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Societal preferences for granting orphan drugs special status in reimbursement decisions

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ABSTRACT

Background: Orphan drugs, for patients with a rare disease, are increasingly available but often do not meet standard cost-effectiveness criteria for reimbursement. Consequently, policymakers regularly face the dilemma whether to relax these criteria for reimbursing orphan drugs. We examined whether—and why—there would be societal support for such differential treatment of orphan drugs.

Methods: We conducted a labelled discrete choice experiment in a sample of the adult population (n = 1,172) in the Netherlands. Respondents were presented with ten choices on whether to reimburse an orphan drug given that a non-orphan drug with similar characteristics would not be reimbursed, because it was not cost-effective, and asked to explain their choices. We used random-intercept logit regression models and inductive coding for analysing the quantitative and qualitative data.

Results: Of the respondents, 36.4% consistently chose *for* reimbursing the orphan drug, mostly because "everyone is entitled to live a healthy life and good quality healthcare", and 17.3% consistently for *not* reimbursing the orphan drug, mostly because "[this] is unfair to patients with a common disease". The remaining 46.3% made alternating choices and were more likely to choose *for* reimbursing orphan drugs when patients were aged between 1 and 70 years, had moderate disease severity, and considerable health gain from treatment.

Conclusions: This study finds considerable support but also strong preference heterogeneity amongst members of the public in the Netherlands for differential treatment of orphan drugs in reimbursement decisions, when these drugs do not meet common cost-effectiveness criteria. However, a substantial minority opposes differential treatment, mostly on moral grounds.

Introduction

Orphan drugs are pharmaceuticals indicated for the diagnosis, prevention, or treatment of patients with a rare disease. The definition of 'rare disease' is not universal. It is often based on the prevalence of the disease, but—depending on (supra-) national legislation and policy—may also account for the severity of the disease and the (limited) availability of alternative treatment options for patients [1]. For example, in the United States a rare disease is defined as "any disease or condition that affects fewer than 200,000 (or ~6 per 10,000) people" [2] and in the European Union as "a life-threatening, seriously debilitating or serious and chronic condition that may not affect more than 5 per 10,000 people" [3].

The number of available orphan drugs has increased considerably following legislation introduced that counteracts the lack of incentives for researching and developing new drugs for patients with a rare disease [4,5]. When available, the markets for orphan drugs tend to be small, often leading to claims from manufacturers that high prices are required to generate sufficient returns on investments [4]. Orphan drugs generally are more expensive than non-orphan drugs and often do not meet standard cost-effectiveness criteria for reimbursement from public funding [4,6,7]. Consequently, policymakers are regularly faced with the dilemma whether to grant orphan drugs special status, for example, by relaxing the cost-effectiveness criteria that apply to non-orphan drugs [6,8,9]. The reasons for such differential treatment of orphan drugs can be diverse and may, for example, include addressing an unmet need of patients with a rare disease and giving these patients access to a new drug to which they—like patients with a common disease—should be

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entitled [8]. Furthermore, the financial risk of reimbursing an orphan drug may be considered small because of the limited budget impact that is (often) associated with reimbursing a new drug for a small patient group [8].

We identified 18 studies that investigated societal support for granting orphan drugs special status in hypothetical reimbursement decisions [6,10–26]. All these studies elicited preferences in scenarios that described a decision-making context in which the healthcare budget is limited, and the opportunity costs of reimbursement are known. In these studies, members of the public were asked to choose (or to divide a budget) between treatments for patients with a rare disease and for patients with a common disease that competed for reimbursement [6, 10–26]. The results of these studies indicate that societal support for differential treatment of orphan drugs may be limited, at least when it is made explicit that reimbursing the orphan drug comes at the cost of not reimbursing a non-orphan drug.

The objective of the current study was to provide further insight into the societal support in the Netherlands for differential treatment of orphan drugs in reimbursement decisions. These decisions are commonly informed based on the assessment and appraisal of evidence regarding the necessity (operationalized as disease severity [27]), effectiveness, cost-effectiveness, and feasibility (including the budget impact) of (reimbursing) a new pharmaceutical—usually for a single medical indication [28]. To meet the objective of the current study, we designed a labelled discrete choice experiment (DCE) with hypothetical scenarios that aimed to resemble the actual decision-making context of policymakers. That is, we elicited preferences of members of the public for reimbursing an orphan drug that was not cost-effective, given the circumstance that a non-orphan drug with similar characteristics would not be reimbursed. This presented them with the choice of treating the orphan drug similarly (i.e., also not reimburse it) or differently (i.e., reimburse it) from the non-orphan drug in the decision-making process. Furthermore, we examined the main reasons of members of the public for (not) reimbursing the orphan drug, and which circumstances (described based on patient, disease, and treatment characteristics) affect societal support for reimbursing the orphan drug. The results of this study may inform specific reimbursement decisions as well as general policies on reimbursement of orphan drugs from public funding.

