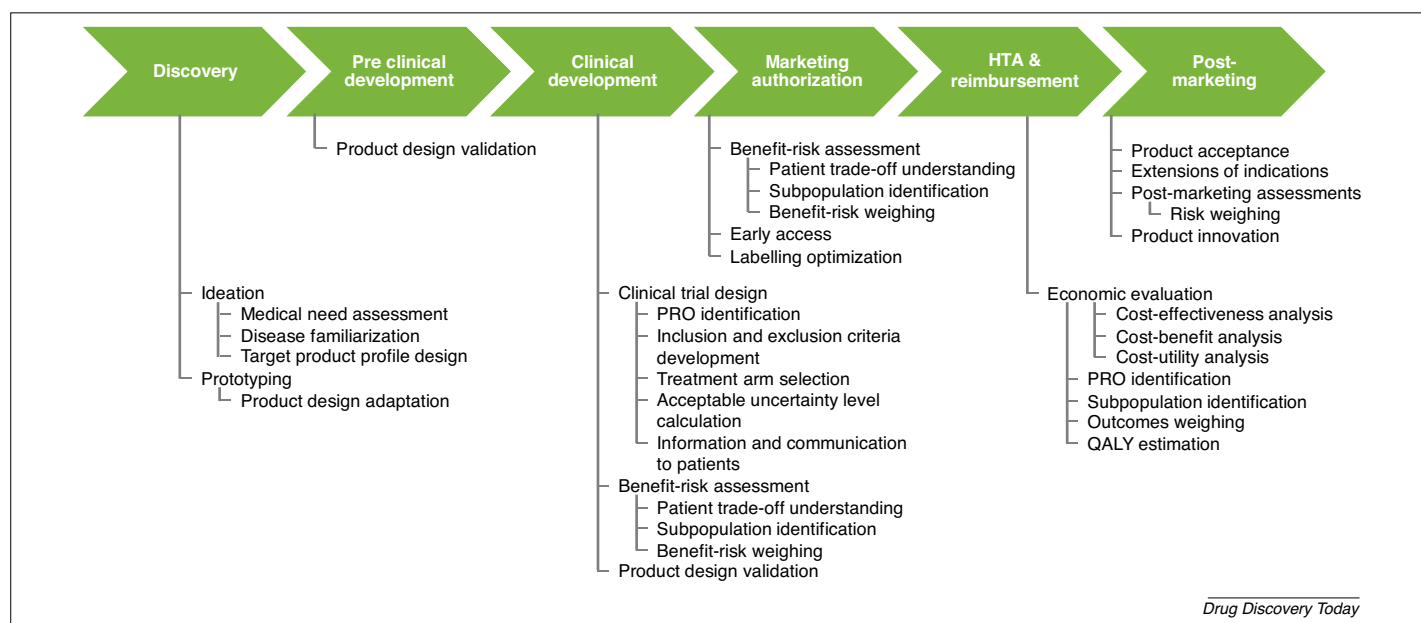
By performing a systematic literature search and review (see SP.I in the Supplemental information online) focused on the current measurement and use of patient preferences in Europe and the US, here we provide an overview of factors and situations that influence the value of patient preference studies. We also investigated applications of patient preferences in assessments and decision making along the MPLC.

## Overview of applications of patient preferences along the medical product lifecycle

A total of 113 publications were included in the literature review (see SP.II in the Supplemental information online). Before we explore the factors and situations that influence the value of patient preference studies in assessments and decision making along the MPLC, first we give a short overview of how patient preferences can be used in MPLC phases. Several publications described that patient preferences can be used in every phase of the MPLC, from discovery until post marketing [3,29]. Here, we describe the applications of patient preferences following the structure of the MPLC (Fig. 1). An overview of the availability of guidelines and frameworks on the use of patient preferences throughout these phases is given in Table 1. Currently, the Innovative Medicines Initiative (IMI) Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project is working on providing recommendations on how patient preferences can inform decision making throughout the MPLC [9].

### Discovery

Patient preferences are used in the discovery of new medical products [30,31]. They can inform ideation and prototyping. During ideation, the elicitation of patient preferences can help

**FIGURE 1**

Applications of patient preferences along the medical product lifecycle (MPLC). Applications of patient preferences were mapped along the phases of the MPLC. Applications were identified for all phases of the MPLC. Stages of the MPLC and their organization were identified as they emerged from the literature. Abbreviations: HTA, Health Technology Assessment; PRO, patient-relevant outcomes; QALY, quality-adjusted life year.

**TABLE 1****Availability of guidance on the use of patient preferences along the MPLC<sup>a</sup>**

Phase of MPLC	Availability of guidance	Refs
Discovery	Lack of guidance reported	[98]
Preclinical development	No guidance identified	
Clinical development	No guidance identified	
Marketing authorization	Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. US Department of Health and Human Services, FDA, Center for Devices and Radiological Health and Center for Biologics Evaluation and Research MDIC Patient-Centered Benefit–Risk Project Report: A Framework for Incorporating Information on Patient Preferences regarding Benefit and Risk into Regulatory Assessments of New Medical Technology ICH Harmonized Guideline: Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH	[4] [3] [127]
HTA and reimbursement	Kleme <i>et al.</i> : Patient perspective in health technology assessment of pharmaceuticals in Finland Kievit <i>et al.</i> : Taking patient heterogeneity and preferences into account in health technology assessments Lack of guidance reported	[107] [20] [10,128]
Post marketing	No guidance identified	

<sup>a</sup>Abbreviations: ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

to identify unmet medical needs, also referred to as unmet healthcare needs. For instance, this is demonstrated by the patient preference study on fragile X syndrome (FXS) by Cross *et al.* [32], described in the report of Selig [3,4,30]. Selig described how stakeholders sought to get a better understanding of unmet needs in FXS. Caregiver preferences were quantified for six treatment outcomes. Caregivers found the ability of patients to control their psychological, gestural, and verbal behavior to be the most important treatment outcome. Cross *et al.* [32] stated that these results would have the potential to inform future drug development in FXS [30]. In addition to identifying unmet medical needs, they can lead to a better understanding of the disease, personal

experiences of patients with the disease, and the acceptability of benefits and risks [3,4,30,33]. Patient preferences can even be used to inform the design of the target product profile, ensuring that patient needs are met [34]. During prototyping, patient preferences can inform adaptation of the design of the medical product [3,4,11].

**Preclinical development**

Almost no evidence was found on applications of patient preferences in preclinical development. Patient preference were suggested to ensure that the patient needs are addressed by the medical product in design validation during preclinical testing

[3]. No literature was retrieved demonstrating the actual use of patient preferences during preclinical development.

#### Clinical development

Patient preferences can be elicited during clinical development to inform clinical trial design, product design validation, and benefit–risk assessment [3]. Patient preferences are currently taken into account in clinical trial design [3,4,11,30], during which patient preferences can be used to identify patient-relevant outcomes that can inform the selection of clinical endpoints [4,22,35–37]. Also, patient preferences can inform the development of reasonable inclusion and exclusion criteria. Moreover, they can be used to define experimental or control treatment arms in doubly randomized preference trial (DRPT) designs. In DRPT designs, the effect of preferences on clinical outcomes can be analyzed [24,25,38–44]. Patient preferences can also be used in clinical trial designs to calculate the acceptable level of uncertainty (significance level and power) in clinical trials [45,46] and to inform development of information that will be provided to patients during clinical trials, including background information and study results [23].

