Health Policy 123 (2019) 152–158

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

Using a stated preference discrete choice experiment to assess societal value from the perspective of decision-makers in Europe. Does it work for rare diseases?

J. López-Bastida[a,*], J.M. Ramos-Goñi[b], I. Aranda-Reneo[c], M. Trapero-Bertran[d], P. Kanavos[e], B. Rodriguez Martin[a]

[a] University of Castilla-La Mancha, Faculty of Occupational Therapy, Speech Therapy and Nursing, Talavera de la Reina, Toledo, Spain
[b] Axentiva Solutions, Tacoronte, Spain
[c] University of Castilla-La Mancha, Faculty of Social Science, Talavera de la Reina, Toledo, Spain
[d] Universitat Internacional de Catalunya (UIC), Faculty of Economics and Social Sciences, Barcelona, Spain
[e] London School of Economics and Political Science, London, UK

ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form
25 November 2018
Accepted 26 November 2018

Keywords:
Discrete choice experiments
Preference
Rare disease(s)
Orphan drugs
Priority setting
Attribute(s)

ABSTRACT

Objectives: To pilot the feasibility of using a discrete choice experiment (DCE) design to investigate individual preferences from the decision-maker perspective regarding the use of public funding for orphan drugs and generate prior information for future experimental designs.

Methods: A DCE was used on a convenience sample of participants from five European countries (England, France, Germany, Italy and Spain), exploring their preferences in distinct healthcare scenarios involving orphan drugs. A preliminary review of the empirical literature on distributive preferences informed the selection of attributes and their levels in the design. An online questionnaire was used to conduct the DCE survey.

Results: A total of 199 questionnaires were completed. The five country model showed relative preference for some attributes over others: cost of treatment, improvement in health, value for money and availability of treatment alternatives received the greatest attention. However, disease severity, beginning of life, waiting times and side effects were also shown to be important social values that should not be ignored.

Conclusions: The findings presented in this study provide insight about the preferences that can influence decisions on orphan drugs in different countries. This study also provides valuable prior information that could inform future DCE designs in this area.

1. Introduction

There is no single commonly accepted definition for rare diseases [1], although the European Commission and international literature agree that these are life-threatening or chronically debilitating conditions that affect no more than five in 10 000 individuals and necessitate long-term specialist and costly formal and informal care [2,3]. Although rare diseases are by definition characterised by a low prevalence, more than 5000 such diseases have been recognised to date, affecting a total of over 30 million EU citizens.

Decision makers in health systems around the globe must deal with the conflict generated by competing demands and insufficient resources: it is impossible to provide all the potentially beneficial healthcare services to those who might benefit from them, and priorities must be established. Medicines used to treat rare diseases (orphan drugs) may be costly to develop, but the population size they serve is small, and the need to recoup R&D costs is often reflected in high prices.

Decisions regarding orphan drug designation and marketing authorisation are currently taken at the European Union (EU) level, whereas reimbursement is a national concern. The availability and affordability of orphan drugs have become high priority issues for policy makers. The governments of the United States, Japan, and some EU countries have introduced special financial incentives for the development of drugs for rare diseases [4,5]. However, such policies are of limited value if the treatments developed ultimately

* Corresponding author at: Facultad de Terapia Ocupacional, Logopedia y Enfermería, Universidad de Castilla-La Mancha, Avda Real Fábrica de Seda s/n, 45600 Talavera de la Reina, Toledo, Spain.
E-mail address: julio.lopezbastida@uclm.es (J. López-Bastida).

https://doi.org/10.1016/j.healthpol.2018.11.015
0168-8510/

fail to obtain coverage from governments due to their limited cost-effectiveness.

There is as yet no consensus as to how the value of orphan drugs should be assessed. Clinical evidence on their safety and efficacy is often weak due to the small number of patients in randomised clinical trials and the reliance on surrogate markers of effectiveness that are not always well-linked to final patient outcomes [6]. Given that many orphan drugs are more expensive than treatments for other, more prevalent conditions, relatively high incremental cost-effectiveness ratios and/or poor value for money lead to denial of coverage [6], jeopardizing patient access to such therapies.

