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Health Preference Research in Europe: A Review of Its Use in Marketing Authorization, Reimbursement, and Pricing Decisions—Report of the ISPOR Stated Preference Research Special Interest Group

Kevin Marsh, PhD,* Janine A. van Til, PhD, Elizabeth Molsen-David, RN, Christine Juhnke, MA, Natalia Hawken, PhD, Elisabeth M. Oehrlein, PhD, MS, Y. Christy Choi, PharmD, Alejandra Duenas, PhD, Wolfgang Greiner, PhD, Kara Haas, MD, MPH, FACS, RAC, Mickael Hiligsmann, PhD, Kimberley S. Hockley, PhD, Ilya Ivlev, MD, PhD, Frank Liu, PhD, Jan Ostermann, PhD, Thomas Poder, PhD, Jiat L. Poon, PhD, Axel Muehlbacher, PhD

A B S T R A C T

Objective: This study examines European decision makers' consideration and use of quantitative preference data.

Methods: The study reviewed quantitative preference data usage in 31 European countries to support marketing authorization, reimbursement, or pricing decisions. Use was defined as: agency guidance on preference data use, sponsor submission of preference data, or decision-maker collection of preference data. The data could be collected from any stakeholder using any method that generated quantitative estimates of preferences. Data were collected through: (1) documentary evidence identified through a literature and regulatory websites review, and via key opinion leader outreach; and (2) a survey of staff working for agencies that support or make healthcare technology decisions.

Results: Preference data utilization was identified in 22 countries and at a European level. The most prevalent use (19 countries) was citizen preferences, collected using time-trade off or standard gamble methods to inform health state utility estimation. Preference data was also used to: (1) value other impact on patients, (2) incorporate non-health factors into reimbursement decisions, and (3) estimate opportunity cost. Pilot projects were identified (6 countries and at a European level), with a focus on multi-criteria decision analysis methods and choice-based methods to elicit patient preferences.

Conclusion: While quantitative preference data support reimbursement and pricing decisions in most European countries, there was no utilization evidence in European-level marketing authorization decisions. While there are commonalities, a diversity of usage was identified between jurisdictions. Pilots suggest the potential for greater use of preference data, and for alignment between decision makers.

Keywords: benefit-risk assessment, European regulatory, health preferences, health technology assessment, marketing authorization, preference research, pricing, quantitative preference data, reimbursement, stakeholder preferences.

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Introduction

Evidence-based medicine has revolutionized the provision of healthcare through its emphasis on the collection and use of clinical data.[1] Although this achievement should not be underestimated, it has, to date, largely addressed only part of the challenge facing healthcare decision makers.[2] The practice of evidence-based medicine means integrating this clinical evidence with the preferences of stakeholders, such as patients.[3–5] As such, evidence-based medicine allows for strengthened patient centricity, with a focus on patient-centered outcomes and preferences.[6]

In addition to reviewing clinical evidence, healthcare decision makers have to assess which trade-offs are acceptable. For instance, marketing authorization decisions involve an appraisal of whether the benefits of a technology are sufficient to outweigh its risks. Reimbursement and pricing decisions require an appraisal of whether the benefits associated with a therapy are worth its cost or which patient groups' outcomes should be prioritized for funding.[7]

European healthcare decision makers have demonstrated interest in using health-preference data to inform these assessments.[8] This interest is reflected in 2 European Union (EU)–funded projects. The first is the Innovative Medicine's Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT). Its goal is to strengthen the understanding of the benefit-risk profile of medicines in Europe, including incorporating preference data into benefit-risk assessment.[9] The second

* Address correspondence to: Kevin Marsh, PhD, The Ark, 201 Talgarth Rd, Hammersmith, London W6 8BJ, England, United Kingdom. Email: kevin.marsh@evidera.com

is Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER). Its objective is to generate recommendations on when and how to collect and how to use patient preferences to support decision making by industry, regulatory authorities, and health technology assessment (HTA) bodies.[10]

More specifically, there has been growing interest in supporting these assessments with quantitative preference data. It has been hypothesized that the use of such data can improve the reliability, consistency, and transparency of health-related decisions.[11–17] If quantitative preference data are defined as numerical estimates of stakeholders' trade-offs between conflicting objectives,[18–22] several methods could be used to generate this data (see the "Methods" section).

Reviews have identified an increasing amount of health-preference research.[17,23–25] The reviews focused on the publication patterns of preference research. They did not indicate the actual use of these studies to support decisions. There is no overarching summary on European decision makers' use of preference data—either the guidance they offer or whether the data have been used in decisions. These are important gaps to address, especially for those developing evidence-generation strategies or drafting guidance on the use of preference data to support decision making. To fill this gap, the ISPOR Stated Preference Research Special Interest Group examined European decision makers' consideration, use, and recommendations on the use of quantitative preference data to support decisions on marketing authorization, reimbursement, and pricing.

Methods

A multimethod approach was used to collect, analyze, and integrate multiple sources to provide a comprehensive picture of preference data usage in Europe. The scope of the review was defined as follows:

- Countries: 28 EU member states, Norway, the Russian Federation, and Switzerland
- Decisions: Marketing authorization, reimbursement, and pricing decisions at a European, national, or local level

- Stakeholders: Preference data from any stakeholder, including citizens, patients, caregivers, healthcare professionals, payers, regulators, manufacturers/sponsors, and other experts
- Uses of preference data: Any of (1) decision-maker guidance on the collection and use of preference data, (2) sponsor inclusion of preference data in their submission, (3) the decision-making agency collecting preference data to inform its decisions, or (4) the agency piloting an approach (any exercise that demonstrated or promoted preference data but in which the data were not used by decision makers was excluded)
- Preference elicitation methods (see Table 1): All quantitative estimates of preference[17,26–28] including (1) matching methods, such as time trade-off (TTO), standard gamble (SG), or contingent valuation; (2) choice-based methods, such as discrete choice experiment (DCE) or best-worst scaling; and (3) rating methods, such as the simple multiattribute rating technique (SMART) or SMART with swings; (4) ranking methods, such as SMART exploiting rankings; and (5) pairwise comparison methods, such as the analytical hierarchy process (AHP).