#### Marketing authorization

The use of patient preferences in regulatory marketing authorization was discussed in 46 out of 113 (41%) publications. Regulatory authorities such as the FDA [4] and the European Medicines Agency (EMA) [1] are currently exploring the use of patient preferences [11–13]. However, they do not require the submission of patient preferences [16]. The FDA accepts the submission of patient preference information in approval applications for medical devices either as supporting evidence or for informational purposes [4,47].

Patient preferences can be used at the marketing authorization stage in benefit–risk assessment, assessment for early access [11], and for optimizing labeling that will inform patients on benefits and risks [3,4]. Use of patient preferences in benefit–risk assessment has given rise to patient-centered benefit–risk (PCBR) assessments [48,49]. Several initiatives are working on incorporating patient preferences in benefit–risk assessments, such as the MDIC Patient Centered Benefit-Risk Project, IMI PREFER, and the FDA's Center for Devices and Radiological Health (CDRH) Patient Preference Initiative [9,50]. In benefit–risk assessments, patient preferences can provide information on maximum acceptable risk, minimum acceptable benefit, net clinical benefit, quality-adjusted time without symptoms and toxicity, and relative value-adjusted number needed to treat through multiple-criteria decision analysis, benefit–less-risk analysis, the Gail assessment, and probabilistic simulation methods [49,51–56]. These assessments are informed by patient preferences through understanding the trade-offs that patients make between benefits and risks [36]. Moreover, the results of patient preference studies can not only show a range of preferences, but also be used to identify subpopulations for whom the benefits outweigh the risks [3,4,16,52,57]. Finally, patient preferences can help to weigh the benefits and risks in benefit–risk assessments based on the relative importance of outcomes, benefits, and risks for the patients [51,58].

#### Health technology assessment & reimbursement

Although different publications described that patient preferences can inform reimbursement decisions during the HTA and reim-

TABLE 2

#### Main US and European HTA bodies and payers interested in patient preferences<sup>a</sup>

Country	Organization
Belgium	Belgian Health Care Knowledge Centre (KCE)
England	National Institute for Health and Care Excellence (NICE)
Finland	Finnish Medicines Agency (Fimea)
France	High Authority of Health (HAS)
Germany	Institute for Quality and Efficiency in Health Care (IQWiG)
Scotland	Scottish Medicines Consortium (SMC)
The Netherlands	Care Institute Netherlands (CVZ)
USA	Centers for Medicare & Medicaid Services (CMS)

<sup>a</sup> Based on Refs [19,29,61,62,65,66,78,81,129].

bursement stage [3,59–62], Dirksen *et al.* [63] reported that not much evidence is available on the actual use of patient preferences in reimbursement decision making and that multiple countries do not consider patient preferences as an explicit prioritization criterion. The use of patient preferences in HTA was discussed by 49 out of 113 (43%) publications. Although cases have been described where HTA bodies are reluctant towards considering patient preferences in their assessments, European and US HTA bodies and payers have increasingly shown interest in using patient preferences in their assessments (Table 2) [2,8,10,11,31,64–67].

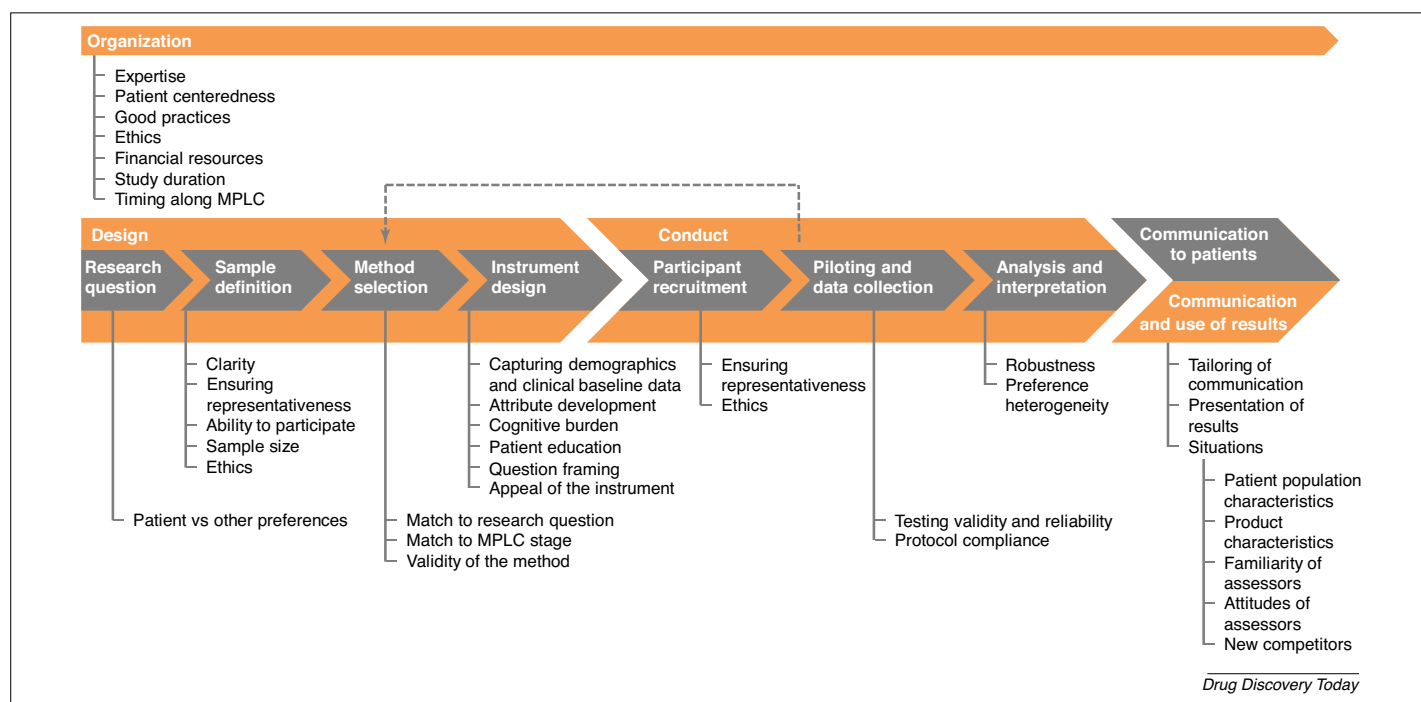
Twelve publications specifically mentioned the use of patient preferences in economic evaluations, including cost-effectiveness, cost–benefit, and cost–utility analyses [60,61,68–77]. In these analyses, patient preferences can inform the identification of patient-relevant outcomes, and the identification of subpopulations for whom the benefits outweigh the risks [20,52,61,75]. In addition, patient preferences can help to weigh outcomes according to their relative importance to patients [20,61,75,78]. This could be done by incorporating patient preferences and other evidence into a multicriteria decision analysis [52,55]. Lastly, Bewtra *et al.* [76] described that the utility values resulting from patient preference studies can be used as quality-of-life weights in the calculation of quality-adjusted life years (QALYs). QALYs and EuroQol five dimensions (EQ-5D) utilities are frequently used in HTA, but their classical use has been criticized by some, because they only cover benefit for generic quality-of-life dimensions rather than for all factors that important to patients [73,79,80].

#### Post marketing

Although some applications of patient preferences described above might also be applicable to the postmarketing phase, some additional postmarketing-specific applications were identified in the MDIC report [3] and the FDA guidance [4]. During the postmarketing phase, patient preferences could inform product acceptance by patients, extensions of indications, postmarketing assessments through risk weighing, and product innovation [3,4].