These restrictions may not be in line with societal preferences; when it comes to allocative decisions, members of the public are known to be willing to make sacrifices in terms of a reduction in the total amount of health gain generated to achieve a more equitable distribution and respond to the needs of those in severe ill health [7,8]. Indeed, since treatments for rare diseases are unlikely to provide value for money in view of their high price and often modest effectiveness, additional criteria are already used to inform reimbursement decisions in some countries, such as severity of disease, improvement in health and availability of other treatments [9]. International initiatives to more precisely calculate the value of orphan medicines are widespread among policy makers and payers [10,11]. Different approaches have been proposed to appraise interventions for rare diseases based on multiple factors, leading to the recommendation of different sets of decision making criteria [11–13].

When more than one criterion is relevant, multi-criteria decision analysis (MCDA) can be a good aid for decision-making. In MCDA, the influence of each criterion on the decision is defined along with its relative importance [14]. Although MCDA is not yet widespread in the context of coverage decisions, its use is becoming more frequent [15,16]. Indeed, MCDA is gaining recognition as a valuable tool to address complex decisions where multiple conflicting criteria, goals or objectives must be taken into account. MCDA provides opportunities for evaluation of process effects and non-health outcomes, in addition to the traditional Quality Adjusted Life Year (QALY) model. MCDA models can also provide physicians with more information on which to base their choice of treatment, helping to clarify which are the best therapies for patients [17].

One MCDA technique, the Discrete Choice Experiment (DCE) has become increasingly popular. The DCE technique can provide a basis of stated-preference information and indicate whether particular attributes are a predictor of choice over different scenarios, as well as the relative importance of the attributes used to describe the alternatives in choice sets [18]. DCEs are increasingly used in health economics to address a wide range of health policy-related concerns. Their scope of application is expanding in an increasing number of countries, with more sophisticated approaches to DCE design and analytical techniques apparently improving the quality of the final output [19]. The feasibility and acceptability of the DCE approach for the elicitation of general preferences to inform priority-setting in healthcare is supported by a growing body of evidence [18,20].

In the context of rare diseases, issues such as uncertainty, ethical dilemmas, and the difficulty in appraising related interventions, indicate that a MCDA based on an extended, holistic understanding of value is uniquely suited to guide decision-making. Such a framework could be used to set up a flexible platform that would respond to the issues that most strongly influence decision-making depending on the context. Thus, assume that having a decision-making framework beyond the Cost-QALY, one which includes more criteria in the decision-making process, will be fairer for rare diseases. The aim of this study is to pilot the elicitation of preferences from the perspective of decision-makers in European countries, in order to generate information useful for supporting decision-making processes that consider criteria beyond cost and QALY. Specifically, we explore the DCE framework by using forced-pair comparisons of two scenarios described by multiple criteria.

2. Methods

The DCE survey in this study was carried out in accordance with the methods used previously by Green and Gerard (2009) [18].

2.1. Attributes and levels

The selection of attributes (i.e. the features of the research objects in a DCE, in this case the criteria that influence distributive decisions) was based on a previously conducted systematic review of the empirical literature on distributive preferences [21], which aimed precisely at identifying attributes to design a DCE for rare diseases.

To select attributes for this study, a two-step approach was used. First, a list was created based on frequency of use as identified in the systematic review [21]; this list comprised seven attributes, including: improvement in health; cost of treatment; side effects; waiting time; severity of the disease; availability of other treatments; and value for money. The list was then discussed with methodological experts and healthcare decision-makers to confirm its validity. As a result, one more attribute was added: beginning of life (i.e. patients are younger than 10 years of age). Subsequently, a pilot test was carried out to determine the importance of each criterion relative to the others and create an attribute ranking in order to optimize the presentation of information during the DCE. Following another round of discussion with experts based on the pilot results, the final ranking of the eight attributes was created. Finally, a formal pilot study with 10 respondents was carried out to test the comprehensibility and usability of the survey tool used for the DCE, with positive results.

The selection of levels per attribute (i.e. the defined dimensions each criterion can take) was driven by two main considerations: preserving the number of attributes (as they were selected based on their importance in relevant decision-making processes) and ensuring the feasibility of the experimental design. More levels per attribute would require a bigger sample size to produce reliable results. By contrast, fewer levels would not capture the difference in preferences necessary for balanced decisions. The selected attributes and levels are shown in Table 1.

2.2. Experimental design

The design used an orthogonal, main-effects approach that included 36 pairs of scenarios distributed into two blocks of 18 pairs each. Each scenario described a combination of attributes and levels, with known efficiency, and it used fold-over copies to create the necessary subsequent choices in the choice set. In this design, it was assumed that interactions among attributes were insignificant in all two-way and higher-order interactions (see [18]). A blocking approach was selected to limit respondent burden and the design was evenly balanced across the blocks.