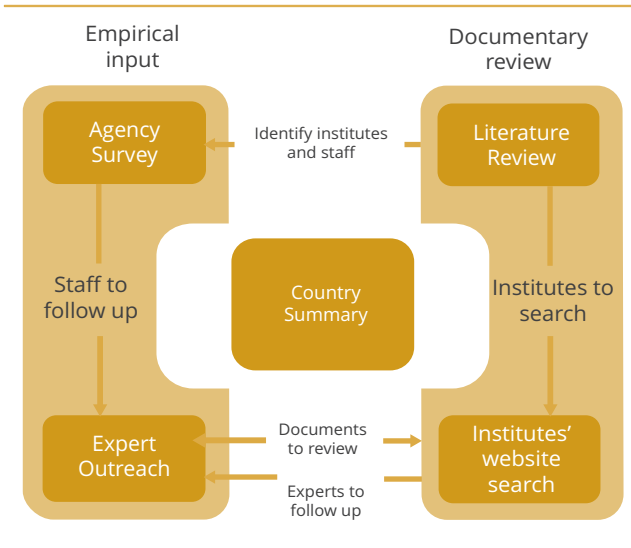Figure 1 describes the sources of data and how they were used in this study to develop each country's summary.

1. Documentary review
   a. Literature review: Medline, Embase, and EconLit were searched on June 26, 2017, for English-language sources using the search terms reported in Appendix 1 in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.11.009), without date restrictions. To ensure consistent reviewing, 40 titles and abstracts were reviewed by 4 authors (K.M., C.C., E.M.O., and N.H.), and differences were discussed and resolved. Each title and abstract was reviewed by 2 authors.
   b. Review of institution websites: The websites of institutions responsible for relevant decisions in each country were searched, staggered over the period from December 2017 to June 2018. Details on the websites reviewed and the search approach used are available in Appendix 2 in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.11.009). The review focused on English-language sources,

Table 1. Preference method typology.

Method	Form of elicitation question	Example approaches (data elicited)	Healthcare illustration
Ranking	Respondents rank attributes that distinguish alternatives	SMART exploiting rankings (ranking of attributes in order of importance)	Evaluation of oral anticoagulants for stroke prevention[29]
Rating	Respondents score attributes that distinguish alternatives	SMART with swings (score ranges of performance on each attribute a scale of 0-100)	EMA Benefit Risk Methodology Project, field testing of method to inform benefit-risk assessment[30]
Pairwise comparison	Respondents score the importance of attributes in a pairwise manner	AHP	IQWiG piloted AHP to prioritize patient-relevant outcomes from an antidepressant drug treatment[31]
Choice based	Respondents make choice(s) between 2 or more discrete alternatives	DCE (best from 2 or more alternatives) Best-worst scaling (best and worst from 3 or more alternatives)	IQWiG piloted DCE to prioritize patient-relevant outcomes from an antiviral therapy for chronic hepatitis[32]
Matching	Respondents provide a number(s) that will make them indifferent to the outcome being valued	TTO (time spent in a health state) Contingent valuation (willingness to pay for an outcome)	NICE recommends that TTO is used to estimate utility values for health states[33]

AHP indicates, analytical hierarchy process; DCE, discrete choice experiment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE, National Institute for Health and Care Excellence; SMART, simple multiattribute rating technique; TTO, time trade-off.

Figure 1. Overview of methods.

from (1) contact details identified by the European Commission's mapping of HTA organizations,[29] (2) the authors of publications identified in the review, (3) a search of agency websites, (4) ISPOR's membership database, and (5) author contacts. The survey was also sent to the general email address for relevant institutions. An example of the survey questions is available in Appendix 4 in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.11.009). Descriptive analysis (frequencies) was used to analyze the survey responses, identifying use of preference data, the method used to elicit the preference data, and the stakeholder group from which the preferences were elicited.

b. KOL outreach: Two forms of expert outreach were undertaken. First, agency staff who responded to the survey (step 2a) and provided their name and email address were contacted for more information on the use of preference data. Second, local experts were identified via the literature and the website review, the ISPOR regional chapter leadership, the ISPOR database, and author contacts. (See Appendix 2 in Supplementary Materials found at https://doi.org/10.1016/j.jval.2019.11.009 for lists of the experts consulted.) They were contacted to identify how decision-maker preference data are used in their country.
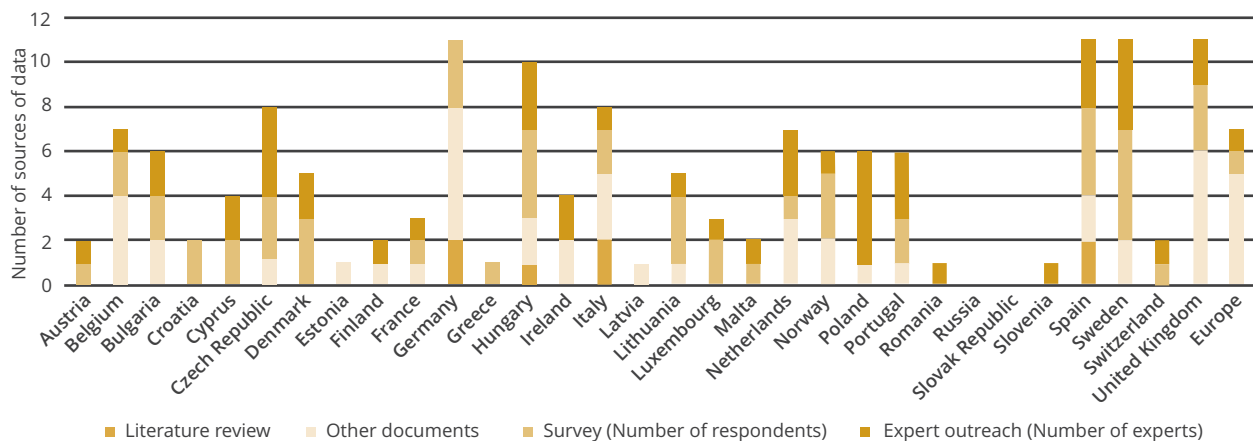
A descriptive analysis was used to identify decision-method-stakeholder combinations (a particular method used to elicit a particular stakeholder groups' preferences to support a particular decision). Where such uses were identified, they were organized into the following hierarchy: (1) there is guidance that recommends or requires this use of preference data; (2) there is no guidance, but there are documented examples of that use of preference data; and 3) there is neither guidance nor documented examples, but experts identified the use of preference data.