#### Factors and situations influencing the value of patient preference studies

Many factors and situations were identified that can influence the value of patient preference studies (Fig. 2) [18,81]. Factors were defined by the researchers as a fact or influence that occurs during the organization, design, conduct, or communication of results of the study and that contribute to, or affect, the value of results from

**FIGURE 2**

Factors and situations influencing the value of patient preference studies. Factors and situations were mapped along the organization, design, conduct, and communication and use of results of patient preference studies. Stages and steps of patient preference studies and their organization were identified as they emerged from the literature. Abbreviations: MPLC, medical product lifecycle.

patient preference studies. Situations were defined as a circumstance or condition that occurs during the use of results and that contributes to, or affects the value of, results from patient preference studies. Situations were considered to be external to the preference study and not controllable by the researcher. These factors and situations are described below following the different stages and steps of a patient preference study. Although there are alternative ways to describe the stages of patient preference studies and the different steps that they encompass, we identified steps and their organization as they emerged from the literature, in addition to the organizational context (see SP.III in the supplemental information online). Stages included study design, study conduct, and communication and use of the results.

### Organizational context

Multiple organizational factors were identified that determine the value of patient preference studies, as discussed below.

#### Expertise

Clinical, medical product development, patient, methodological, and statistical expertise of the conducting parties will have considerable impact on whether and how a preference study is performed [2,3,12,28,30,50,82,83]. Partnerships between industry, academia, and patient organizations can be established to acquire the needed expertise [28], but agreements on sharing and using the data need to be established [28,30]. Expertise must be shared between parties to ensure appropriate conduct by trained staff and common understanding [4,28,30].

#### Patient centeredness

Patient centeredness of patient preference studies is an important factor for success. The FDA guidance [4] states that the patient

should be 'the central focus of the study'. Patients and patient representatives can participate in the study design to guarantee comprehensibility of the information and questions provided to patients, to improve recruitment, and to ensure correct interpretation and communication of results [4,16,28].

#### Good practices

Following good research practices, similar to Good Clinical Practices [84] and Good Pharmacoepidemiology Practices [85], will ensure a correct design and conduct of the study and the value of the results [30,86]. However, patient preference study-specific guidance is often lacking (Table 3). Different initiatives are working on addressing methodological issues and providing recommendations and guidance on the design and conduct of patient preference studies (Table 4).

#### Ethics

Compliance with ethics requirements associated with questioning patients is necessary in setting up a patient preference study, and different measures have to be taken to meet these ethics requirements [14,60]. This process is time consuming. Obtaining ethics and/or institutional review board (IRB) approval when questioning patients can especially be challenging for industry, and will not always give direct access to patients and their data [31,83]. Postmus *et al.* [16] described that they did not collect demographic and clinical data in their patient preference study to avoid the complexity of data protection, but stated that not having these data limited their analysis.

#### Financial resources

Conducting patient preference studies comes with a financial burden that can differ among methods. Budgets of US\$100 000–400 000 (€90 000 to €370 000) have been quoted for quantitative patient preference studies [2,3,12,30,31,50,82,83,87].

TABLE 3

**Availability of guidance on design and conduct of patient preference studies<sup>a</sup>**

Topic	Availability of guidance	Refs
Good research practices	ISPOR method-specific good research practices	[4,78,103]
Choice of preference exploration/elicitation method	Lack of guidance reported	[3,18,98]
Selection of attributes	Lack of guidance reported	[3]
Whose preferences should be measured	Lack of guidance reported	[3,60]
Validity assessment	Janssen <i>et al.</i> : Improving the quality of discrete-choice experiments in health: how can we assess validity and reliability?	[109]
	Lack of guidance reported	[3]

<sup>a</sup> Abbreviations: ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

TABLE 4

**Initiatives working on addressing methodological issues and providing recommendations and guidance on the design and conduct of patient preference studies**

Initiative	Website
IMI PREFER	<a href="http://www.imi-prefer.eu">www.imi-prefer.eu</a>
International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Patient Preferences Special Interest Group	<a href="http://www.ispor.org/sigs/Stated-Preference-Methods.asp">www.ispor.org/sigs/Stated-Preference-Methods.asp</a>
International Academy of Health Preference Research (IAHPR)	<a href="http://iahpr.org">http://iahpr.org</a>
International Health Economics Association (iHEA), Health Preference Research Special Interest Group	<a href="http://www.healtheconomics.org/page/HealthPreference">www.healtheconomics.org/page/HealthPreference</a>

**Study duration**

The conduct of a patient preference study is time-consuming, ranging from 6 months to 2 years in complex cases [2,12,30,82,83]. The recruitment of patients can particularly take more time than is anticipated [82,83].

**Timing along MPLC**

It is not clear when patient preference studies should be conducted because the submission of patient preferences is currently not required by regulatory authorities and HTA bodies and/or payers, but can be accepted as supporting evidence in a submission dossier [3,4,50,55]. Currently, the study sponsor themselves needs to decide whether information on patient preferences is needed and to assess when and how to best collect it [3].

**Patient preference study design**

If patient preferences are elicited in well-designed and well-conducted patient preference studies, patient preferences are considered to be valid scientific evidence that can be valuable in informing decision making [4]. Thus, the design phase of a patient preference study is a crucial phase. Inadequate design will negatively influence the value of the study and make it unlikely that outcomes will be considered by decision makers [12]. Design factors that could influence the value of the study are discussed below per step in the design process (Fig. 2).

**Research question**

The formulation of the research question will influence the value of the study and choice of preference elicitation, or exploration method, because the applicability of measuring patient preferences depends on the research question being asked [3,30]:

**Patient versus other preferences**

Decision making might not be sensitive to patient preferences when preferences of other stakeholders, such as the general public or clinicians, or other evidence, are found to be more important than those of the patient [3]. This might be particularly important when setting up a study to inform HTA because some reimbursement decision-makers might wish to take the preferences of the general public, as a healthcare payer, into account [55,63,88].

**Sample definition**

Besides obtaining ethics and/or IRB approval and access to patients as described above, additional factors can influence the value of patient preference studies during sample definition:

**Clarity**

Clearly defining the patient sample will ensure inclusion of the right patients and value of results. Setting up inclusion and exclusion criteria can safeguard a clear definition of the patient sample [3].

**Ensuring representativeness**

Ensuring heterogeneity in the patient sample will result in generalizable results that are representative of the preferences of the full patient population for which the medical product is intended to be launched [3,4,21,30,36,50,89,90]. Generalizability of the results might be limited because of the eligibility criteria of the sample, especially when patient preference studies are performed alongside clinical trials [39,72,89,91–96].

**Ability to participate**

In the following patient populations, it might be more difficult to measure preferences and it might be necessary to pay more attention to the design of the exploration or elicitation instrument: (i) low reading level or vision difficulties; (ii) not able to use a pencil or a computer mouse; (iii) no access to the internet; (iv) physically disabled; (v) cognitive impairments; and (vi) pediatric patient populations [3,4,70,83,97]. If preferences cannot be elicited directly from patients themselves, preferences can be elicited from informal caregivers, including parents and family members [3,4,33]. Parents can be included to represent their children and family members to represent older relatives [3,4,30,49,70,93,98]. However, their preferences might differ from those of the patients because they might not assign the same values to various risks and benefits [4,99].

**Sample size**

During the design phase of patient preference studies, sample size and power calculations can be made to allow for statistical analyses later on [14,100]. If sample size calculations do not take heterogeneity into account, it might be impossible to do subpopulations analysis when results are available [89,90,93,95,97]. Required sample sizes differ among methods. For example, in general, smaller samples are required for swing weighting compared with DCEs [87].