Respondents were asked to make a series of choices about the reimbursement of health technologies, involving two alternative healthcare scenarios (paired comparisons). The attributes and levels were presented as features of health technologies, and the respondents were asked to put themselves in the role of a decision-maker faced with difficult priority-setting decisions. Respondents had to select one of the two alternative scenarios in each choice set, based on the premise that the decision maker would not be able to fund all health technologies due to resource constraints. Fig. 1 shows an example of a survey question.

Table 1
Discrete choice experiment: attributes and levels.

Attribute	Description	Levels
Severity of the disease	Refers to the **pre-treatment health state of patients;** *the descriptive system of EQ-5D-5, a generic quality of life tool, was used; it spans the* following dimensions: mobility; self-care; performance of usual activities; extreme pain or discomfort; extreme anxiety or depression.	Moderate Severe
Improvement in health	Refers to the benefits that **the patient *feels following* treatment** along the five dimensions in the EQ-5D-5 L.	Large Moderate Small Very small
Waiting times	Refers to the time a patient must wait for treatment.	Short Moderate Long
Availability of other treatments	Refers to the existence of alternative treatments for the same disease.	Yes No
Side effects	Refers to the undesired effects caused by the treatment, as any medical treatment carries risks.	Few Moderate Many
Value for money	Refers to *how efficiently* National Health System resources *are used* (e.g., *doctor's* time, *hospital beds, drugs) and this* is based on t*he relationship* between the cost of treatment and *the* health benefits produced.	Very good Fairly good Fairly poor Very poor
Beginning of life	Refers to the age patients are diagnosed with the disease, *with particular* reference to diseases where the patients are younger than 10 years of age (children).	Yes No
Cost of treatment	Refers to the resources that must be mobilized to ensure financing the treatment. *For the purpose of the experiment, we assumed that the provision of care* is financed through general taxation (as in Spain; in reality, health systems financing is complex, varies substantially across countries and is often based on an insurance system), *and that* patients may be subject to co-payments *for* some treatments. If future treatments were to have higher costs, higher taxes and/or higher co-payments would be required for patients.	Zero Lower Moderate High