Results

Overview of Data Sources

Figure 2 summarizes the sources from which the country summaries were constructed:

- Documentary review: The scientific literature review identified only 7 studies in 4 countries on preference data usage by decision makers.[21,30–33,34,35] Most of the evidence (47 sources) was discovered through website searches or through interviews with agency staff or experts.

except where the review was undertaken by an author fluent in the local language (this was the case for Belgium, France, Germany, Luxembourg, The Netherlands, and Switzerland).

c. Key opinion leader (KOL) outreach: The authors of relevant publications were contacted as KOLs in step 2b below.

For each country, 1 author extracted the data from publications identified in the literature review and website search. (See the extraction template in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.11.009) The extraction was then reviewed by another author, and any disagreement was resolved.

For each country, a summary of the use of preference data was generated by 1 author based on the data extraction and then reviewed by another author. The working group co-chairs updated these summaries as further documentary evidence was identified via KOL outreach.

2. Expert insight: Data on the nondocumented use of preference data was identified from local experts through the following:

a. Decision-maker agency staff survey: A survey was distributed among policy makers in the target countries between July and November 2018. The sample frame was constructed

Figure 2. Overview of data sources.

- Empirical insight: Sixty-six survey responses and 48 responses from KOLs were received. Of the survey responses, 14 were deleted owing to duplicate IP address and organization, leaving 52 valid responses from 22 countries. If entries were deleted as a result of duplicate IP address and affiliations, the most complete data set was kept (usually the second). Responses that were deleted because of an incomplete data set contained only the organization details. No information on the use of preference data was excluded. Entries that provided any information on the use of preference information were kept, even if they were not complete. Many respondents reported that their agencies were responsible for supporting more than 1 type of decision, with 63.5% (n = 33) supporting marketing authorization decisions, 61.5% (n = 32) supporting reimbursement decisions, and 63.5% (n = 33) supporting pricing decisions.

Respondents reported that their agencies supported these decisions in multiple ways: 75.0% (n = 39) by assessing health technologies (synthesizing evidence), 53.8% (n = 28) by appraising health technologies (consideration of the evidence to make decisions), 44.2% (n = 23) by compiling an HTA report, 5.8% (n = 3) by conducting primary research, and 7.7% (n = 4) by conducting secondary research.

Forty-two percent (n = 22) of agencies had the final say on one of the decisions of interest (more details on the agencies and respondents is available in Appendix 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.11.009).

Use of Preference Data in Reimbursement and Pricing Decisions

Details on the use of preference data in each country are available in Appendix 2 in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.11.009). Table 2 provides an overview of the country summaries.

No use of preference data was identified in 9 countries: Croatia, Cyprus, Greece, Luxembourg, Malta, Romania, the Russian Federation, the Slovak Republic, and Switzerland.

The most prevalent use of preference data was citizen preferences to support reimbursement or pricing decisions through the estimation of utility tariffs, including in 19 of the 31 countries reviewed: Belgium,[36] Bulgaria,[37,38] Czech Republic,[39] Estonia,[40] Finland,[41] France,[42] Hungary,[43] Ireland,[44] Italy,[32] Latvia,[40] Lithuania,[40] The Netherlands,[45] Norway,[46] Poland,[47] Portugal,[48] Spain,[34,35] Sweden,[49] and the United Kingdom (England and Wales[50] and Scotland[51]). In 16 of these countries, it was explicitly stated that either TTO or SG methods should be used to estimate

Table 2. Country-level use of preference data for reimbursement and pricing decisions (source: all).

Country	Stakeholder					
	Patients	Citizens	Decision makers	Experts	Providers	Caregivers
Austria			P	P		
Belgium	Rk	C(S), M		Rk		
Bulgaria		Rt, M				
Czech Republic	M	M(S)		Rk, Rt	Rk, Rt	
Denmark	TBD~					
Estonia		?				
Finland		M				
France	C	M	C			
Germany	Rk P(S), C(S)					
Hungary	C	Rt, M	Rt			C
Ireland		M				
Italy		M	Rt			
Latvia		?				
Lithuania		?				
Netherlands	Rt, P(S), C, M(S)	C, M	Rt C	P, M	M	M
Norway		M(S)				
Poland		M				
Portugal		M(S)		M		
Slovenia			P			
Spain		M				
Sweden	Rk, Rt, C, M	Rt, M(S)		Rk, Rt, M		
United Kingdom	C(S)	C(S), M(S)				

Note. Empty boxes indicate no use of preference data identified.
C indicates choice-based method; M, matching method; P, pairwise comparison; Rk, ranking method; Rt, rating method; (S), were also identified in the survey of agency staff (applies only when the source is indicated as either "guidance" or "examples"). Table shading indicates the following:
  Guidance on the use of preference data identified.
  No guidance identified, but documented examples of the use of preference data identified.
  Neither guidance or examples identified, experts identified use of preference data.

utility tariffs. In 15 countries, this use of citizen preferences was identified in a guidance document, but this use was confirmed by ag ency staff in only 7 of these countries.

A smaller group of countries use other preference data to inform reimbursement and pricing decisions. Two types of preference data utilization are distinguished:

1. Capturing a broader set of impacts on patients. This group contains 2 approaches:
    a. Eliciting citizen preferences using choice-based methods for outcomes not captured by the quality-adjusted life-year (QALY; England and Wales, The Netherlands, Scotland)
    b. Eliciting patient preferences, either in place of the QALY (Germany) or supplementing the QALY (Sweden)
2. Capturing value other than the impact on patients. This group contains 2 additional approaches:
    a. Formalizing preferences for nonhealth factors in reimbursement and pricing decisions, using either rating or pairwise methods with decision makers (Austria, Hungary, Italy), choice-based methods with citizens (Belgium), or matching methods with caregivers (France).
    b. Estimating opportunity cost or willingness-to-pay (WTP) threshold. Most countries did not adopt preference-based approaches to estimating opportunity cost, instead adopting World Health Organization recommendations to value the QALY at multiples of gross domestic product (Czech Republic, Hungary and Poland[52]) or basing the threshold on the efficiency of treatments already available within the healthcare system (the National Institute for Health and Care Excellence [NICE] in the United Kingdom). Our review identified 2 countries in which preference methods were used to estimate WTP for the QALY (The Netherlands, Sweden). More detail on these uses of preference data can be found in Table 3.