**Method selection**

Many different types of preference exploration (qualitative) and elicitation (quantitative) methods exist and can be used in patient

preference studies [3,4,14,81]. Factors that determine the value of patient preference studies are discussed below.

### **Match to research question**

The optimal method for patient preference elicitation or exploration will depend on the study objective and primary use of results, and can be discussed with the stakeholders affected by, or evaluating, the results in advance to increase the value of the study [4,12,18,81,101]. Elicitation methods can quantify personal preferences, are structured, have clearly defined data types, have limited response options, allow for statistical analysis, and are recommended to be used when the aim is to explore preference heterogeneity in different patient profiles [3,4,45,56]. Exploration methods, such as interviews and focus groups, are recommended for concept exploration and gaining in-depth knowledge of the value of medical products [3,10,18]. Although it is important to match the method to the research question, this specificity and lack of standard measures is also what makes it hard to compare preference studies across conditions, limiting their value for some HTA agencies or reimbursement decision-makers [55].

### **Match to MPLC stage**

The appropriate choice of the method depends on the phase in the MPLC. During discovery, interactive exploration methods, such as focus groups, have been described as being particularly useful [4]. In informing clinical trial design, both exploration and elicitation methods have been used [24,25,35–37,39,102]. For benefit–risk assessments, elicitation methods, such as DCE and AHP, as well as exploration methods can be useful [12,53,59,103]. In HTA, elicitation methods that can examine willingness to pay are also described as being useful [59,60,69,70,81,104,105]. However, until now, HTA has mainly focused on patient involvement using preference exploration methods [55,106,107].

### **Validity of the method**

Given that participant responses might depend on the preference elicitation method used [105,108], weights or values obtained through different methods might not be comparable [82]. Therefore, guidance on which methods to use are of important to ensure the value of patient preference studies in decision making. There is a lack of guidance on how to assess the validity of a patient preference study [3] (Box 5). However, work is underway on approaches to assess the validity of patient preference studies. For example, Janssen *et al.* [109] created a conceptual model for the assessment of validity in DCEs. The manner in which **internal validity** can be ensured or assessed depends on the method used. Tervonen *et al.* [87] compared swing weighting (SW) to DCEs and stated that internal validity is automatically enforced with SW because of the exact nature of the collected preferences, whereas the internal validity of DCE results needs to be assessed manually. Assessment of **external validity** of stated-preference methods, requiring a comparison between stated and actual choices, is difficult to perform because of the use of hypothetical choices [3,100].

### **Instrument design**

Depending on the objective of a patient preference study, the preference exploration or elicitation instrument can be designed to explore or elicit preferences for health states, treatment attributes, or treatment alternatives [81]. Different factors related to the design of the instrument influence the value of the study, as discussed below.

### **Capturing demographics and clinical baseline data**

Collecting demographic and clinical data is important if subgroup analysis is planned to be performed [16].

### **Attribute development**

Attributes could be identified through patient and caregiver involvement, via a combination of literature reviews, interviews, and meta-analyses of clinical data, and possibly via trial economic evaluations [49,73,89,110]. Identifying attributes and their **levels** that are relevant and do not overlap is necessary to produce results that can be used to assess trade-offs [4,16,49]. When the real-life attributes and levels are not sufficiently different and do overlap, hypothetical choices can be included. This inclusion is often mentioned as a limitation, because hypothetical choices can reflect benefit and risk profiles other than of the actual therapies that will be approved [3,36,91,93,96]. The number of attributes that can be included in the instrument differs among methods. For example, DCEs have been argued to not allow the inclusion of many attributes and, thus, their applicability to contexts with many attributes is limited [87].

### **Cognitive burden**

Cognitive burden varies among methods, and minimization of this burden will assure the value of the results [4,87]. In patient preference elicitation studies, the cognitive burden for participants can be high because of the use of hypothetical choices and the large number and representation of questions, attributes, and levels [3,4,14,52,59,82,83,89,91,111]. Exploration methods, including interviews and focus group discussions, have a low cognitive burden for participants [61]. The patient population should be able to perform the method-specific tasks and understand the questions to realize results that can be used to assess meaningful trade-offs [3,4,16,49,83,112]. Survey administration via interviews or workshops instead of online administration could provide support to patients in understanding the questions [87,112].

### **Patient education**

The extent to which patients are informed on the benefits and risks of the medical product when participating in a patient preference study is a determining factor for the value of the results [4,16]. Effective communication on benefits, risk, uncertainties, and probabilities [30] can overcome cognitive burden [96] through the use of appropriate numeric, verbal, and graphic representations [4,52,82]. Effective communication is especially important when the instrument is designed on a self-administered basis [4,30]. The amount of, and how, information is provided to patients on the disease, risks, and benefits can influence their preferences and the validity of the study [24,30,63,83,98,110,11–115]. In describing outcomes to patients, Hockley *et al.* [83] recommend defining the name of the outcome, the description, recurrence, duration, and whether the outcome is treatable. Although no further guidance on patient education in patient preference studies was found, other sources that might provide information on how to educate patients include the guidance of the FDA on communicating benefits and risks [116], the IMI EUPATI project [117], and the criteria for judging the quality of patient decision aids from the International Patient Decision Aid Standards (IPDAS) [118].

### **Question framing**

When eliciting patient preferences, the framing of the questions can influence preferences and the validity of the study [119,120].

Bowling *et al.* [119] stated that ‘patients’ perceptions of risk and preferences for treatment are difficult to measure because of the large influence of question framing and presentation effects (positive/negative question wording biases). In addition, Howard *et al.* [120] demonstrated in a DCE study that attribute framing can influence patient preferences.

### **Appeal of the instrument**

The selection of a method and design of the instrument can depend on how engaging the instrument is to prevent dropout. Minimal dropout can be achieved when the instrument is engaging through inclusion of engaging stimuli and exclusion of complex formats and difficult to answer questions [3,83].

### **Patient preference study conduct**

Relevant factors influencing the value of the study and related to the study conduct are discussed below, based on each step of study conduct (Fig. 2).

#### *Participant recruitment*

Besides obtaining ethics and/or IRB approval and access to patients, as described above, another factor related to the recruitment of participants that will influence the value of the study is representativeness. Obtaining a representative sample of the patient population is a recruitment challenge for many patient preference studies [2,100]. Sample bias can be caused by over-inclusion of motivated patients, for example because of the recruitment of patients via a sole patient organization [16,36,49,78,93,121]. However, even in case of sample bias, the results of patient preference studies might still be meaningful for subpopulations [16].

#### *Piloting and data collection*

### **Testing validity and reliability**

Performing pilot studies before the main data collection is done will allow testing of validity and reliability of the preference method and instrument [78,83].

### **Protocol compliance**

During data collection, compliance with the protocol is a crucial determinant of the validity and reliability of the results [4,30].

#### *Analysis and interpretation*

### **Robustness**

When the robustness of the analysis is ensured, results of the analysis will lead to appropriate interpretation [4,30]. However, the value of the analysis can be reduced if the design of the study was not well set up [82]. In quantitative patient preference studies, statistical analysis can be performed, resulting in estimates and uncertainties (confidence intervals or standard errors), which can create a value model [4,16,33]. A sensitivity analysis can be performed to assess the importance of the different values in the model [4,33]. It might be necessary to use advanced regression techniques in quantitative patient preference studies, such as the mixed logit model [89,93]. For qualitative patient preference studies, statistical analysis is not appropriate [92].