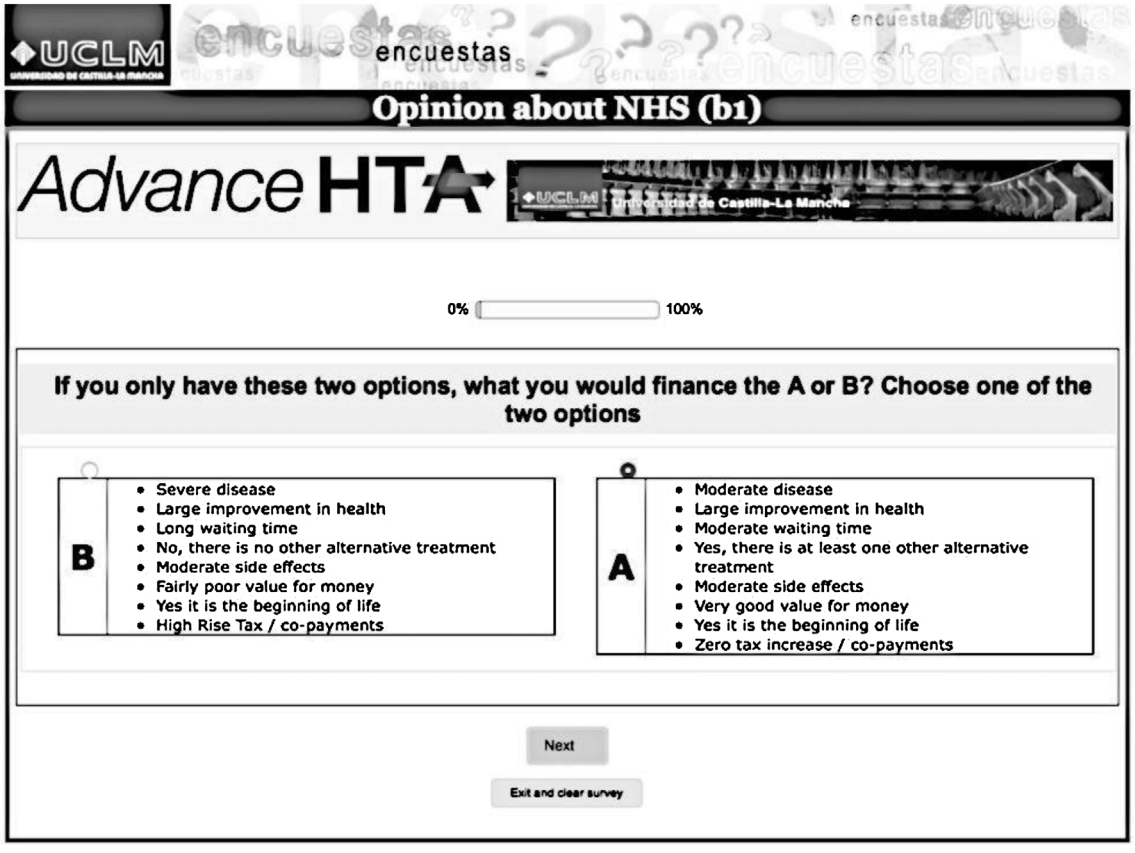

Fig. 1. An example of a survey question.

2.3. Data collection

We used an online questionnaire to conduct the DCE survey described above in five European countries (England, France, Germany, Italy and Spain). Partners of the EU-funded project Advance-HTA (see acknowledgements) were contacted to provide a list of technical experts in each country, including health care managers, clinicians and/or health economists, working in the private or public sector, with no political affiliation. Potential participants were then invited to participate in the survey by electronic mail. A maximal sample size was sought, with a minimum of 10 responses per country and per block to allow sufficient variance in

Table 2
Decision makers' characteristics by country.

	England n = 17	France n = 36	Germany n = 26	Italy n = 35	Spain n = 76
Sample size: Block 1	7	18	10	20	36
Sample size: Block 2	10	19	16	15	40
Mean age, mean (SD)	44 (13.62)	36.47 (12.22)	30.77 (7.91)	56.46 (8.74)	46.72 (9.77)
Household members, mean (SD)	2.53 (1.46)	1.39 (1.18)	2.19 (6.36)	2.43 (1.12)	3.3 (1.22)
Health status (%)					
Good	76.5	94.7	84.6	65.7	90.8
Average	23.5	5.3	7.7	34.3	9.2
Bad	0	0	7.7	0	0
Interview duration (seconds), mean (SD)	651.58 (398.4)	896.43 (578.61)	869.92 (834.38)	627.16 (581.87)	700.3 (408.16)
Task time (seconds), mean (SD)	33.9 (70.38)	46.02 (95.59)	45.15 (133.38)	32.81 (97.36)	35.54 (61.58)
Were the questions easy to understand (%)					
Agree	52.9	31.6	29.6	25.7	67.1
Somewhat agree	17.6	39.5	38.5	31.4	18.4
Indifferent	11.8	2.6	3.8	20	3.9
Somewhat disagree	17.6	23.7	11.5	17.1	7.9
Disagree	0	2.6	19.2	5.7	2.7
It was easy to choose the answer (%)					
Agree	23.5	18.4	7.7	20.0	28.9
Somewhat agree	5.9	21.1	11.5	37.1	28.9
Indifferent	29.4	7.9	15.4	14.3	11.8
Somewhat disagree	35.3	44.7	57.7	17.1	15.8
Disagree	5.9	7.9	7.7	11.4	14.5

the observed choice probabilities. This allows the probabilities to be at a minimum level to serve as prior information for subsequent efficient Bayesian designs.

2.4. Data analysis

Descriptive analysis was used to present the background characteristics of the respondents. Means and standard errors were used for continuous variables, and proportions for dichotomous variables. We have summarized the observed responses by pair and country using proportions and sample sizes. The DCE paired comparisons yielded binary choice data, with '1' representing the option being chosen and '0' the one not chosen. Conditional logit modelling was used to obtain relative weights.

In a DCE, utilities are not directly observable but have to be estimated. Following McFaden's framework, based on the random utility theory, estimations are based on the assumption that participants chose scenario A over scenario B, scenario A because it gave them a higher utility. Therefore, a conditional logistical model [22] can be applied and the coefficients of the model represent the relative weights of each level of each attribute, allowing for both the interpolation and extrapolation of utilities that have not been observed within the population. In other words, the coefficients of the model can be interpreted to denote the relative importance that the sample gave to the movement from the reference level for a given attribute to a different level. Given the codification of the levels by attribute (a = reference case, b = 1, c = 2 and so on), there could be positive and negative coefficients. For example, for the attribute related to the availability of treatment alternatives, the reference case (a) is "Yes", so that the coefficient of level b will show the change in the utility when moving from "Yes" to "No". In this case, we expect a positive coefficient; if there is no other existing treatment, the chance of being funded is higher. However, for the attribute related to disease onset at the beginning of life, the opposite is the case and we would expect a negative coefficient.