Methods

Discrete choice experiment

In DCEs, respondents are often asked to make discrete choices for one out of two (or more) alternatives that are described in terms of relevant attributes and levels [29]. In the current study, we asked respondents to make discrete choices for reimbursing an orphan drug from public funding in the Netherlands (yes/no)—given the circumstance that a non-orphan drug with otherwise similar characteristics would not be reimbursed because it was not cost-effective. The patient group for which the orphan drug was indicated was labelled as having "a rare disease" and the group for which the similar, non-orphan drug was indicated was labelled as having "a common disease". The circumstances were identical for the orphan and non-orphan drug regarding the age of patients, disease severity, health gains from treatment, and level of cost-effectiveness. However, they were different regarding the number of patients and, consequently, the health-insurance premium increase and budget impact associated with reimbursement (Supplementary Information S1 includes example choice tasks presented to respondents in version A and B of the questionnaire).

We assessed whether respondents' choices for (not) reimbursing the new drug for patients with a rare disease resulted from preferences regarding the rarity of the disease or the budget impact of reimbursement by randomly assigning them to one of two questionnaire versions (labelled A and B). These versions were identical (see subsection 2.4), except for the labels that we used in the choice tasks and the order in which we introduced the labels to respondents, along with the attributes and levels (see subsection 2.2). In version A, the labels referred to the type of disease (i.e., common or rare disease) and we introduced these labels first and the budget impact of reimbursement last. In version B, the labels referred to the budget impact of reimbursement (i.e., 2 billion or 10 million euros) and we introduced these labels first and the type of disease last. Following random utility theory, we assumed that in each choice task respondents would choose the option that maximized their individual utility, and that the utility function could be decomposed into a systematic component associated with the labels, attributes and levels, and a random component [30]. We anticipated that a majority of respondents would be of the opinion that patients with a rare disease have an "equal right to treatment" as patients with a common disease [31], and hence would consistently choose for (not) reimbursing the orphan drug. We asked respondents to explain their main reason for their choices after they completed the choice tasks.

Attributes and levels

To identify relevant attributes for this DCE, we reviewed the empirical literature on societal support for granting orphan drugs special status [6,10–26] and for prioritising treatments based on patient, disease, and treatment characteristics [32–34]. In addition, we inspected recent policy reports on reimbursing orphan drugs in the Netherlands [35,36]. Based on this literature, we selected the attributes patients' age, disease severity, and health gains from treatment as relevant for preferences for reimbursement. The levels for the attributes were determined on the basis that they would enable us to (i) examine preferences in hypothetical reimbursement scenarios that resembled the actual decision context of policymakers, also in terms of patient, disease, and treatment characteristics, (ii) compare our results to those of the reviewed studies, and (iii) predict under which circumstances (regarding patients' age, disease severity, and health gains from treatment) societal support for reimbursing the orphan drug will be more or less likely, given that a similar, non-orphan drug would not be reimbursed.

Table 1 presents an overview of the labels (see subsection 2.1), attributes, and levels.

We used Ngene version 1.2.1 (ChoiceMetrics, 2018) to construct a Bayesian D-efficient design with informed priors, consisting of 40 choice tasks. The design was divided into four blocks while retaining level balance, so that each block consisted of ten choice tasks.

Table 1
Overview of labels, attributes, and levels.

Labels	Attributes[a]	Levels	
Type of disease		Common disease	Rare disease
	Number of patients	10,000 patients	50 patients
	Age (in years)	1; 10; 40;70	
	QOL before treatment (in points on VAS)	20; 40; 60; 80	
	LE before treatment (in years)	1; 5; 10; 15	
	QOL gain (in points on VAS)	10; 20	
	LE gain (in years)	1; 5; 10; 15	
	Treatment costs per patient (in € per year)	200,000	
	Health-insurance premium increase (in € per month)	11.90	0.06
Budget impact (in € per year)		2 billion	10 million

LE, life expectancy; QOL, quality of life; VAS, visual analogue scale (ranging from 0 "worst health you can imagine" to 100 "best health you can imagine").
[a] Number of patients and health-insurance premium increase were fixed across choice tasks. The latter attribute applied to all adult (18+) inhabitants in the Netherlands and was calculated as (number of patients * treatment costs per patient / 4000,000 adult inhabitants / 12 months).

Sample and data collection

The DCE was administered online by a professional sampling agency. Respondents were quota sampled to be representative of the adult population of the Netherlands by age (18–75 years), sex, and education level. Before conducting the main study in December 2020, we conducted a pilot study ($n = 300$) to assess the clarity of the labels, attributes, levels, and choice tasks and to obtain prior estimates for optimising the DCE design for the main study ($n = 872$). The pilot results did not lead to any modifications to the questionnaire, and hence we pooled the pilot and main data (total sample $n = 1{,}172$) for the analyses.