### **Preference heterogeneity**

Given that individual preferences are measured in patient preference studies, it is possible that there are differences between patients in how they perceive and weigh the attributes

[4,50,60,95,122]. Some patients might accept higher risks for a certain benefit than other patients [3,4,50]. The detection of these differences could not only reveal population-level preferences for the medical product, but might also lead to the identification of subpopulations tolerating the risks [3,4,50,52,62]. Using statistical analysis tools that allow for detection of variation and distribution of preferences, for example latent class analysis, makes subgroup analysis possible [48,78,89,123]. However, the number of subgroups that can be evaluated is limited [48]. Allowing for the identification of subpopulations for whom the benefits outweigh the risks will increase the value of the study for benefit–risk assessments and HTA [3,4,16,20,52,57].

### **Communication and use of the results from patient preference studies**

The results of patient preferences studies can be communicated to, and used by, different stakeholders in decision making during the MPLC. Besides the communication of results to stakeholders for use in decision making, results can also be communicated back to patients. However, the communication of results to patients should be done in a different manner than communication to assessors. During the use of the results, stakeholders’ attitudes toward the use of patient preferences, but also clinical and market situations can influence the value of patient preferences studies.

#### *Factors arising in communication of results*

### **Tailoring of communication**

Results of patient preference studies can inform many stakeholders, including industry, regulators, HTA bodies, payers, physicians, patient organizations, and patients. However, these stakeholders have different needs and, therefore, tailoring of the language, format, and venue of the study results to the stakeholder group can enhance the value of the results to the stakeholders. Patient organizations can participate in the communication of results to patients to ensure comprehensibility of the disseminated results [28].

### **Presentation of results**

Visualizing results can prevent their misinterpretation, and can be achieved through the use of tables, forest plots, and bar charts [82].

#### *Situations influencing the value of patient preference studies*

### **Patient population characteristics**

Patient preferences might be especially useful in a population with unmet medical needs or in rare diseases [3,4,49]. However, if the medical product is developed for an unmet medical need with severe symptoms and high mortality, or if the outcomes of treatment with the medical product are more favorable than the outcomes of the disease treated with best-available care, it might be less valuable to elicit patient preferences [3].

### **Product characteristics**

The characteristics of the investigational product and its alternatives influence the value of patient preferences in decision making [3,4,50]. Patient preferences can be useful for decision making when: (i) it concerns a self-use medical product; (ii) there are significant benefits and risks compared with alternatives; (iii) there are different alternatives with different profiles (**preference-sensitive situations**); (iv) the importance of the benefits and risks is similar (uncertain benefit–risk profiles); (v) benefits and harms do



not occur simultaneously; (vi) technologies new to a certain disease area are used; (vii) risks can be identified for which no benefit can compensate; and (viii) clinical experiences and end-points are subjective [3,4,45,50,89,105,110]. When approval is likely because of important benefits and nonsevere risks or because of superiority compared with alternatives, patient preferences might become less valuable [3].

### **Familiarity of assessors**

Eliciting patient preferences might be especially valuable in patient populations with which regulators are not familiar [50]. When sponsors and regulators know the disease area and technologies well, patient preferences become less valuable [3]. In addition, the value of elicited quantitative patient preferences for decision making can be limited by unfamiliarity with preference methods among assessors interpreting the results [82,98].

### **Attitudes of assessors**

There is no consensus on the role of patient preferences in decision making along the MPLC. A consensus on this role might be difficult to achieve because of distrust in the use of patient preferences resulting from the false impression that preferences can only be used as averages, fear that patient preferences will replace existing clinical evidence, barriers to ‘cultural change’, the lack of consensus on the definition of patient preferences, and disappointment risk (i.e., the possibility that patient preference studies might yield unexpected results; e.g., some patients might not want to accept the risks of a new product) [1,3,4,12,30,31,36,47,50,63,64,66,70,81–83,98,124,125].

### **New competitors**

If new treatment options become available, or if new benefits and risks are identified, the results of previously performed patient preference studies might no longer be valid and might need to be reconducted [82].

### **Concluding remarks**

Although limited evidence was found on the actual use of patient preferences in decision making, they are gaining attention in processes along the MPLC. We believe that additional guidance on the use of patient preferences in assessments and decision making is necessary to increase their use. Moreover, use of patient preferences could increase if regulatory authorities, HTA bodies, and payers would inform the industry about whether and how they would use patient preferences in their processes, or would state in what situations they find patient preferences valuable or even require the submission of results from patient preference studies.

Many factors and situations have to be taken into account when designing and conducting a patient preference study to obtain

valuable results that can be used in assessments and decision making. The main trends among the factors that we described here that will contribute to the value of a patient preference study are: (i) having a multidisciplinary team; (ii) ensuring patient centeredness in the design as well as the conduct and communication of results; (iii) matching the sample and the method to the research question; (iv) safeguarding validity in the method selection and instrument design; (v) reducing cognitive burden; (vi) providing adequate patient education; (vii) guaranteeing that preference heterogeneity can be measured and interpreted; and (viii) tailoring communication of results to the audience. Further research should focus on validating these results through the exploration of stakeholder perspectives and by conducting patient preference studies.

### **Competing interests**

The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115966. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA. This text and its contents reflects the PREFER project’s view and not the view of IMI, the European Union or EFPIA. J.J. declares the following competing interests: employee of Sanofi, a global biopharmaceutical company focused on human health; and ownership of shares in Sanofi. B.L. declares the following competing interests: employee of Janssen Research and Development, LLC; and stockholder in Johnson & Johnson and in a portfolio that at times includes other pharmaceutical and health care-related companies. J.K. declares the following competing interests: representing CSL Behring on IMI PREFER; scientific consultant working for the pharmaceutical industry; and stockholder in a portfolio that includes pharmaceutical and health care-related companies.

### **Acknowledgments**

The authors would like to thank all members of the PREFER project for their input and support during the conduct of this literature review. A special thanks to Judith Gulpers from Erasmus University Rotterdam who helped refining and running the search queries. Furthermore, the authors are indebted to the anonymous reviewers for their insights and suggestions.

### **Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.drudis.2018.09.015>.

### **References**

- EMA (2013) *The Patient’s Voice in the Evaluation of Medicines*. EMA
- Abelson, J. *et al.* (2016) Public and patient involvement in health technology assessment: a framework for action. *Int. J. Technol. Assess. Health Care* 32, 256–264
- MDIC (2015) *Patient Centered Benefit–Risk Project Report: A Framework for Incorporating Information on Patient Preferences regarding Benefit and Risk into Regulatory Assessments of New Medical Technologies*. MDIC
- Anon (2016) *Patient Preference Information – Voluntary Submission, Review in Pre-market Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*. US Department of Health and Human Services, FDA, Center for Devices and Radiological Health and Center for Biologics Evaluation and Research
- Meredith, Y.S. *et al.* (2016) Patient engagement at a tipping point—the need for cultural change across patient, sponsor, and regulator stakeholders: insights from the DIA conference, ‘Patient Engagement in Benefit Risk Assessment Throughout the Life Cycle of Medical Products’. *Ther. Innov. Regul. Sci.* 50, 546–553
- Soekhai, V. *et al.* (2017) Compendium of methods for measuring patient preferences in medical treatment. *Value Health* 20, A684–A685