We applied an exclusion criterion for respondents who took 200 s or less to complete the survey to eliminate random (non-meaningful) responses. The number of respondents and the observed choice probabilities per country before and after exclusions can be found in Supplementary Table 1 (online appendix).

All statistical analyses were performed using STATA MP [23].

3. Results

A total of 199 questionnaires were completed. Of these, nine were excluded from the analysis in line with the exclusion criterion described above. Thus, the valid sample comprised 190 respondents, with the majority coming from Spain (76), followed by France (36), Italy (35), Germany (26) and England (17). Sample sizes by block mostly surpassed our expectations (>10 respondents). While only seven respondents completed block 1 in England, no respondents in that country were excluded from the analysis. The application of the exclusion criterion eliminated a higher share of respondents from Italy (6 out of 35) but did not have a big impact on the observed probabilities, indicating similar preferences between included and excluded respondents (Supplementary Table 1). The main characteristics of our sample are shown in Table 2. The mean time to complete each task was similar in England and Spain, while longer in Germany and France, and short in Italy.

The observed choice probabilities differed from country to country. In England, observed probabilities ranged from 0% to 100% whereas in Spain, they ranged from 38.9% to 69.4% (Supplementary Table 1). This means that different decisions would be made in Spain for a single scenario depending on who made the decision, while in England, there was better consensus on decisions. Responses from Germany and Italy showed a similar pattern to the Spanish, albeit in different scenarios.

The coefficients in Table 3 reflect the utilities related to the changes in each of the attribute levels relative to the reference case. For example, a health technology scenario with very good value for money has a greater level of utility (social value) than scenarios with fairly good or a fairly poor value for money, all else being equal. All the logit model coefficients showed similar patterns. Many coefficients are close to 0, which is due to the response of the model to the observed probabilities. The closer these probabilities are to 50%, the smaller the distance in the expected utility between the two options of the DCE. Since in Spain the probabilities are all close to 50%, the model obviously does not reflect any substantial preference (as there is none). However, the English models show the same relative preference for attributes. Improvement in health, value for money, cost of treatment and availability of other treatment are the attributes that received the most attention, while less important were severity of the disease, waiting times, beginning of life and side effects. Fig. 2 shows the observed choice probabilities and those predicted by the model for each country.

Table 3
Logit models, coefficients by country.

Criteria	Levels	Country				
		England	France	Germany	Italy	Spain
Severity of the disease	Severe	0.216	−0.057	−0.055	0.035	0.082
Improvement in health	Moderate	−0.626	0.294	0.153	0.264	0.047
	Small	−1.235	0.422	0.061	0.023	−0.081
	Very small	−2.804	−0.014	0.043	−0.344	0.012
Waiting times	Moderate	0.375	0.103	−0.206	0.158	−0.176
	Long	−0.259	−0.141	0.09	−0.123	−0.081
Availability of other treatment	No	0.766	0.347	0.044	0.06	−0.126
Side effects	Moderate	−0.419	−0.037	−0.039	−0.461	−0.009
	Many	−0.624	0.093	−0.032	0.261	0.043
Value for money	Fairly good	−0.799	−0.303	−0.034	0.053	−0.032
	Fairly poor	−0.663	0.269	0.08	0.161	0.023
	Very poor	−1.86	0.129	−0.117	0.115	−0.011
Beginning of life	No	−0.537	0.121	0.101	−0.048	−0.027
Cost of treatment[a]	Low	0.878	0.207	0.022	0.012	−0.027
	Moderate	0.018	−0.1	−0.023	−0.433	0.122
	High	−0.786	0.2	0.061	−0.029	0.045

Note: None of this coefficient was statistically significant; variance-covariance matrix of each model can be found as supplemental material of this manuscript.
[a] (measured by tax increase / co-payments).