Before respondents completed the questionnaire, we explained that healthcare resources are scarce and that policymakers use different sources of information for deciding on the reimbursement of a new drug such as (cost-) effectiveness and societal preferences. Next, we explained that this study focused on societal preferences for the reimbursement of new drugs for patients with a rare disease and for patients with a common disease. After respondents completed the questionnaire, they received a participation fee of €2.30 that they could save in a personal deposit or donate to a charity of choice. We obtained approval for conducting this study from the Research Ethics Review Committee of the Erasmus School of Health Policy & Management (reference: 20–33 Reckers-Droog).

Questionnaire

The questionnaire consisted of five parts. In part one, we introduced and, as such, sensitised respondents to reimbursement decisions in the collectively funded healthcare system of the Netherlands, by asking them to indicate their current health-insurance premium (in € per month) and level of agreement (on a seven-point Likert scale ranging from 1 "strongly disagree" to 7 "strongly agree", with a score of 4 indicating "neither disagree nor agree") with 15 general statements on arguments that may be deemed relevant in reimbursement decisions in the Netherlands (Supplementary Information S2 includes an overview of the statements and respondents' mean (SD) level of agreement with each of them). In part two, we introduced respondents in three steps to the labels, attributes, levels, and choice tasks used in the DCE. Each step included a practice choice task that built up in complexity to the eventual choice task. After the third step, we asked respondents to assess the level of clarity of the labels, attributes, levels, and choice tasks (on a seven-point Likert scale (ranging from 1 "very unclear" to 7 "very clear", with a score of 4 indicating "neither unclear nor clear"). In part three, we asked respondents to complete ten choice tasks and, in part four, we asked them to explain the main reason for their choices whether to reimburse the orphan drug. In the final part of the questionnaire, we asked respondents about their socio-demographic characteristics.

Data analysis

First, we identified three subgroups of respondents; those who made (1) consistent choices *for* reimbursing the orphan drug, (2) consistent choices for *not* reimbursing it, or (3) alternating choices for (not) reimbursing it—given that a similar drug would not be reimbursed for patients with a common disease.

We then used a two-step procedure for analysing the choice data. In step one, we assessed the impact of the attributes and levels on the preferences of subgroup 3 (i.e., those who made alternating choices) using a random-intercept logit regression model. The model took into account that choices were nested and that some respondents might be more inclined to choose for reimbursing the drug for patients with a rare disease than others, independent from the attributes and levels presented in the choice tasks. We assumed a normal distribution for the random intercept and used dummy coding for the attribute levels. In step 2, we used the regression results to predict the proportion of respondents who would likely support reimbursement under three reimbursement scenarios, labelled typical, high support and low support. We constructed the typical scenario based on patient, disease, and treatment characteristics that, by approximation, corresponded with those described in the policy reports on the reimbursement of orphan drugs in the Netherlands [35,36]. This scenario described a group of patients aged 10 years, with a health-related quality of life (QOL) of 20 points (on a visual analogue scale ranging from 0 "worst health you can imagine" to 100 "best health you can imagine") and a life expectancy (LE) of 10 years *before* treatment, and a QOL gain of 10 points and LE gain of 1 year *from* treatment. The high (low) support scenario was constructed based on the patient, disease, and treatment characteristics that were associated with the highest (lowest) coefficient estimates obtained in the previous step, respectively. We estimated the total level of support for reimbursing the orphan drug in the three scenarios by combining the observed proportion of respondents in subgroup 1 (i.e., those who made consistent choices *for* reimbursement)—under the assumption that these respondents would also choose for reimbursing the orphan drug in these three scenarios—with the estimated proportion of respondents within subgroup 3 (i.e., those who made alternating choices) who would likely choose *for* reimbursing the orphan drug in the three scenarios. We estimated the latter as the average of 1,000 predicted probabilities, each with a different random intercept. We also followed the two-step procedure for versions A and B of the questionnaire (see Box 1) separately to assess the impact of the labels 'type of disease' and 'budget impact' on the level of support in the three scenarios. We obtained 95% confidence intervals (CIs) for the predicted levels of support by bootstrapping the two-step procedure in 2,000 iterations. Finally, we examined the robustness of these results by repeating the two-step procedure while *excluding* respondents who reported a low clarity score for the labels, attributes, levels, and choice tasks (<4 on the seven-point Likert scale) and *including* respondents who made consistent choices for (not) reimbursing the orphan drug (results included as Supplementary Information S3). Note that the former subgroup was included, and the latter was excluded from the principal analysis.

We used inductive coding for analysing the main reasons that respondents provided to explain their choices. We first coded the main reason provided by each respondent. Then, we clustered the codes into categories and overarching themes and selected illustrative quotes, which we translated from Dutch into English. We interpreted the categories and themes making use of descriptive and explanatory accounts [37] that provided insight into the range and diversity of the reasons underlying respondents' choices. We estimated the proportions of respondents whose main reason fell into the developed themes and categories, and then explored differences in reasons provided by respondents in versions A and B of the questionnaire. Furthermore, we explored differences in reasons provided by respondents who made consistent choices and respondents who made alternating choices for (not) reimbursing the orphan drug (results included as Supplementary Information S4).