The agency staff survey and the KOL engagement identified many uses of quantitative preference data that were not found in the literature and website reviews (Table 2). These related to the use of preferences of stakeholders other than citizens: patients (Belgium, Czech Republic, Denmark, Hungary, and Sweden), decision makers (Austria, The Netherlands, Slovenia), providers (Czech Republic, The Netherlands), experts (Austria, Belgium, Czech Republic, The Netherlands, Portugal, Sweden), and caregivers (Hungary, The Netherlands). There was no obvious trend toward the use of any particular method among different stakeholder groups.

Use of Preference Data in Marketing Authorization Decisions

No use of preference data for marketing authorization decisions was identified in the literature or website review. Table 4 summarizes country-level use of preference data to support marketing authorization decisions identified in the decision-maker survey. These data are diverse, both in terms of methods (ranking and/or rating methods used in the Czech Republic and Italy, and choice-based and/or matching methods used in Hungary, Norway, and the United Kingdom) and in terms of the stakeholder whose preferences are elicited (patients, citizens, experts, and providers).

There are also many instances of sponsor inclusion of preference data in a market authorization submission, despite the fact that the data are neither required nor even recommended. The exception to this is in Bulgaria, where a representative of the National Centre of Public Health and Analyses reported that it is recommended that decision makers, experts, and other stakeholders' preferences be elicited using a variety of methods.

Pilots of Preference Data Usage

The European Medicines Agency (EMA) has piloted the use of preference data to support marketing authorization decisions, although no evidence was found that this was used to inform actual decisions. EMA pilot work includes the following:

- The EMA Benefit Risk Assessment (BRA) Methodology Project[63] undertaken between 2008 and 2014. It explored methods for implementing quantitative BRA and whether this information would be useful in regulatory decision making. After reviewing available methods, the project undertook a number of pilots on the use of swing weighting methods to elicit Committee for Medicinal Products for Human Use member preferences[63] and the use of Measuring Attractiveness through a Categorical Based Evaluation (MACBETH) for eliciting patient preferences.[64]
- More recently, EMA member countries are piloting adapted swing weighting to elicit the preferences of patient and provider populations to inform regulatory decision making.[65,66]

A number of institutions have ongoing research that may support the further use of preference data in pricing and reimbursement decisions, such as the following:

- Belgium: An MCDA was piloted, assessing the therapeutic need, societal need, and added value of health technologies. The preference inputs in the MCDA were derived from a DCE undertaken with citizens.[67–69]
- Denmark: Correspondence with staff from the Danish Medicines Council identified ongoing pilot work on how to collect and use quantitative data on patient preferences.
- Germany: One of the first pilots of preference data usage was conducted by Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and tested the applicability and feasibility of DCE and AHP methods for elicitation of patient preferences.[21,33,59,62]
- Ireland: The National Centre for Pharmacoeconomics Evaluations (NCPE) states on its website that it was seeking funding to use TTO and DCE to gather patient-preference data and to incorporate these data into a model to assess the impact on decisions.[70]
- The Netherlands: A pilot project implemented by the National Health Care Institute (ZIN) and academic researchers investigated the use of MCDA for decision making.[71] The aim was to facilitate the use and acceptability of MCDA in HTA decisions. Decision-maker preferences were elicited using rating methods.
- United Kingdom: In England and Wales, NICE has recently initiated a pilot to explore the use of quantitative methodologies to incorporate patient preferences into HTAs (personal correspondence with NICE).

The decision-maker survey also pointed to further pilot work not yet in the public domain, including the use of ranking methods to elicit decision-maker preferences (Czech Republic) and the use of several types of methods (ranking, rating, choice based, and matching) to elicit patient preferences (Sweden).

IMI PREFER[10] has established a formal structure to incorporate regulatory input from other agencies into its activities, including the HTA and Payers Advisory Group coordinated by the Belgian Health Care Knowledge Centre (KCE), the Belgian National Institute for Health and Disability Insurance (INAMI-RIZIV),

Table 3. Uses of preference data other than utility tariff estimation (source: literature, websites, experts).

Perspective	Method	Valuing a broader set of impacts on patients	Value other than impacts on patients
Decision maker	Stated preference Rating		Both Italy (region of Lombardy)[33] and Hungary[31] have applied MCDA to support decision making. In each case, decision makers' and experts' preferences for decision criteria are elicited in a workshop setting using a rating methods: Likert scales in Italy and point allocation in Hungary.
	Stated preference Pairwise		Austria: pairwise elicitation methods were used to inform the development of the value framework within which reimbursement decisions are made. In 2005, 60 to 65 members of the Organization of Austrian Social Insurance staff and 12 to 15 clinicians were interviewed and asked to complete a set of pairwise attribute ranking questions. These informed the existing decision-making framework that provides guidance on how prices should vary with, for instance, clinical benefit, safety, and innovativeness.[53]
General population	Stated preference Choice based	The Netherlands: The National Health Centre Institute (ZIN) guidelines mention DCE and "other conjoint methods for eliciting citizen preferences as potential additional sources of quality of life evidence." In particular, DCE and MCDA are recommended for devices or diagnostics, for which the QALY is not be able to capture the technology's value.[45] England: There is precedent for using DCE with a citizen sample to estimate procedural utility, specifically, the disutility associated with the process of receiving a drug as an infusion compared with an oral formulation.[54] This evidence was incorporated into the economic analysis submitted by the sponsor. Scotland: The Scottish Medicine Consortium guidelines suggest that DCE can be used with a citizen sample where the QALY fails to capture the technology's value, such as when it is associated with an improved delivery system.[51]	Belgium: A DCE was undertaken with 4000+ citizens to determine the relative value of disease severity, changes in life expectancy, and changes in quality of life.[55] A pilot study has been undertaken to test the use of preference data in an MCDA for evaluating technologies.
	Stated preference Matching	Scotland: The Scottish Medicine Consortium guidelines suggest that WTP can be used with a citizen sample where the QALY fails to capture the technology's value, such as when it is associated with an improved delivery system.[51] No detail is provided on which methods should be used to estimate 'WTP'.	
	Revealed preference		Sweden: The cost per QALY threshold value is based on societal WTP. Although it does not have a definite threshold value, the Dental and Pharmaceutical Benefits Agency (TLV) has a range of such values "inspired" by estimates of the value of statistical life.[56] The Netherlands: ZIN applies a cost/QALY range of €20 000 to €80 000, varying the maximum WTP depending on the burden of the disease targeted by the treatment.[57] This estimate is based on yearly costs of a nursing home, comparison with other countries/institutions, the tariff proposed by the World Health Organization, and a prior analysis of the worth of a statistical life, by the Dutch Public Health Council.[58]