- 7 MDCI (2015) *Medical Device Innovation Consortium (MDIC) Patient Centered Benefit–Risk Project (PCBR): Appendix A: Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies*. MDIC
- 8 EPF (2013) *Patient Involvement in Health Technology Assessment in Europe: Results of the EPF Survey*. EPF
- 9 de Bekker-Grob, E.W. *et al.* (2017) Giving Patients' preferences a voice in medical treatment life cycle: the PREFER Public–Private Project. *Patient* 10, 263–266
- 10 Facey, K. *et al.* (2010) Patients' perspectives in health technology assessment: a route to robust evidence and fair deliberation. *Int. J. Technol. Assess. Health Care* 26, 334–340
- 11 Breckenridge, A. (2011) Patient opinions and preferences in drug development and regulatory decision making. *Drug Discov. Today Technol.* 8, e11–e14
- 12 van Til, J.A. and Ijzerman, M.J. (2014) Why should regulators consider using patient preferences in benefit-risk assessment? *Pharmacoeconomics* 32, 1–4
- 13 Menon, D. *et al.* (2014) Involving patients in reducing decision uncertainties around orphan and ultra-orphan drugs: a rare opportunity? *Patient* 8, 29–39
- 14 Hockley, K. *et al.* (2014) *Study Protocol: Eliciting Patient Preferences on the Benefits and Risks of Treatments for Relapsing Remitting Multiple Sclerosis*. IMI
- 15 Mol, P.G. *et al.* (2015) Understanding drug preferences, different perspectives. *Br. J. Clin. Pharmacol.* 79, 978–987
- 16 Postmus, D. *et al.* (2016) Incorporating patient preferences into drug development and regulatory decision making: Results from a quantitative pilot study with cancer patients, carers, and regulators. *Clin. Pharmacol. Ther.* 99, 548–554
- 17 Mt-Isa, S. *et al.* (2014) Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. *Pharmacoeconom. Drug Saf.* 23, 667–678
- 18 Egbrink, M.O. and IJzerman, M. (2014) The value of quantitative patient preferences in regulatory benefit–risk assessment. *J. Mark. Access. Health Policy* 2, 1 <http://dx.doi.org/10.3402/jmahp.v2.22761>
- 19 Menon, D. and Stafinski, T. (2011) Role of patient and public participation in health technology assessment and coverage decisions. *Expert Rev. Pharmacoecon. Outcomes Res.* 11, 75–89
- 20 Kievit, W. *et al.* (2017) Taking patient heterogeneity and preferences into account in health technology assessments. *Int. J. Technol. Assess. Health Care* 33, 562–569
- 21 Gaudiano, B.A. *et al.* (2013) Patients' treatment expectancies in clinical trials of antidepressants versus psychotherapy for depression: a study using hypothetical vignettes. *Compr. Psychiatry* 54, 28–33
- 22 Bloom, D. *et al.* (2018) The rules of engagement: CTTI recommendations for successful collaborations between sponsors and patient groups around clinical trials. *Ther. Innov. Regul. Sci.* 52, 206–213
- 23 Lim, S.S. *et al.* (2017) Simulating clinical trial visits yields patient insights into study design and recruitment. *Patient Prefer. Adherence* 11, 1295–1307
- 24 Franco, M.R. *et al.* (2013) Methodological limitations prevent definitive conclusions on the effects of patients' preferences in randomized clinical trials evaluating musculoskeletal conditions. *J. Clin. Epidemiol.* 66, 586–598
- 25 Marcus, S.M. *et al.* (2012) Estimating the causal effect of randomization versus treatment preference in a doubly randomized preference trial. *Psychol. Methods* 17, 244–254
- 26 Utens, C.M.A. *et al.* (2014) The use of research evidence on patient preferences in pharmaceutical coverage decisions and clinical practice guideline development: exploratory study into current state of play and potential barriers. *BMC Health Serv. Res.* 14, 540
- 27 Levitan, B. *et al.* (2017) The ball is in your court: agenda for research to advance the science of patient preferences in the regulatory review of medical devices in the United States. *Patient* 10, 531–536
- 28 Wolka, A.M. *et al.* (2017) Effective partnering in conducting benefit-risk patient preference studies: perspectives from a patient advocacy organization, a pharmaceutical company, and academic stated-preference researchers. *Ther. Innov. Regul. Sci.* 52 (4), 507–513
- 29 Marsh, K. (2016) *Incorporating Patient Preferences into Product Development and Value Communication: Why, When and How?* The Evidence Forum
- 30 Selig, W.K.D. (2016) *Key Considerations for Developing & Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study*. Biotechnology Innovation Organization
- 31 Lowe, M.M. *et al.* (2016) Increasing patient involvement in drug development. *Value Health* 19, 869–878
- 32 Cross, J. *et al.* (2016) Caregiver preferences for the treatment of males with fragile X syndrome. *J. Dev. Behav. Pediatr.* 37, 71–79
- 33 Morel, T. *et al.* (2016) Quantifying benefit–risk preferences for new medicines in rare disease patients and caregivers. *Orphanet. J. Rare Dis.* 11, 70
- 34 Stewart, K.D. *et al.* (2016) Preference for pharmaceutical formulation and treatment process attributes. *Patient Prefer. Adherence* 10, 1385–1399
- 35 Ervin, C.M. *et al.* (2014) Assessment of treatment response in chronic constipation clinical trials. *Clin. Exp. Gastroenterol.* 7, 191–198
- 36 Minion, L.E. *et al.* (2016) Endpoints in clinical trials: what do patients consider important? A survey of the Ovarian Cancer National Alliance. *Gynecol. Oncol.* 140, 193–198
- 37 Stamuli, E. *et al.* (2017) Identifying the primary outcome for a randomised controlled trial in rheumatoid arthritis: the role of a discrete choice experiment. *J. Foot Ankle Res.* 10, 57
- 38 Walter, S.D. *et al.* (2017) Estimation of treatment preference effects in clinical trials when some participants are indifferent to treatment choice. *BMC Med. Res. Methodol.* 17, 29
- 39 Gryczynski, J. *et al.* (2013) Patient perspectives on choosing buprenorphine over methadone in an urban, equal-access system. *Am. J. Addict.* 22, 285–291
- 40 Olschewski, M. *et al.* (1992) Analysis of randomized and nonrandomized patients in clinical trials using the comprehensive cohort follow-up study design. *Control Clin. Trials* 1, 226–239
- 41 King, M. *et al.* (2005) Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials. *Health Technol. Assess.* 9, 1–186
- 42 Preference Collaborative Review Group (2008) Patients' preferences within randomised trials: systematic review and patient level meta-analysis. *BMJ* 337, a1864
- 43 Johnson, R.E. *et al.* (2007) Active exercise, education, and cognitive behavioral therapy for persistent disabling low back pain: a randomized controlled trial. *Spine* 32, 1578–1585
- 44 George, S.Z. and Robinson, M.E. (2010) Preference, expectation, and satisfaction in a clinical trial of behavioral interventions for acute and sub-acute low back pain. *J. Pain* 11, 1074–1082
- 45 Chaudhuri, S.E. *et al.* (2018) Patient-centered clinical trials. *Drug Discov. Today* 23, 395–401
- 46 Montazerhodjat, V. *et al.* (2017) Use of Bayesian decision analysis to minimize harm in patient-centered randomized clinical trials in oncology. *JAMA Oncol.* 3 (9), e170123 <http://dx.doi.org/10.1001/jamaoncol.2017.0123>
- 47 Anon (2016) *Patient Perspective Value Framework (PPVF): Draft Methodology*. Avalere and Milken Institute
- 48 Janssen, E.M. *et al.* (2017) Education and patient preferences for treating type 2 diabetes: a stratified discrete-choice experiment. *Patient Prefer. Adherence* 11, 1729–1736
- 49 Hollin, I.L. *et al.* (2017) Patient-centered benefit-risk assessment in Duchenne Muscular Dystrophy. *Muscle Nerve* 5, 626–634
- 50 Ho, M. *et al.* (2016) A framework for incorporating patient preferences regarding benefits and risks into regulatory assessment of medical technologies. *Value Health* 19, 746–750
- 51 Marsh, K. *et al.* (2017) Amplifying each patient's voice: a systematic review of multi-criteria decision analyses involving patients. *Appl. Health Econ. Health Policy* 15, 155–162
- 52 Marsh, K. *et al.* (2018) Patient-centered decision making: lessons from multi-criteria decision analysis for quantifying patient preferences. *Int. J. Technol. Assess. Health Care* 34, 105–110
- 53 Hauber, A.B. *et al.* (2013) Quantifying benefit-risk preferences for medical interventions: an overview of a growing empirical literature. *Appl. Health Econ. Health Policy* 11, 319–329
- 54 Marrone, A.K. *et al.* (2017) The regulatory perspectives on endoscopic devices for obesity. *Gastrointest. Endosc. Clin. N. Am.* 27 (2), 327–341 <http://dx.doi.org/10.1016/j.giec.2016.12.004>
- 55 Mott, D.J. (2018) Incorporating quantitative patient preference data into healthcare decision making processes: is HTA falling behind? *Patient* XX, YYY–ZZZ
- 56 Puhan, M.A. *et al.* (2012) A framework for organizing and selecting quantitative approaches for benefit–harm assessment. *BMC Med. Res. Methodol.* 12, 173
- 57 Irony, T. *et al.* (2016) Incorporating patient preferences into medical device benefit-risk assessments. *Stat. Biopharm. Res.* 8, 230–236
- 58 Puhan, M.A. *et al.* (2015) Quantitative benefit–harm assessment for setting research priorities: the example of roflumilast for patients with COPD. *BMC Med.* 13, 157
- 59 Weernink, M.G.M. *et al.* (2014) A systematic review to identify the use of preference elicitation methods in healthcare decision making. *Pharm. Med.* 28, 175–185
- 60 Mott, D.J. and Najafzadeh, M. (2016) Whose preferences should be elicited for use in health-care decision-making? A case study using anticoagulant therapy. *Expert Rev. Pharmacoecon. Outcomes Res.* 16, 33–39
- 61 IQWiG (2013) *Analytic Hierarchy Process (AHP) – Pilot Project to Elicit Patient Preferences in the Indication 'Depression'*. IQWiG
- 62 IQWiG (2014) *Choice-Based Conjoint Analysis – Pilot Project to Identify, Weight, and Prioritize Multiple Attributes in the Indication 'Hepatitis C'*. IQWiG