We used Stata 17.0 (Stata Corp LP, College station, Texas) to perform the analyses.

Results

Table 2 presents the descriptive statistics of the sample ($n = 1{,}172$) and the reference population in the Netherlands for age, sex, and education level. The statistics indicate that our sample was representative for the general population in terms of sex but was slightly older and higher educated.

Of the respondents, 632 (53.9%) completed version A and 540 (46.1%) completed version B of the questionnaire. The mean (SD) clarity score for the labels, attributes, levels, and choice tasks was 5.4 (1.4) on the seven-point Likert scale and 109 respondents (9.3%) reported a score <4.

Table 3 presents the observed proportions of respondents who made

Table 2
Sample characteristics (n = 1,172).

	Sample		General public	
	%	Mean (SD)	%	Mean
Age (Years)		48.7 (16.4)		46.3
Sex (Female)	50.6		50.3	
Education level[c]				
Low	5.4		7.8	
Medium	64.6		56.4	
High	30.0		34.2	
Unknown	0.0		1.6	
Household income (€ after tax)				
<€1,999	22.9			
€2,000 – €3,999	41.3			
≥€4,000	15.8			
NS	20.0			
Children (Yes)	59.5			
QOL (0–100 VAS)		74.9 (21.7)		

DCE, discrete choice experiment; NS, not stated; QOL, health-related quality of life; VAS, visual analogue scale (ranging from 0 "worst health you can imagine" to 100 "best health you can imagine").
[b] Age is based on statistics for population aged 18–75 years, sex is based on statistics for the overall population, and education level is based on statistics for population aged 15–75 years. Population statistics for 2020, source: Statistics Netherlands (https://opendata.cbs.nl/statline).
[c] Low = lower vocational and primary school, Medium = middle vocational and secondary school, High = higher vocational and academic education.

Table 3
Observed proportions of respondents who made consistent or alternating choices, in n (% of total).

			Questionnaire	
(#)	Subgroup	Total (n = 1,172)	Version A (n = 632)	Version B (n = 540)
1	Consistent choices *for* reimbursing orphan drug	427 (36.4)	213 (33.7)	214 (39.6)
2	Consistent choices for *not* reimbursing orphan drug	203 (17.3)	136 (21.5)	67 (12.4)
3	Alternating choices	542 (46.3)	283 (44.8)	259 (48.0)

consistent or alternating choices for (not) reimbursing the drug for patients with a rare disease—given that a similar drug would not be reimbursed for patients with a common disease. Of the respondents, 427 (36.4%) made consistent choices *for* reimbursing the orphan drug and 203 (17.3%) made consistent choices for *not* reimbursing it. The remaining 542 (46.3%) made alternating choices. In version A (where the labels referred to the type of disease), a smaller proportion of respondents made consistent choices for reimbursing the orphan drug than in version B (where the labels referred to the budget impact of reimbursement), while a larger proportion made consistent choices for not reimbursing the drug.

Table 4 presents the regression results for respondents who made alternating choices for (not) reimbursing the orphan drug. The results indicate that these respondents were more likely to choose for reimbursing the drug when patients with a rare disease were aged between 1 and 70 years, and when their QOL or LE *before* treatment was higher (i.e., when their disease severity was lower). These respondents were also more likely to choose for reimbursing the orphan drug when the health gains *from* treatment, particularly the LE gains, were larger.

The results included as Supplementary Information S3 indicate that there was little difference in preferences between versions A and B of the questionnaire (Table S3.1). The direction and size of the coefficients were similar between the two versions, except for smaller coefficients for QOL before treatment and larger coefficients for QOL gains in Version A. The variances of the random intercepts indicate considerable preference heterogeneity in both versions. The results of the sensitivity analysis—using a sample *excluding* respondents who reported a low clarity score for the labels, attributes, levels, and choice tasks and a sample *including* respondents who made consistent choices (i.e., the total sample)—show that the direction and size of the coefficients are robust to different subsets of the data (Table S3.2). The results further indicate that respondents were less likely to choose for reimbursing the orphan drug in version A than in version B of the questionnaire.

Table 4
Regression results of respondents with alternating preferences (n = 542).