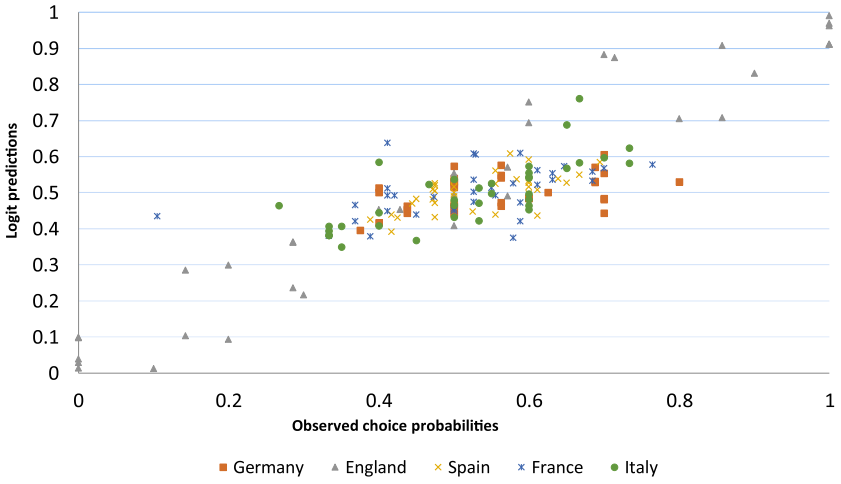

Fig. 2. Observed choice probabilities versus logit models prediction by country.

4. Discussion

When policy makers are involved in the exercise of priority-setting, they are often faced with difficult decisions between different options that may all be regarded as potentially beneficial. Policy debate about funding criteria for treatments in rare diseases is gaining importance. It is argued that society should not give up on the most severely ill individuals who need very specialised, often unaffordable treatments (orphan drugs) and who have no other treatment options available [24,25]. As treatments for rare diseases do not usually meet the cost-effectiveness thresholds used to evaluate new drugs, perhaps only a societal preference would justify granting exceptions to cost-effectiveness thresholds for orphan drugs. The DCE approach allows for individual preferences to be observed by adding criteria to the traditional cost per QALY models. Indeed, DCE outcomes may be more appropriate for demonstrating the relative importance of the attributes of a healthcare intervention than for predicting real choice.

In recent years, a number of frameworks have been published using MCDA to guide reimbursement decisions for orphan drugs [11,12,26] or aiming to support public policy on the funding of drugs for rare diseases [27–29]. Preference elicitation for the prioritization of healthcare interventions (including medicines) using DCEs has also been the subject of previous work [18,30,31]. Such approaches have the potential to be of use to health technology assessment bodies and payers [11]. Previous work has shown that DCE data can contribute to determining the strength of preferences between alternative scenarios in a priority setting context, adding to the sparse literature on 'social' preferences [18], and confirmed the importance of disease severity and treatment effectiveness as important dimensions shaping preferences for the public funding of medicines [30]. Furthermore, there is evidence to support that willingness to gain benefit despite increased risk increases as a function of disease severity, impairment or disability, and the absence of suitable therapies [31].

Here, preferences regarding the public funding of drugs to combat rare diseases were studied from the decision-maker's perspective. A pilot MCDA study with a DCE design was carried out to develop and apply a framework of weighted attributes that could serve to determine the value of orphan medicinal products. We consider it a pilot study, as it relied on a convenience sample of participants in five European countries. The principal motivation for this study was the absence of explicit, weighted value frameworks for the reimbursement of orphan drugs in the literature. DCEs for orphan drugs have mostly been used by health care payers attempting to prioritize options at a relatively high level. We are not aware that any health technology assessment (HTA) institutions or pricing and reimbursement authorities currently apply DCE methods.

The DCE method allows utility weights to be obtained from groups of decision-makers with homogeneous preferences; when preferences are heterogeneous, the method can fail. This was an issue in all countries participating in the study except for England, where it was only a minor concern. There could be two possible reasons for these results. First, many respondents may have completed the survey randomly in the other countries, but not in England. If this were true, the time spent completing the survey should be longer in England, on the assumption that a random response would be quicker than a meditated response. However, this was not the case. The second explanation appears more likely: it is possible that the strong tradition of HTA in England has led to a more defined role for certain criteria in decision-making compared to other countries. Therefore, decision-makers probably agree more often on how these criteria should be weighted. In other countries, where policies are not so clear (like Spain), each decision-maker may have different preferences, leading to different decisions for the same scenario when multiple decision-makers are involved at different levels (e.g. regions). This produces inconsistent model results, as the probabilities do not define clear rules to make a decision.

In terms of relative changes in utility (logit function) for the attribute levels, even taking into account the issues discussed above, the models for the five countries showed relative preferences for some attributes over others, with variability between countries.