Table 3. Continued

Perspective	Method	Valuing a broader set of impacts on patients	Value other than impacts on patients
Patient	Stated preference Choice based	Germany: IQWiG piloted the use of DCE to elicit patient preferences.[59,60] This use of DCE is recommended in IQWiG's method guide to support the estimation of aggregate benefit in an economic evaluation.[61]	
	Stated preference Matching	Sweden: A TLV staff member reported that TTO and WTP methods can be used to elicit patient preferences where the QALY is thought to be inappropriate. Examples include short-term pain or medical device evaluation. No detail is provided on which methods should be used to estimate "WTP."	
	Stated preference Pairwise	Germany: IQWiG piloted the use of AHP to elicit patient preferences.[62] This use of AHP is recommended in IQWiG's method guide to support the estimation of aggregate benefit in an economic evaluation.[61]	
Caregiver	Stated preference Matching		France: It is recommended that CUA should include the cost of carers' time, when it is expected to be significant. WTP is one method for estimating the value of carers' time.[42]

AHP indicates analytical hierarchy process; CUA, cost–utility analysis DCE, discrete choice experiment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; QALY, quality-adjusted life-year; TTO, time trade-off; WTP, willingness to pay.

the German Federal Joint Committee (Gemeinsamer Bundesaus-schuss; G-BA), and the Austrian Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA). These agencies sit on the Stakeholder Advisory Group, ensuring that the needs of HTA bodies are considered in PREFER, both in the development of the project and the resulting recommendations.

Discussion

Quantitative preference data are used to support healthcare decisions in many European countries; this review identified such use in all but 9 of the 31 European countries reviewed. Nevertheless, evidence suggests that the usage to date has limited visibility, with the exception of the use of TTO and SG methods to inform QALY estimation. First, documented evidence for all uses of preference data was not publicly available. For instance, the evidence for the use of preference data to support marketing authorization decisions came exclusively from the agency staff survey, with the exception of the EMA's pilot work. Second, only a small proportion of the evidence reviewed (7 publications) was published in peer-reviewed journals. Although it is possible that more peer-reviewed preference research articles were used to support decisions, this was not identified in the publications themselves.

Much of the use of preference data can be placed within the standard framework of economic analysis adopted by many HTA agencies, in the form of one of the following:

- Standard approaches to estimate QALYs
- Ways to broaden the health technology's impacts on patients captured in the QALY, for example, incorporating impacts on change in mode of administration (process utility) into the QALY
- Means to weigh the impact on patients with other decision-making criteria, such as disease severity or innovativeness

These varying objectives suggest that different stakeholders will be responsible for collecting preference data. Responsibility

for the latter objective—how impacts on patients will be weighed against other criteria—will tend to sit with the agencies themselves. Examples of agencies collecting these data include citizen surveys (Belgium, estimating the relative value of need and added value), decision-maker surveys (Austria, estimating the relative value of benefits, safety, and innovativeness), and decision-maker workshops (Italy, Hungary). Ongoing pilot work in Belgium and The Netherlands is exploring the use of MCDA to support decision makers considering this larger set of factors. Responsibility for the second objective (incorporating a wider set of impacts on patients into QALY estimates) is more likely to be submission specific and will thus will be the responsibility of the technology sponsor.

Agencies have yet to provide detailed guidance on when manufacturers should collect these data and how they should go about it. At best, agencies provide illustrations of when such data might be useful and the type of methods that might be considered. For instance, the method guidance from the Scottish Medicines Consortium (SMC), ZIN, and Sweden's Dental and Pharmaceutical Benefits Agency (TLV) only provide suggestions as to which methods might be appropriate. In other instances, the use of preferences has yet to be incorporated into guidelines. Nevertheless, previous submissions have established a precedent. For instance, procedural utility estimated using a DCE with a citizen sample was incorporated into an economic analysis in a submission to NICE.[72]

Where guidance exists, it suggests that preferred methods vary across countries. In Scotland, WTP or DCE methods might be used to elicit citizen preferences to estimate the utility impact of different delivery systems; in The Netherlands, DCE or MCDA might be appropriate to estimate the value of technologies, such as devices or diagnostics; and in Sweden, WTP or DCE methods can elicit patient preferences to capture the value of health impacts, such as reductions in acute pain. If there is a consistency between countries, it is the use of TTO and SG to estimate QALYs and then DCE to elicit citizen preferences for impacts that are not captured in the QALY. One obvious exception to this trend is in Germany, where rejection of the QALY has led to the use of DCE or

Table 4. Country-level use of preference data for regulatory approval decisions: number of survey responses identifying use of preference data (source: survey of agency staff).

Country	Method	Stakeholder								
		Patients			Citizens			Decision makers		
		Require	Recommend	Submitted*	Require	Recommend	Submitted*	Require	Recommend	Submitted*
Bulgaria	Ranking							1		
	Rating							1		
	Pairwise									1
	Choice based							1		
	Matching								1	
	Other ("MCDA")								1	
Czech Republic	Ranking									
	Rating									
Hungary	Choice based			1						
	Matching			1			1			
Italy	Ranking			1			1			
Norway	Matching				1		1			
Portugal	Matching					1				
Sweden	Other ("James Lind Alliance")			1						
United Kingdom	Choice based			1						
	Matching			1			1			

*Preference data were included in a sponsor submission.

AHP to elicit patient preferences and to allow the weighting of multiple endpoints into an overall estimate of benefit.

Given the number of countries piloting the use of DCE to elicit patient preference to support reimbursement and pricing decisions—Denmark, Ireland, and the United Kingdom—these data might be used more for this purpose in the future. Such pilots are mirrored by the EMA, which recently has been involved in a pilot of adapted swing weighing methods for eliciting patient preferences. This raises the prospect of greater alignment across reimbursement agencies and between reimbursement and regulatory agencies.

Further insight into the possible uses of preference data can be found in the specific frameworks that inform HTA agency work. EUnetHTA's HTA Core Model is the framework most referenced by agencies. In Croatia, Germany, 3 Italian regions (Emilia-Romagna, Veneto, and Lazio), The Netherlands, and a Spanish region (Andalusia), agencies either apply the framework, draw on reports produced by EUnetHTA using the framework, or identify it as helpful.