DV: reimburse orphan drug yes/no		B (SE)	95% CI
Age (in years)	1	–	–
	10	0.30 (0.09)	0.12; 0.48
	40	0.19 (0.09)	0.00; 0.37
	70	−0.48 (0.10)	−0.68; −0.29
QOL before treatment (in points on VAS)	80	–	–
	60	0.09 (0.09)	−0.10; 0.27
	40	−0.20 (0.09)	−0.37; −0.02
	20	−0.36 (0.09)	−0.54; −0.17
LE before treatment (in years)	15	–	–
	10	−0.13 (0.11)	−0.34; 0.08
	5	−0.10 (0.11)	−0.32; 0.12
	1	−0.34 (0.09)	−0.51; −0.17
QOL gain (in points on VAS)	10	–	–
	20	0.13 (0.06)	0.01; 0.25
LE gain (in years)	1	–	–
	5	0.89 (0.09)	0.70; 1.07
	10	1.02 (0.10)	0.82; 1.23
	15	1.26 (0.10)	1.06; 1.46
Questionnaire version	A	–	–
	B	0.09 (0.09)	−0.09; 0.27
Random intercept		−0.19 (0.13)	−0.44; 0.07
Variance of random intercept		0.63 (0.08)	0.50; 0.81

Table 5 presents the predicted level of support for reimbursing the orphan drug in the typical, high support, and low support reimbursement scenarios based on the regression coefficients from Table 4. The predicted levels of support ranged from 44.1% in the low support scenario (Version A) to 78.8% in the high support scenario (Version B), while support for reimbursing the orphan drug in the typical scenario lies somewhere in the middle. In all three scenarios, the level of support for reimbursing the orphan drug was higher in version B than in version A of the questionnaire. The results of the sensitivity analysis—using a sample *excluding* respondents who reported a low clarity score for the labels, attributes, levels, and choice tasks and a sample *including* respondents who made consistent choices (i.e., the total sample)—show that the predicted levels of support in the three scenarios are robust to different subsets of the choice data (Table S3.3).

Table 6 presents an overview and descriptions of the 6 themes and 17 categories that we developed based on the inductive coding and clustering of the main reasons respondents provided to explain their preferences. The table further presents the proportions of respondents by theme and category for the total sample and for versions A and B of the questionnaire separately.

The results indicate that treatment characteristics, particularly the size and type of health gains (category C.1), were considered most relevant by the largest proportion of respondents (35.2% of total sample) and disease characteristics, particularly the cause of illness (category B.4), by the smallest proportion of respondents (6.1% of total sample). The reasons underlying respondents' preferences were similar in versions A and B of the questionnaire, except for the relevance of moral arguments, particularly those regarding uniform decision-making (category D.2). In version A (where labels referred to the type of disease), this was considered most relevant by twice as many respondents (14.9% vs 7.4% of total sample) than in version B (where labels referred to the budget impact of reimbursement). The results included as Supplementary Information S4 (Table S4.1) indicate some differences between the main reasons provided by respondents who made consistent choices *for* reimbursing the orphan drug (i.e., subgroup 1), consistent choices for *not* reimbursing the orphan drug (i.e., subgroup 2), or

Table 5
Predicted level of support for reimbursing the orphan drugs in% (95% CI).

Scenario	Charactistics					Questionnaire	
	Age (in years)	QOL before treatment (in points on VAS)	LE before treatment (in years)	QOL gain (in points on VAS)	LE gain (in years)	Version A % (95% CI)	Version B % (95% CI)
Typical	10	20	10	10	1	52.5 (48.3; 56.8)	60.7 (56.3; 65.0)
High support	10	60	15	20	15	69.7 (65.9; 73.2)	78.8 (75.3; 82.2)
Low support	70	20	1	10	1	44.1 (40.1; 48.0)	51.4 (47.3; 55.6)

alternating choices for (not) reimbursing the orphan drug (i.e., subgroup 3). Respondents who made consistent choices *for* reimbursing the orphan drug more often considered perceived entitlements, particularly those regarding health and healthcare (category E.1), most relevant for deciding on reimbursing the orphan drug (36.1% vs. 15.4% of total sample; see Table 6). Respondents who made consistent choices for *not* reimbursing the orphan drug more often considered moral arguments, particularly regarding uniform decision-making (category D.2), most relevant (60.1% vs. 11.4% of total sample). Finally, respondents who made alternating choices more often considered patient characteristics, i.e., their age (category A.1), and treatment characteristics, particularly the size and type of health gains (category C.1), most relevant (14.4% vs. 6.8% and 41.0% vs. 20.2%, respectively).

Discussion

The objective of this study was to provide insight into societal support in the Netherlands for granting orphan drugs special status in reimbursement decisions. To meet this objective, we elicited the preferences of members of the public for reimbursing an orphan drug—given that a similar, non-orphan drug would not be reimbursed because it was not cost-effective.

Our main findings indicate that a considerable part of the public likely supports such differential treatment of orphan drugs. Of the respondents, 36.4% made consistent choices *for* reimbursing the orphan drug and 17.3% made consistent choices for *not* reimbursing the drug. The remaining 46.3% made alternating choices and were more likely to prefer reimbursement when patients were aged between 1 and 70 years, had moderate disease severity, and considerable health gains from treatment. The predicted level of support for reimbursing the orphan drug ranged between 44.1% in the low support scenario and 78.8% in the high support scenario. Treatment characteristics (particularly the size and type of health gains) were considered most relevant by the largest proportion of respondents, while disease characteristics (particularly regarding the cause of illness) were considered most relevant by the smallest proportion of respondents. Few respondents ($n = 2$, not in table) considered the rarity of the disease most relevant for deciding on reimbursing the orphan drug.