The findings in this study are in line with earlier work from England, where face-to-face interviews were used on a sample from the general population, and where improvement in health and value for money were the attributes that provided the strongest indication of social value (preference) [18]. While our findings show that severity of disease, waiting times, onset of the condition early on in life and side effects remain relevant social values and should not be ignored, they also confirm that cost of the treatment, improvement in health, value for money and the availability of treatment alternatives can provide a strong indication of the social value (preference) associated with a healthcare intervention in many instances.

This study has a number of limitations. The experimental design is not based on prior information. The implementation of the small orthogonal design induced multicollinearity of at least one parameter for each model. A larger number of choice sets per respondent could have increased granularity but also task complexity; an optimal study design would need to further balance these two dimensions. The results presented here are based on a simple analytical framework, using the conditional logistic model. We consider this sufficient, as it was not the aim of this study to establish a definitive framework but rather to generate the prior information necessary to inform future Bayesian designs. A further limitation is the absence of objective data on non-random responses in the sample due to the internet-based nature of the survey. Based on the relatively short times some respondents took to complete the survey, we cannot be confident about the quality of all responses. However, there is no validated method to address this issue; we attempted to correct resulting bias by excluding responses completed in very short times from the analysis. Additionally, the sample used may not provide a good representation of the perspective of decision-makers in the five countries. As this is a pilot study, we were satisfied with being able to infer even a degree of generalisability of the findings.

Overall, we are convinced that our results are useful and indicative of what may be possible in future research of this type. The application of flexible and better adapted DCE designs and econometric methods is being reinforced through the enhanced use of qualitative methods to complement the DCE process. However, qualitative research is employed less frequently to drive attribute selection, potentially introducing a bias in DCEs through the omission of variables if the decision framework is not defined prior to performing the research. The attributes employed to design this study appear to be important, yet this does not exclude the use of other attributes in similar future studies. In future work, it would be important to consider the use of face-to-face interviews and other qualitative methods (interviewer-administered DCEs), which could provide more information on the interpretation of attributes, better insight on how choices are made and a stronger incentive for thoughtful engagement in the research.

Continued prioritisation of rare diseases by policy makers is recommended by some to drive continued development of orphan drugs, along with better alignment of payers and regulatory frameworks, value-based pricing and instruments that favour long-term economic sustainability. These recommendations also point to the need to establish more coherent frameworks and to encourage interactions between all stakeholders, including research-based industry, clinicians, payers, patients and patient associations [10]. While we sought to use a simple design, our study confirms the feasibility of similar exercises and these preliminary findings can be used to set up more detailed studies in the future to serve this purpose. Case studies could be conducted to test the approach empirically, by applying the logit coefficients of the attributes in this study to drugs for specific conditions (e.g. spinal muscular atrophy).

5. Conclusions

Our results suggest that a "beyond Cost-QALY" framework could be created by using DCEs, especially to support "fair play" in the decision-making process for rare diseases. However, our research also highlights that a number of methodological aspects still need to be considered in order to design an appropriate experiment, particularly regarding the use of face-to-face interviews instead of online surveys. The insights gained from this work could be useful for the design of future research following similar approaches.

Funding

This research was funded by the European Commission's FP7 Framework Programme and was undertaken under the auspices of Advance-HTA (Grant number 305983). The results presented here reflect the author's views and not the views of the European Commission. The European Commission is not liable for any use of the information communicated.

Conflict of interest statement

The author(s) have no conflict of interests to declare.

Acknowledgements

We would like to thank Domenica Taruscio and Armando Magrelli at the Istituto Superiore di Sanita (National Centre for Rare Diseases), Isabelle Durand-Zaleski at Université Paris Est Créteil and Sabine Fuchs at the Technische Universität Berlin for helping the authors to contact stakeholders so that they may complete the questionnaire.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.healthpol.2018.11.015.