- 63 Dirksen, C.D. (2014) The use of research evidence on patient preferences in health care decision-making: issues, controversies and moving forward. *Expert Rev. Pharmacoecon. Outcomes Res.* 14, 785–794
- 64 Moes, F. *et al.* (2017) Contested evidence: a Dutch reimbursement decision taken to court. *Health Econ. Policy Law* 12, 325–344
- 65 Pisa, G. (2015) *A Step Towards Patient-Centricity: Analysis of HTA Requirements for Patient Preference Data Collection in Germany*. Kantar Health
- 66 Mühlbacher, A.C. *et al.* (2016) Patient-focused benefit-risk analysis to inform regulatory decisions: the European Union perspective. *Value Health* 19, 734–740
- 67 Hailey, D. *et al.* (2013) Involvement of consumers in health technology assessment activities by Inahta agencies. *Int. J. Technol. Assess. Health Care* 29, 79–83
- 68 Bilvick Tai, B.W. *et al.* (2016) A systematic review of health economic evaluation studies using the patient's perspective. *Value Health* 19, 903–908
- 69 Rodriguez, J.M. *et al.* (2011) The use of quality-adjusted life-years in the economic evaluation of health technologies in Spain: a review of the 1990–2009 literature. *Value Health* 14, 458–464
- 70 Thebaut, C. (2013) Dealing with moral dilemma raised by adaptive preferences in health technology assessment: the example of growth hormones and bilateral cochlear implants. *Soc. Sci. Med.* 99, 102109
- 71 Terris-Prestholt, F. *et al.* (2016) Parameterising user uptake in economic evaluations: the role of discrete choice experiments. *Health Econ.* 25 (Suppl. 1), 116–123
- 72 Martin-Fernandez, J. *et al.* (2014) Willingness to pay for a quality-adjusted life year: an evaluation of attitudes towards risk and preferences. *BMC Health Serv. Res.* 14, 287
- 73 Tinelli, M. *et al.* (2016) What, who and when? Incorporating a discrete choice experiment into an economic evaluation. *Health Econ. Rev.* 6, 31
- 74 Goto, D. *et al.* (2017) Regression-based approaches to patient-centered cost-effectiveness analysis. *Pharmacoeconomics* 35, 685–695
- 75 Mühlbacher, A.C. and Sadler, A. (2017) The probabilistic efficiency frontier: a framework for cost-effectiveness analysis in Germany put into practice for Hepatitis C treatment options. *Value Health* 20, 266–272
- 76 Bewtra, M. and Johnson, F.R. (2013) Assessing patient preferences for treatment options and process of care in inflammatory bowel disease: a critical review of quantitative data. *Patient* 6, 241–255
- 77 Finnell, S.M.E. *et al.* (2012) Application of classic utilities to published pediatric cost-utility studies. *Acad. Pediatr.* 12, 219–228
- 78 Mühlbacher, A.C. *et al.* (2017) Preferences for antiviral therapy of chronic hepatitis C: a discrete choice experiment. *Eur. J. Health Econ.* 18, 155–165
- 79 Kay, S. and Ferreira, A. (2014) Mapping the 25-item national eye institute visual functioning questionnaire (NEI VFQ-25) to EQ-5D utility scores. *Ophthalmol. Epidemiol.* 21, 66–78
- 80 Beresniak, A. *et al.* (2015) Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOOUTCOME European project. *Pharmacoeconomics* 33, 61–69
- 81 Gutknecht, M. *et al.* (2016) A systematic review on methods used to evaluate patient preferences in psoriasis treatments. *J. Eur. Acad. Dermatol. Venereol.* 30, 1454–1464
- 82 Hughes, D. *et al.* (2013) *Recommendations for the Methodology and Visualisation Techniques to be Used in the Assessment of Benefit and Risk of Medicines*. IMI
- 83 Hockley, K. *et al.* (2013) *Patient and Public Involvement Report: Recommendations for Patient and Public Involvement in the Assessment of Benefit and Risk of Medicines*. IMI
- 84 ICH (2016) *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6 (R2)*. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH
- 85 Public Policy Committee, and International Society of Pharmacoeconomics, (2016) *Guidelines for good pharmacoepidemiology practice (GPP)*. *Pharmacoeconom. Drug Saf.* 25, 2–10
- 86 Torgerson, D.J. *et al.* (1996) Patient preferences in randomised trials: threat or opportunity? *J. Health Serv. Res. Policy* 1, 194–197
- 87 Tervonen, T. *et al.* (2017) MCDA swing weighting and discrete choice experiments for elicitation of patient benefit-risk preferences: a critical assessment. *Pharmacoeconom. Drug Saf.* 26, 1483–1491
- 88 Janssen, I.M. *et al.* (2016) Importance of hemodialysis-related outcomes: comparison of ratings by a self-help group, clinicians, and health technology assessment authors with those by a large reference group of patients. *Patient Prefer. Adherence* 10, 2491–2500
- 89 Tinelli, M. *et al.* (2012) What determines patient preferences for treating low risk basal cell carcinoma when comparing surgery vs imiquimod? A discrete choice experiment survey from the SINS trial. *BMC Dermatol.* 12, 19 <http://dx.doi.org/10.1186/1471-5945-12-19>
- 90 Gries, K.S. *et al.* (2016) Preferences for prostate cancer outcomes: a comparison of the patient perspective, the general population perspective, and a population at risk for prostate cancer. *Value Health* 19, 218–225
- 91 Katz, E.G. *et al.* (2016) Physician and patient benefit-risk preferences from two randomized long-acting injectable antipsychotic trials. *Patient Prefer. Adherence* 10, 2127–2139
- 92 Svedsater, H. *et al.* (2013) Qualitative assessment of attributes and ease of use of the ELLIPTA™ dry powder inhaler for delivery of maintenance therapy for asthma and COPD. *BMC Pulmon. Med.* 13, 72 <http://dx.doi.org/10.1186/1471-2466-13-72>
- 93 Peay, H.L. *et al.* (2014) A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. *Clin. Ther.* 36, 624–637
- 94 Roy, A.N. *et al.* (2015) A discrete choice experiment to elicit patient willingness to pay for attributes of treatment-induced symptom relief in comorbid insomnia. *Manag. Care* 24, 42–48
- 95 Silverman, S. *et al.* (2013) Patient weighting of osteoporosis medication attributes across racial and ethnic groups: a study of osteoporosis medication preferences using conjoint analysis. *Osteoporosis Int.* 24, 2067–2077
- 96 Ho, M.P. *et al.* (2015) Incorporating patient-preference evidence into regulatory decision making. *Surg. Endosc.* 29, 2984–2993
- 97 Nafees, B. *et al.* (2016) Managing neurogenic bowel dysfunction: what do patients prefer? A discrete choice experiment of patient preferences for transanal irrigation and standard bowel management. *Patient Prefer. Adherence* 10, 195–204
- 98 Smith, M.Y. *et al.* (2016) Patient engagement at a tipping point—the need for cultural change across patient, sponsor, and regulator stakeholders: insights from the DIA conference, 'Patient Engagement in Benefit Risk Assessment Throughout the Life Cycle of Medical Products'. *Ther. Innov. Regul. Sci.* 50, 546–553
- 99 Faggioli, G. *et al.* (2011) Preferences of patients, their family caregivers and vascular surgeons in the choice of abdominal aortic aneurysms treatment options: the PREFER study. *Eur. J. Vasc. Endovasc. Surg.* 42, 26–34
- 100 Gonzalez, J.M. *et al.* (2017) Patient and physician preferences for anticancer drugs for the treatment of metastatic colorectal cancer: a discrete-choice experiment. *Cancer Manag. Res.* 9, 149–158
- 101 Gold, D.T. *et al.* (2011) Development, reliability, and validity of a new preference and satisfaction questionnaire. *Value Health* 14, 1109–1116
- 102 Stewart, M.J. *et al.* (2008) Patient and clinician treatment preferences do not moderate the effect of exercise treatment in chronic whiplash-associated disorders. *Eur. J. Pain* 12, 879–885
- 103 Johnson, F.R. and Zhou, M. (2016) Patient preferences in regulatory benefit-risk assessments: a US perspective. *Value Health* 19, 741–745
- 104 Sánchez Martínez, F.I., Pinto Prades, J.L., Abellán Perpiñán, J.M., Martínez Pérez, J. E. *The role of non-transparent matching methods in avoiding preference reversals in the evaluation of health outcomes*, Published online. [cited 15 May 2017]. Available from: <http://www.revecap.com/encuentros/trabajos/s/pdf/193.pdf>.
- 105 MacLean, S. *et al.* (2012) Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141 (2 Suppl), e15–e235
- 106 Gagnon, M.P. *et al.* (2011) Introducing patients' and the public's perspectives to health technology assessment: a systematic review of international experiences. *Int. J. Technol. Assess. Health Care* 27, 31–42
- 107 Kleme, J. *et al.* (2014) Patient perspective in health technology assessment of pharmaceuticals in Finland. *Int. J. Technol. Assess. Health Care* 30, 306–311
- 108 Ijzerman, M.J. *et al.* (2012) A comparison of analytic hierarchy process and conjoint analysis methods in assessing treatment alternatives for stroke rehabilitation. *Patient* 5, 45–56
- 109 Janssen, E.M. *et al.* (2017) Improving the quality of discrete-choice experiments in health: how can we assess validity and reliability? *Expert Rev. Pharmacoecon. Outcomes Res.* 17, 531–542
- 110 Swinburn, P. *et al.* (2011) Preferences for antimuscarinic therapy for overactive bladder. *BJU Int.* 108, 868–873
- 111 Eliasson, L. *et al.* (2017) Evaluation of psoriasis patients' attitudes toward benefit-risk and therapeutic trade-offs in their choice of treatments. *Patient Prefer. Adherence* 11, 353–362
- 112 Postmus, D. *et al.* (2018) Individual trade-offs between possible benefits and risks of cancer treatments: results from a stated preference study with patients with multiple myeloma. *Oncologist* 23, 44–51
- 113 Fraenkel, L. *et al.* (2017) Subjective numerosity and the influence of order and amount of audible information on perceived medication value. *Med. Decis. Mak.* 37, 230–238
- 114 von Arx, L.B. *et al.* (2017) Be careful what you ask for: effects of benefit descriptions on diabetes patients' benefit-risk tradeoff preferences. *Value Health* 20, 670–678
- 115 Louviere, J.J. (2006) What you don't know might hurt you: some unresolved issues in the design and analysis of discrete choice experiments. *Environ. Res. Econ.* 34, 173–188
- 116 Fischhoff, B. *et al.* (2011) *Communicating Risks and Benefits: An Evidence-Based User's Guide*. FDA
- 117 EUPATI (2018) *What is EUPATI?* EUPATI