Our main findings further indicate that respondents were more likely to choose *for* reimbursing the orphan drug when the labels of the choice tasks referred to the budget impact of reimbursement (in version B of the questionnaire) than when they referred to the type of disease (in version A). The finding that public support for reimbursing an orphan drug that is not cost-effective may depend on how 'rarity' is framed in decisions (e.g., in terms of prevalence of budget impact) raises the question what normative conclusion can be drawn in relation to future value assessments in this context. Further research is warranted to examine the answer to this question from various (stakeholder) perspectives. Further research is also warranted to examine the robustness of this 'framing effect' in relation to different levels of health-insurance premium increase and budget impact, particularly following multiple decisions on reimbursing (different) orphan drugs.

Our finding that a considerable part of the public would likely support reimbursing an orphan drug—given that a similar, non-orphan drug would not be reimbursed—is not in accordance with the findings of previous studies, which suggested that such support may be limited [6, 10–26]. This difference in findings may be explained by the difference in decision-making context that was outlined to respondents in the choice tasks. However, in accordance with the findings of previous studies, we find that there may not be "something special" about orphan drugs as societal support for differential treatment in reimbursement decisions did not result from considerations regarding the rarity of the disease. Rather, considerations regarding, for example, patient characteristics (i.e., their age), treatment characteristics (e.g., the size and type of health gains), and the limited budget impact that may be associated with their reimbursement were relevant for societal support. Furthermore, in accordance with the findings of previous studies, we find that preferences are heterogeneous. Indeed, a substantial minority of the public did not support reimbursing an orphan drug when a similar, non-orphan drug was not reimbursed. Perhaps counterintuitively, we found lower societal support for differential treatment of orphan drugs when patients with a rare disease are more severely ill [33,38]. This finding is at odds with reimbursement policies in countries such as England and Wales [9], Norway [39], Sweden [40], and the Netherlands [41], which prioritise more severely ill patients in reimbursement decisions. Nonetheless, this finding is not uncommon and was reported before, for example, in studies examining societal support for reimbursing a new treatment for patients at the end of life or with an undesirable end point after treatment (e.g. [42–44]). Finally, our findings are in accordance with those of other studies suggesting that societal support for reimbursing a new treatment may be lower when patients are older and when health gains from treatment are relatively small (e.g. [32–34]). Like those studies, we find that societal support for reimbursing an orphan drug when a similar, non-orphan drug is not reimbursed may be lower when patients are aged 70 years and when health gains, particularly LE gains, are considered small.

The main strength of our study lies in the design of the DCE, which enabled us to provide original insights into societal support for differential treatment of orphan drugs by policymakers. Another strength lies in combining the DCE with qualitative methods for examining whether and why respondents consistently or alternatingly chose for (not) reimbursing the orphan drug. This enabled us to provide insight into the diversity and range of reasons underlying respondents' choices, including those that extend beyond the criteria commonly considered in reimbursement decisions in the Netherlands (i.e., the necessity, effectiveness, and cost-effectiveness of orphan drugs, and the feasibility of their reimbursement). Policymakers may also want to consider other patient, disease, and treatment characteristics—that either hold or lack societal value (e.g., QOL gains of 10 points and LE gains of 1 year may be considered 'negligible' by members of the public)—in their decisions, particularly if policymakers' aim is to align the outcomes of decisions with societal preferences or increase public support for such decisions.

Combining the DCE with qualitative methods furthermore enabled us to provide insight into the differences in underlying reasons between versions A and B of the questionnaire and between respondents who made consistent or alternating choices. The use of qualitative methods further made it possible to provide an explanation for the (unexpected) negative coefficients for QOL and LE before treatment. These data showed that respondents—at least in some scenarios—considered the disease to be so severe that they preferred not to prolong the suffering of patients and, therefore, chose for *not* reimbursing the orphan drug.

An important limitation concerns our assumption that respondents

Table 6
Thematic framework and proportions of main reasons provided by respondents, in n (% of total).