References

[1] Institute of Medicine of the National Academies (IMNA). Rare diseases and orphan products. Accelerating research and development. The National Academies Press; 2010.
[2] European Commission (EC). Improving access to orphan medicines for all affected EU citizens; 2004.
[3] López-Bastida J, Oliva-Moreno J, Linertová R, Serrano-Aguilar P. Social/economic costs and health-related quality of life in patients with rare diseases in Europe. The European Journal of Health Economics 2016;17:1–5.
[4] Cheung RY, Cohen JC, Illingworth P. Orphan drug policies: implications for the United States, Canada, and developing countries. Health Law Journal 2004;12:183–200.
[5] Dear JW, Lilitkarntakul P, Webb DJ. Are rare diseases still orphans or happily adopted? The challenges of developing and using orphan medicinal products. British Journal of Clinical Pharmacology 2006;62:264–71.
[6] Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. International Journal of Technology Assessment in Health Care 2007;23:36–42.
[7] Cookson R, Dolan P. Public views on health care rationing: a group discussion study. Health Policy 1999;49:63–74.
[8] Dolan P, Shaw R, Tsuchiya A, Williams A. QALY maximisation and people's preferences: a methodological review of the literature. Health Economy 2005;14:197–208.
[9] Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet Journal of Rare Diseases 2011;6:42.
[10] Gutierrez L, Patris J, Hutchings A, Cowell W. Principles for consistent value assessment and sustainable funding of orphan drugs in Europe. Orphanet Journal of Rare Diseases 2015;10:53.
[11] Sussex J, Rollet P, Garau M, Schmitt C, Kent A, Hutchings A. A pilot study of multicriteria decision analysis for valuing orphan medicines. Value Health 2013;16:1163–9.
[12] Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? Orphanet Journal of Rare Diseases 2012;7:74.
[13] Paulden M, Stafinski T, Menon D, McCabe C. Value-based reimbursement decisions for orphan drugs: a scoping review and decision framework. Pharmacoeconomics 2015;33:255–69.
[14] Devlin NJ, Sussex J. Incorporating multiple criteria in HTA – methods and processes. London: Office of Health Economics 2011.
[15] Postmus D, Tervonen T, van Valkenhoef G, Hillege HL, Buskens E. A multi-criteria decision analysis perspective on the health economic evaluation of medical interventions. The European Journal of Health Economics 2014;15:709–16.
[16] Thokala P, Duenas A. Multiple criteria decision analysis for health technology assessment. Value Health 2012;15:1172–81.
[17] Migliore A, Integlia D, Bizzi E, Piaggio T. Is it the time to rethink clinical decision-making strategies? From a single clinical outcome evaluation to a Clinical Multi-criteria Decision Assessment (CMDA). Medical Hypotheses 2015;85:433–40.
[18] Green C, Gerard K. Exploring the social value of health-care interventions: a stated preference discrete choice experiment. Health Economy 2009;18:951–76.
[19] Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in health economics: a review of the literature. Pharmacoeconomics 2014;32:883–902.
[20] Krabbe PF, Devlin NJ, Stolk EA, Shah KK, Oppe M, van Hout B, et al. Multinational evidence of the applicability and robustness of discrete choice modeling for deriving EQ-5D-5L health-state values. Medical Care 2014;52:935–43.
[21] Trapero-Bertrán M, Rodriguez-Martin B, Lopez-Bastida J. Which attributes should include a Discrete Choice Experiment for rare diseases: a systematic literature review. XXXV Jornadas de Economia de la Salud 2015. Granada, Spain.
[22] McFadden D. Conditional logit analysis of qualitative choice behavior. In: Zarembka P, editor. Frontriers in econometrics. New York: Academic Press; 1974.
[23] StataCorp. Stata statistical software: release 14. Texas: StataCorp LP; 2015.
[24] Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? QJM: Monthly Journal of the Association of Physicians 2005;98:829–36.
[25] NICE Citizens Council. NICE citizens council report: ultra orphan drugs. London: National Institute for Health and Clinical Excellence; 2004.
[26] Kolasa K, Zwolinski KM, Kalo Z, Hermanowski T. Potential impact of the implementation of multiple-criteria decision analysis (MCDA) on the Polish pricing and reimbursement process of orphan drugs. Orphanet Journal of Rare Diseases 2016;11:23.
[27] Mycka J, Dellamano R, Lobb W, Dellamano L, Dalal N. Orphan drugs assessment in Germany: a comparison with other international HTA agencies. Value Health 2015;18:A550–1.
[28] Nicod E. Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries. The European Journal of Health Economics 2017;18:715–30.
[29] Winquist E, Bell CM, Clarke JT, Evans G, Martin J, Sabharwal M, et al. An evaluation framework for funding drugs for rare diseases. Value Health 2012;15:982–6.
[30] Mentzakis E, Stefanowska P, Hurley J. A discrete choice experiment investigating preferences for funding drugs used to treat orphan diseases: an exploratory study. Health Economics, Policy, and Law 2011;6:405–33.
[31] Morel T, Ayme S, Cassiman D, Simoens S, Morgan M, Vandebroek M. Quantifying benefit-risk preferences for new medicines in rare disease patients and caregivers. Orphanet Journal of Rare Diseases 2016;11:70.