- 118 Anon (2005) *Criteria for Judging the Quality of Patient Decision Aids*. International Patient Decision Aid Standards
- 119 Bowling, A. and Ebrahim, S. (2001) Measuring patients' preferences for treatment and perceptions of risk. *Qual. Health Care* 10 (Suppl. 1), i2–i8
- 120 Howard, K. and Salkeld, G. (2009) Does attribute framing in discrete choice experiments influence willingness to pay? Results from a discrete choice experiment in screening for colorectal cancer. *Value Health* 12, 354–363
- 121 Mühlbacher, A. and Bethge, S. (2016) What matters in type 2 diabetes mellitus oral treatment? A discrete choice experiment to evaluate patient preferences. *Eur. J. Health Econ.* 17, 1125–2240
- 122 EMA (2014) *Regulatory and Methodological Standards to Improve Benefit–Risk Evaluation of Medicines*. EMA
- 123 Hernandez Alava, M. *et al.* (2012) Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. *Value Health* 15, 550–561
- 124 Brennan, D.F. (1995) Patient preferences. *Ann. Emerg. Med.* 26, 240–241
- 125 Brooker, A.S. *et al.* (2013) Quantitative patient preference evidence for health technology assessment: a case study. *Int. J. Technol. Assess. Health Care* 29, 290–300
- 126 Ryan, M. *et al.* (2017) *Using Discrete Choice Experiments in Health Economics: Theoretical and Practical Issues*. University of Aberdeen
- 127 ICH (2016) *ICH Harmonised Guideline: Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH*. ICH
- 128 Brazier, J.E. *et al.* (2012) Developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome). *Health Technol. Assess.* 16, 1–114
- 129 Danner, M. *et al.* (2011) Integrating patients' views into health technology assessment: analytic hierarchy process (AHP) as a method to elicit patient preferences. *Int. J. Technol. Assess. Health Care* 27, 369–375