Theme		Category		Description	Total sample (n = 1,172)	Questionnaire	
						Version A (n = 632)	Version B (n = 540)
A	Patient characteristics			Characteristics of the patients that were considered relevant for deciding on reimbursing the orphan drug by respondents.	80 (6.8)	39 (6.2)	41 (7.6)
		A.1	Age	Respondents mentioned being more willing to grant the orphan drug special status when patients were relatively young, because they "still have a future" and it was "more important to extend their lives". Respondents mentioned that they "couldn't bring themselves to say no" when the decision concerned patients aged 10 years. This was less the case for patients aged 70 years, because they "already have a whole life behind them".	80 (6.8)	39 (6.2)	41 (7.6)
B	Disease characteristics			Characteristics of the disease that were considered relevant for deciding on reimbursing the orphan drug by respondents.	72 (6.1)	43 (6.8)	29 (5.4)
		B.1	Disease severity	Respondents mentioned being less willing to grant the orphan drug special status when patients' QOL and LE before treatment were low. Respondents believed that patients' "suffering shouldn't be prolonged" in such cases, especially not when patients were 1 year old and when the QOL and LE gains from treatment were small. Respondents believed that "these patients (and their families) will suffer for a lifetime" and that this should be avoided.	27 (2.3)	16 (2.5)	11 (2.0)
		B.2	Rule of rescue	Respondents mentioned that every human life is precious and "worth more than money". They believed that "every life counts" and that "everything should always be done" to improve patients' QOL and extend their LE.	16 (1.4)	6 (1.0)	10 (1.9)
		B.3	Prevalence	Respondents considered the prevalence of a disease irrelevant in deciding on reimbursing the orphan drug because "rare diseases aren't any different from common diseases" and "patients with a rare disease are not more pitiable than those with a common disease". Few respondents believed that the orphan drug should be reimbursement "especially because it is indicated for patients with a rare disease" and "they should have that opportunity".	17 (1.5)	12 (1.9)	5 (0.9)
		B.5	Cause of illness	Respondents mentioned that the patients neither chose to fall ill, nor chose to have a rare disease. The patients "didn't ask for this" and "have a hard enough time as it is". Therefore, they "shouldn't also be financially burdened" and the orphan drug should be reimbursed, "even if that means higher costs [for society]".	11 (0.9)	8 (1.3)	3 (0.6)
C	Treatment characteristics			Characteristics of the treatment that were relevant considered relevant for deciding on reimbursing the orphan drug by respondents.	413 (35.2)	210 (33.2)	203 (37.6)
1		C.1	Size and type of health gains	Respondents mentioned being more willing to grant the orphan drug special status when the health gains—particularly the LE gains—were relatively large. Because LE gains "are proportionally larger for younger patients", these were considered to be more valuable. Respondents mentioned being less willing to grant the orphan drug special status when the QOL gains were 10 points and the LE gains were 1 year. Such gains "are negligible".	237 (20.2)	129 (20.4)	108 (20.0)
		C.2	Broader benefits	Respondents mentioned that particularly, patients aged 40 years "might leave a family behind" and it was "important for their families that their lives would be prolonged". Patients aged 1 and 10 years "contribute, bluntly said, little to society" and patients aged 70 years "will only cost society more and more". Respondents further noted that reimbursing the orphan drug might "increase knowledge about rare diseases". They expressed the hope that reimbursement would, in time, result in developing and improving treatments for patients with a rare disease.	11 (0.9)	6 (1.0)	5 (0.9)
		C.3	Value for money	Respondents mentioned that the costs were "too high" and the health gains "too small". Because the treatment outcome "is never desirable" and patients "are never cured", respondents believed that reimbursing the orphan drug would be "a waste of money for society" and would only mean "prolonging an undesirable situation for patients".	38 (3.2)	24 (3.8)	14 (2.6)
		C.4	Health-insurance premium increase	Respondents mentioned that "the premium increase is so small" that it was "no longer relevant whether [the orphan drug] helps a little or a lot". It was considered "only reasonable to contribute €0.06 to reimbursing it" so that "the choice of [actually] using the treatment can be left to patients and their physicians (or families)".	76 (6.5)	35 (5.5)	41 (7.6)
		C.5	Budget impact	Respondents mentioned that the budget impact was "negligible in comparison to the total expenditure on healthcare in the Netherlands". Some respondents considered the opportunity costs of reimbursing the orphan drug relevant and mentioned that "it would be better to spend the money" on "research", on "a different disease", or on "more patients" than to spend it on "a small health gain in 50 patients".	51 (4.4)	16 (2.5)	35 (6.5)

(*continued on next page*)

Table 6 (*continued*)