The Core Model provides 2 potential routes for the incorporation of stated preference data into decision making.[73] First, the "cost" and "economic evaluation" domains acknowledge the role of SG, TTO, visual analog scale, person trade-off, or DCE in estimating utility inputs for economic evaluations. Second, the "patients and social aspects" domain identifies issues associated with patients' attitudes, perceptions, preferences, satisfaction, and experience. The Core Model does not mention which methods might be appropriate for capturing these insights.

Another framework referenced by agencies is Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Three agencies (in Demark, Spain [Canary Islands], and

Switzerland) reference GRADE as the basis for their guidelines or specific evaluations. GRADE requires that patients' values and preferences be considered when determining the level of confidence that desirable effects of an intervention outweigh undesirable effects.[74] Like the Core Model, GRADE does not recommend specific preference methods to provide this insight. Nonetheless, applications of GRADE include reviews that capture all types of quantitative preference data.[75]

The study's conclusions should be qualified by acknowledging the limitations that inevitably accompany a study of such breadth. First, it was beyond our scope to review anything other than the sources published in English or to read every submission to every agency. The review of websites will also have missed the use of preference data confined to confidential parts of the submission. To potentially offset these risks, efforts were made to survey local agency staff and engage local KOLs. Nevertheless, such survey data are subject to the limitation that they are self-reported. There is also the risk of bias due to a misunderstanding of what is meant by types of preference data, given the lack of familiarity of the methods typology employed. This risk was partly mitigated in 2 ways. First, greater emphasis was given to the documented use of preference data when interpreting the findings of the study. Second, survey responders were followed up to confirm their answers. Of the 29 responders who provided their contacts details, 15 had indicated a use of preference data by their institutions. Of these, 4 did not respond to a request for more detail, whereas 11 provided more detail that confirmed preference data usage, as stated in their survey responses.

Second, given the multimethod nature of the study, data collection was undertaken over a period of 2 years. The literature

Table 4. Continued

Stakeholder								
Experts			**Providers**			**Caregiver**		
Require	Recommend	Submitted*	Require	Recommend	Submitted*	Require	Recommend	Submitted*
	2				1			
	2				1			
	1							
	1				1			
	1							
1								
		1			1			
		1			1			1
								1
		1			1			
		1			1			
		1						
		1						

review component of the study, which was the first of the data-collection methods to be applied, is thus a little out of date. A notable example of the use of patient-preference data in reimbursement decisions has been published since the review was undertaken: NICE's scientific advice on the use of patient-preference data to inform the selection of endpoints in clinical study.[76] Further, EMA and EUnetHTA have recently initiated a joint process to qualify a general systematic approach to collecting patient-preference data and one method for eliciting patient preferences.[77]

Finally, the study is purely descriptive, identifying uses of preference data. Further work is required to address (1) more normative considerations, such as whose preferences should be used to inform decisions; (2) which methods are more appropriate when eliciting preferences from these stakeholders in diverse circumstances; and (3) understanding more about the experiences of countries adopting preference data, including barriers to their use, and why adoption varies between countries.

Although some emergent trends in preference data usage may be evident from the study, it identified many methods being used to collect many stakeholders' preferences. Future research should consider (1) whether it is possible to standardize the use of preference methods across jurisdictions, including consideration of the role of culture in the use of preference data; (2) whether use can be standardized between marketing authorization and reimbursement agencies; and (3) whether the varying objectives of decision makers necessitate the use of multiple methods. The number of institutions interested in patient preferences elicited using DCE suggests that it would be worthwhile to consider whether a DCE or series of DCEs could be designed to fulfill some,

if not all, of the needs of these institutions. In the immediate term, PREFER could be an important source of insight into how patient-preference data can be used in Europe.[10]

Conclusions

Quantitative preference data support reimbursement and pricing decisions in most countries in Europe. Although there are some commonalities, such as the use of TTO and SG methods to estimate utility, preference data use and the methods for eliciting these data vary among jurisdictions. There was no evidence of quantitative preference data usage in European-level marketing authorization decisions. The use of preference data by EU decision makers is an area of active development, with a number of initiatives being published between the completion of this review and publication. A number of ongoing pilot projects point to the potential for greater alignment of preference data use across jurisdictions and in reimbursement and authorization decisions.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.11.009.

Article and Author Information

REFERENCES

1. Sheridan DJ, Julian DG. Achievements and limitations of evidence-based medicine. *J Am Coll Cardiol*. 2016;68:204–213.

2. Mühlbacher AC, Juhnke C. Patient preferences versus physicians' judgement: does it make a difference in healthcare decision making? *Appl Health Econ Health Policy*. 2013;11:163–180.

3. van Til JA. *Integrating Preferences Into Decision Making: The Treatment of Ankle-Foot Impairment in Stroke* [dissertation]. Enschede, The Netherlands: University of Twente; 2009.

4. Haynes RB, Devereaux P, Guyatt GH. Physicians' and patients' choices in evidence based practice. *BMJ*. 2002;324:1350.

5. Sackett DL, Rosenberg W, Gray J, et al. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71.

6. Mühlbacher AC. Patient-centric HTA: different strokes for different folks. *Exp Rev Pharmacoecon Outcomes Res*. 2015;15:591–597.

7. Tanios N, Wagner M, Tony M, et al. Which criteria are considered in healthcare decisions? Insights from an international survey of policy and clinical decision makers. *Int J Technol Assess Health Care*. 2013;29:456–465.

8. de Bekker-Grob EW, Berlin C, Levitan B, et al. Giving patients' preferences a voice in medical treatment life cycle: the PREFER Public-Private Project. *Patient*. 2017;10:263–266.

9. Innovative Medicines Initiative. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT). 2016. http://www.imi-protect.eu/. Accessed September 2019.

10. Innovative Medicines Initiative. The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER). 2018. https://www.imi-prefer.eu/. Accessed September 2019.

11. Bridges JF. Stated preference methods in health care evaluation: an emerging methodological paradigm in health economics. *Appl Health Econ Health Policy*. 2003;2:213–224.

12. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. *BMJ*. 2000;320:1530–1533.

13. Ryan M, Gerard K. Using discrete choice experiments to value health care programmes: current practice and future research reflections. *Appl Health Econ Health Policy*. 2003;2:55–64.

14. Egbrink MO, IJzerman M. The value of quantitative patient preferences in regulatory benefit-risk assessment. *J Mark Access Health Policy*. 2014;2.

15. van Til JA, Ijzerman MJ. Why should regulators consider using patient preferences in benefit-risk assessment? *Pharmacoeconomics*. 2014;32:1–4.