Theme		Category		Description	Total sample (n = 1,172)	Questionnaire	
						Version A (n = 632)	Version B (n = 540)
D	Moral arguments			Moral arguments that were considered relevant for deciding on reimbursing the orphan drug by respondents.	194 (16.6)	128 (20.3)	66 (12.2)
		D.1	Equal access to treatment	Respondents considered it important that patients have equal access to treatment. "Everyone should have the same opportunities in life", regardless of patient, disease, and treatment characteristics. There should be "no discrimination between patient groups" and "no group should be excluded from [access to] healthcare".	47 (4.0)	30 (4.8)	17 (3.2)
		D.2	Uniform decision-making	Respondents considered uniformity in decision making important for deciding on reimbursing the orphan drug. They believed that "what's sauce for the goose, is sauce for the gander" and that "if the treatment is not reimbursed for patients with a common disease, it is unfair [to them] to reimburse the treatment for patients with a rare disease".	134 (11.4)	94 (14.9)	40 (7.4)
		D.3	Solidarity	Respondents considered solidarity to be the foundation of the healthcare system of the Netherlands. They believed that "patients have a right to healthcare" and that it is "only human" and "our collective duty to contribute to making [access to healthcare] possible" for patients.	14 (1.9)	5 (0.8)	9 (1.7)
E	Perceived entitlements			Perceived entitlements of patients (living in a rich country) that were considered relevant for deciding on reimbursing the orphan drug by respondents.	196 (16.7)	98 (15.5)	98 (18.2)
		E.1	Health and healthcare	Respondents mentioned that everyone is entitled to "live a healthy life" and to have access to "good quality healthcare". They considered "access to healthcare to be a right" that "can't be denied to patients by anyone" and, therefore, that "everything should always be reimbursement".	180 (15.4)	92 (14.6)	88 (16.3)
		E.2	Living in a rich country	Respondents mentioned that there should be "no discussion on whether or not a treatment should be reimbursed" in "a country as rich and prosperous as the Netherlands". For "a first-world country", it should be "a case of honour" to "be able to provide and [also] give the best possible care to patients" and "contribute to advancements in healthcare".	16 (1.4)	6 (1.0)	10 (1.9)
F	Other reasons			Respondents completed the choice tasks from the perspective of a patient (with a common or rare disease) and not always provided a clear explanation for their preference.	217 (18.5)	114 (18.0)	103 (19.1)
		F.1	Patient perspective	Respondents considered their own experience as a patient—with a common or rare disease—or imagined what their preference as a patient would be when choosing for (not) reimbursing the orphan drug. They believed that "anyone would want to have access to a treatment" and "would want that for their families". Some respondents noted that it was difficult for them to state a preference for someone else and that "patients should be able to choose themselves whether they want to undergo a treatment or not".	26 (2.2)	14 (2.2)	12 (2.2)
		F.2	Unclear preferences	Respondents did not always provide a clear and coherent explanation. These respondents, for example, mentioned that their choices were made "based on a feeling" "sometimes emotionally and sometimes rationally" or just "don't know". Some respondents did not provide any reason at all.	191 (16.3)	100 (15.8)	91 (16.9)

QOL, health-related quality of life; LE, life expectancy.

who made consistent choices for reimbursing the orphan drug would make that same choice in the typical, low support, and high support reimbursement scenarios. Although there is no evidence suggesting otherwise, also not based on the qualitative data, it is uncertain whether this assumption holds. If it does not, our findings may overestimate the actual societal support for differential treatment of orphan drugs in reimbursement decisions. A related, second limitation concerns our inability to provide insight into the influence of patient, disease, and treatment characteristics on the preferences of respondents who made consistent choices for (not) reimbursing the orphan drug. Researchers commonly aim to avoid such "non-trading" by respondents, as these respondents do not provide any information on the relative importance of the attributes and levels in a DCE. In the current study, 53.7% of respondents made consistent choices, and hence did not provide any information on the relative importance of the attributes and levels. This concerns a relatively large proportion of the total sample and further research is warranted to examine whether this level of consistency of choices will hold up under different circumstances (i.e., described based on other patient, disease, and treatment characteristics than in the current study). Nonetheless, in the context of our study these consistent choices are still informative. For example, because they provide insight into the baseline societal support and opposition that policymakers may expect when deciding on reimbursing an orphan drug in circumstances where a similar, non-orphan drug would likely not be reimbursed.

Conclusions

The findings of this study indicate that a considerable part of the general population in the Netherlands would likely support reimbursing orphan drugs, even when they do not meet the cost-effectiveness criteria for reimbursement that apply to non-orphan drugs. This support for differential treatment of orphan drugs may be stronger when patients are aged between 1 and 70 years, their disease severity is moderate, and health gains from treatment are considerable. Nonetheless, a substantial minority of the public would likely oppose differential treatment of orphan drugs in reimbursement decisions, mostly based on moral arguments. This suggests that policymakers may expect opposition in society, regardless of whether they give orphan drugs special status.

Data availability

The dataset generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Compliance with ethical standards

The Research Ethics Review Committee of the Erasmus School of Health Policy & Management assessed and waived ethical approval for this study (reference: 20–33 Reckers-Droog). The funders had no role in the study design, data collection and analysis, interpretation of the data, preparation of the manuscript, or decision to submit for publication. The views expressed in this article are those of the authors.

CRediT authorship contribution statement

Vivian Reckers-Droog: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lucas Goossens:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Job van Exel:** Funding acquisition, Supervision, Writing – review & editing. **Werner Brouwer:** Conceptualization, Funding acquisition, Methodology, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

Dr. Reckers-Droog has received research grants from GlaxoSmithKline, AbbVie, and AstraZeneca during the conduct of the study; Dr. Goossens declares that he has no conflict of interest; Dr. van Exel has received research grants from GlaxoSmithKline, AbbVie, and AstraZeneca during the conduct of the study; Dr. Brouwer has received research grants from GlaxoSmithKline, AbbVie, and AstraZeneca during the conduct of the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hlpt.2024.100870.

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