16. Mühlbacher AC, Juhnke C, Beyer AR, et al. Patient-focused benefit-risk analysis to inform regulatory decisions: the European Union perspective. *Value Health*. 2016;19:734–740.

17. Weernink MG, Janus SI, Van Til JA, et al. A systematic review to identify the use of preference elicitation methods in healthcare decision making. *Pharmaceut Med*. 2014;28:175–185.

18. Craig BM, Lancsar E, Muehlbacher AC, et al. Health preference research: an overview. *Patient*. 2017;10:507–510.

19. European Medicines Agency. Pilot phase to involve patients in benefit/risk discussions at CHMP meetings. EMA/372554/2014. Rev. 1 2014. https://www.ema.europa.eu/en/documents/other/pilot-phase-involve-patients-benefit/risk-discussions-chmp-meetings_en.pdf. Accessed September 2019.

20. US Food and Drug Administration. FAQs about the FDA Patient Representative Program℠. 2018. https://www.fda.gov/ForPatients/About/ucm412529.htm. Accessed September 2019.

21. Mühlbacher AC, Bridges JF, Bethge S, et al. Preferences for antiviral therapy of chronic hepatitis C: a discrete choice experiment. *Eur J Health Econ*. 2017;18:155–165.

22. US Food and Drug Administration. Guidance for industry, Food and Drug Administration staff, and other stakeholders: 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. October 2016. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm446680.pdf. Accessed September 2019.

23. Clark MD, Determann D, Petrou S, et al. Discrete choice experiments in health economics: a review of the literature. *Pharmacoeconomics*. 2014;32:883–902.

24. Marsh K, Lanitis T, Neasham D, et al. Assessing the value of healthcare interventions using multi-criteria decision analysis: a review of the literature. *Pharmacoeconomics*. 2014;32:345–365.

25. Hauber AB, Fairchild AO, Johnson FR. Quantifying benefit–risk preferences for medical interventions: an overview of a growing empirical literature. *Appl Health Econ Health Policy*. 2013;11:319–329.

26. Carson RT, Louviere JJ. A common nomenclature for stated preference elicitation approaches. *Environ Res Econ*. 2011;49:539–559.

27. Ali S, Ronaldson S. Ordinal preference elicitation methods in health economics and health services research: using discrete choice experiments and ranking methods. *Br Med Bull*. 2012;103:21–44.

28. Marsh K, IJzerman M, Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making–Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19:125–137.

29. Tervonen T, Ustyugova A, Sri Bhashyam S, et al. Comparison of oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a multi-criteria decision analysis. *Value Health*. 2017;20:1394–1402.

30. European Medicines Agency (EMA). Benefit-risk methodology project: Work package 3 report: Field tests. *August*. https://www.ema.europa.eu/documents/report/benefit-risk-methodology-project-work-package-3-report-field-tests_en.pdf; 2011.

31. Danner M, Hummel JM, Volz F. Integrating patients' views into health technology assessment: Analytic hierarchy process (AHP) as a method to elicit patient preferences. *Int J Technol Assess Health Care*. 2011;27:369–375.

32. Bethge S, Müehlbacher AC, Bridges JF, et al. Preferences for antiviral therapy of chronic hepatitis C: a discrete choice experiment. *Eur J Health Econ*. 2017;18:155–165.

33. National Institute for Health and Care Excellence (NICE). PMG9: Guide to the methods of technology appraisal 2013. *April*. https://www.nice.org.uk/process/pmg9/chapter/foreword; 2013.

34. Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ*. 2018;19:123–152.

35. Rodriguez JM, Paz S, Lizan L, et al. 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*. 2011;14:458–464.

36. Federaal Kenniscentrum Voor De Gezondheidszorg. *KCE Report 183c: Belgian Guidelines for Economic Evaluations and Budget Impact Analyses*. Second Edition. 2012. https://kce.fgov.be/sites/default/files/atoms/files/KCE_183_economic_evaluations_second_edition_Report_update.pdf. Accessed September 2019.

37. The Ministry of Health of Republic of Bulgaria. Summary report of health technology assessment for medicinal product OFEV. 2016. http://ncpha.government.bg/files/komisa%20zdr.tehn./dokladi/Ofev-Report_Eng04052017.pdf. Accessed September 2019.

38. The Ministry of Health of Republic of Bulgaria. Report on health technology assessment for medicinal product ATOZET. 2016. http://ncpha.government.bg/files/komisa%20zdr.tehn./dokladi/Atozet_report_HTA_BG_ENG_ver.pdf. Accessed September 2019.

39. State Institute for Drug Control. SP-CAU-028: procedure for assessing cost-effectiveness analysis. 2017. http://www.sukl.cz/leciva/sp-cau-028. Accessed September 2019.

40. Behmane D, Lambot K, Irs A, et al. Baltic Guidelines on Economic Evaluation of Pharmaceuticals. 2002. https://tools.ispor.org/PEguidelines/source/Baltic-PE-guideline.pdf. Accessed September 2019.

41. Lääkkeiden hintalautakunta. Preparing a health economic evaluation to be attached to the application for reimbursement status and wholesale price for a medicinal product. 2017. http://www.hila.fi/c/document_library/get_file?folderId=1133981&name=DLFE-9844.pdf. Accessed September 2019.

42. Haute Autorité de Santé. Choix méthodologiques pour l'évaluation économique à la HAS. 2011. https://www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf. Accessed September 2019.

43. Hungarian Pharmaceutical Authority for Doctors and Pharmacists. Professional healthcare guideline on the methodology of health technology assessment. *Gyógyszereink*. 2017;67.

44. Health Information and Quality Authority. Guidelines for the economic evaluation of health technologies in Ireland. 2018. https://www.hiqa.ie/sites/default/files/2018-01/HIQA_Economic_Guidelines_2018.pdf. Accessed September 2019.

45. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. 2016. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg. Accessed September 2019.

46. Statens legemiddelverk. Guidelines on how to conduct pharmacoeconomic analyses. 2012. https://tools.ispor.org/PEguidelines/source/Norwegian_guidelines2012.pdf. Accessed September 2019.

47. Agency for Health Technology Assessment. Guidelines for conducting health technology assessment (HTA) version 2.1. 2009. http://www.aotm.gov.pl/assets/files/wytyczne_hta/2009/Guidelines_HTA_eng_MS_29062009.pdf. Accessed September 2019.

48. da Silva EA, Pinto CG, Sampaio C, et al. Guidelines for economic drug evaluation studies. 1998. https://tools.ispor.org/PEguidelines/source/PE%20guidelines%20in%20English_Portugal.pdf. Accessed September 2019.

49. Tandvårds & läkemedelsförmånsverket (TLV). General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2). 2003. https://www.tlv.se/download/18.2e53241415e842ce95514e9/1510316396792/Guidelines-for-economic-evaluations-LFNAR-2003-2.pdf. Accessed September 2019.

50. National Institute for Health and Care Excellence. PMG9: guide to the methods of technology appraisal. April 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed September 2019.

51. Scottish Medicines Consortium. Guidance to manufacturers for completion of New Product Assessment Form (NPAF). 2017. https://www.scottishmedicines.org.uk/media/4219/20190222-guidance-on-npaf.doc. Accessed September 2019.

52. Cameron D, Ubels J, Norstrom F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. *Glob Health Action*. 2018;11:1447828.

53. Österreichischen Sozialversicherung. Official statement of the Austrian Social Security: rules of procedure for the publication of the reimbursement code according to § 351g ASVG-VO-EKO. https://www.ris.bka.gv.at/Dokumente/Avsv/AVSV_2004_0047/AVSV_2004_0047.html. Accessed September 2019.

54. National Institute for Health and Care Excellence (NICE). Migalastat for treating Fabry disease. Highly specialised technologies guidance [HST4]. 2017. https://www.nice.org.uk/guidance/hst4. Accessed September 2019.

55. Federaal Kenniscentrum Voor De Gezondheidszorg. KCE Reports 234: incorporating societal preferences in reimbursement decisions—relative importance of decision criteria according to Belgian citizens. 2014. https://kce.fgov.be/sites/default/files/page_documents/KCE_234_reimbursement_decisions_Report_0.pdf. Accessed September 2019.

56. Svensson M, Hultkrantz L. A comparison of cost-benefit and cost-effectiveness analysis in practice: divergent policy practices in Sweden. *Nordic J Health Econ*. 2017;5:41–53.

57. Zwaap J, Knies S, van der Meijden C, et al, Cost-effectiveness in practice. 2015. https://english.zorginstituutnederland.nl/.../zinl.../Cost-effectiveness+in+practice.pdf. Accessed September 2019.

58. Council for Public Health and Care. *Zinnige en duurzame zorg (Sensible and sustainable Care). Report nr. 06/06*. Raad voor de Volksgezondheid en Zorg (Council for Public Health and Health Care); 2006.

59. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). *Choice-Based Conjoint Analysis—Pilot Project to Identify, Weight, and Prioritize Multiple Attributes in the Indication "Hepatitis C." Executive Summary*. Cologne, Germany: Institute for Quality and Efficiency in Health Care; 2014.

60. Muehlbacher AC, Johnson FR. Giving patients a meaningful voice in European health technology assessments: the role of health preference research. *Patient*. 2017;10:527–530.

61. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). *General Methods. Version 5.0/10.07. 2017*. Köln, Germany: IQWiG; 2017. https://www.iqwig.de/download/Allgemeine-Methoden_Version-5-0.pdf. Accessed September 2019.

62. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Analytic Hierarchy Process (AHP)—Pilot Project to Elicit Patient Preferences in the Indication "Depression." Executive Summary*. Cologne, Germany: Institute for Quality and Efficiency in Health Care; 2013.

63. European Medicines Agency. Benefit-risk methodology. 2011. https://www.ema.europa.eu/en/about-us/support-research/benefit-risk-methodology. Accessed September 2019.

64. European Medicines Agency. Values and preferences for treatment outcomes: the MACBETH approach. https://www.ema.europa.eu/documents/presentation/presentation-workshop-patients-voice-evaluation-medicines-values-preferences-treatment-outcomes_en.pdf. Accessed September 2019.

65. Postmus D, Mavris M, Hillege H, et al. 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*. 2016;99:548–554.

66. Postmus D, Richard S, Bere N, et al. Individual trade-offs between possible benefits and risks of cancer treatments: results from a stated preference study with patients with multiple myeloma. *Oncologist*. 2018;23:44–51.

67. Federaal Kenniscentrum Voor De Gezondheidszorg. KCE report 272: multi-criteria decision analysis for the appraisal of medical needs: a pilot study. 2016. https://kce.fgov.be/sites/default/files/atoms/files/KCE_272_Unmet_needs_Report2.pdf. Accessed September 2019.

68. Castro H, Tringali M, Cleemput I, et al. *Advancing MCDA and HTA into coverage decision-making. Multi-criteria Decision Analysis to Support Healthcare Decisions*. New York, NY: Springer; 2017.

69. Cleemput I, Devriese S, Kohn L, et al. What does the public want? Structural consideration of citizen preferences in health care coverage decisions. *MDM Policy Pract*. 2018;3:2381468318799628.

70. National Centre for Pharmacoeconomics (NCPE) Ireland. Pharmacoeconomic Research 2014. http://www.ncpe.ie/research/pharmacoeconomics/. Accessed September 2019.

71. ZonMw. A roadmap for uncertainty analysis in MCDA. 2016. https://www.zonmw.nl/nl/onderzoek-resultaten/geneesmiddelen/programmas/project-detail/doelmatigheidsonderzoek-farmacotherapie/a-roadmap-for-uncertainty-analysis-in-mcda/verslagen/. Accessed September 2019.

72. National Institute for Health and Care Excellence. TA466: baricitinib for moderate to severe rheumatoid arthritis. 2017. https://www.nice.org.uk/guidance/ta466. Accessed September 2019.

73. EUnetHTA. JA2 WP8 DELIVERABLE: HTA core model version 3.0. 2015. https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf. Accessed September 2019.

74. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ*. 2008;336:1049–1051.

75. Zhang Y, Coello PA, Brozek J, et al. Using patient values and preferences to inform the importance of health outcomes in practice guideline development following the GRADE approach. *Health Qual Life Outcomes*. 2017;15:52.

76. National Institute for Health and Care Excellence. NICE provides first scientific advice on patient preference study design. February 2019. https://www.nice.org.uk/news/article/nice-provides-first-scientific-advice-on-patient-preference-study-design. Accessed September 2019.

77. Fernow J. Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project. Positive feedback on PREFER mid-term review! September 2019. https://www.imi-prefer.eu/news/news-item/?tarContentId=805246. Accessed September 2019