Societal preferences for funding orphan drugs in the United Kingdom

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Title: Societal preferences for funding orphan drugs in the United Kingdom: An application of person trade off and discrete choice experiment methods

Running title: Societal preferences for funding orphan drugs

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Key words:

Orphan drugs, Societal preferences, Person trade-off, Discrete Choice Experiment, Rare disease, Resource allocation

Highlights

1. What is already known about this topic?

Pharmaceutical manufacturers are incentivised to develop orphan drugs which are often recommended by the NHS despite exceeding conventional thresholds of cost-effectiveness.

Previous population surveys suggest little support for the preferential funding of orphan drugs but these are influenced by framing effects.

2. What does the paper add to existing knowledge?

The UK general public does not consider rarity in itself as being sufficient to justify special consideration for additional NHS funding.

Based on public preferences, only five of twelve recently approved orphan drugs would be recommended for NHS use.

3. What insights does the paper provide for informing health care-related decision making?

Policymakers should be cautious when determining special funding status for orphan drugs.

Abstract

Background

It is unclear whether UK National Health Service policies for orphan drugs, which permit funding of non-cost-effective treatments, reflect societal preferences.

Methods

We conducted person trade off (PTO) and discrete choice experiments (DCE) among 3,950 adults selected to be representative of the UK general population. Experimental design was informed by surveys of patients affected by rare diseases, their carers, healthcare staff and policy-makers. Societal preferences were estimated in relation to treating a common disease, increases in waiting lists, or filling of vacant NHS posts. Results of the DCE were applied to recently licensed orphan drugs.

Results

Based on equal cost, the majority of respondents to the PTO (54%; 95%CI, 50,59) chose to allocate funds equally between patients treated for rare and common diseases, with 32% (28,36) favouring rare over common (14%; 11,17), which this reduced to 23% (20,27) when rare disease treatments were 10-times more expensive. When framed differently, more respondents prioritised not increasing waiting list size (43%; 39,48) than to treat rare disease patients (34%; 30,38).

The DCE indicated a greater preference for treating a common disease over a rare disease. Respondents agreed with 5 of 12 positive appraisal recommendations for orphan drugs, even if their list price was higher, but preferred the NHS not to fund the remainder.

Conclusions

The general public does not value rarity as a sufficient reason to justify special consideration for additional NHS funding of orphan drugs. This has implications regarding the appropriateness of operating higher thresholds of cost-effectiveness.

INTRODUCTION

Orphan medicinal products include treatments for rare diseases which are life-threatening or chronically debilitating, and medicines whose development would not be commercially viable without incentives [1]. Legislations aimed at promoting the development of orphan medicinal products have succeeded to the extent that regulatory approval rates are at their highest. Orphan drugs accounted for 40% of new drug approvals in Europe and the USA in 2016 [2,3]. However, ensuring patient access to these medicines has posed significant difficulties for policy makers given their high cost [4] and lack of cost-effectiveness [5].

Concerns about inequity of care –patients being denied effective treatment on the basis of the rarity of their disease– has led to specific NHS policies to facilitate access to many orphan drugs. These include the National Institute for Health and Care Excellence (NICE)'s Highly Specialised Technologies programme which operates a higher threshold for cost-effectiveness (up to £300,000 per quality-adjusted life-year, QALY) [6], and the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group's (AWMSG) permissive policies for appraising orphan drugs [7,8]. Each organisation justifies the value of non-cost-effective orphan drugs on the basis of particular patient, disease or drug feature. These include the magnitude of treatment benefit, the severity of disease, the innovative nature of the drug and availability of alternative treatment. There is evidence of general population support for prioritising patients with greater disease severity as well as interventions that generate larger health gains [9]. There is also evidence that the general population prefers funds to be allocated towards innovations that are scientifically proven and have potential health benefits [10]. Unmet need, however, is only considered important from a personal perspective, and not from a public perspective [11]. The implication of considering these factors in choices concerning investment in new medicines but not in the services they displace, however, is the inequitable position of improvements in health being valued higher in orphan conditions than in others [12,13].

The value judgements of members of society are important in determining the guiding principles of priority setting [14]. NICE involves the public through its citizens' councils which formulate a view on specific topics. A council discussion on ultra-rare diseases found that rarity is not a factor in itself that should warrant additional funding [15]. Previous studies of societal preference conducted in the UK

[16] and internationally [17-20] have also found no evidence of a preference to fund high cost treatments for rare diseases on the basis of rarity alone. While consistent in their findings, these studies have been criticised for being reliant on one method of preference elicitation, potential framing effects affecting the sensitivity of respondents' choices to the questions posed or method used [21], inappropriateness of how opportunity cost is presented to those surveyed [18], and consideration of other features of rare diseases besides prevalence.

We aimed to assess whether there is a UK societal preference to support current NHS policies that justify the acceptance of the opportunity cost associated with the funding of treatments for rare diseases. We further tested whether a sample of recently approved orphan drugs would be recommended based on societal preference.

METHODS

We utilised two separate preference elicitation techniques: a person trade off (PTO) study and a discrete choice experiment (DCE). Both methodologies involve respondents trading between options to estimate their preference, but they allow respondents to engage in the decision-making process in different ways. The PTO method asks respondents to select the number of patients that they would prefer the NHS to allocate resources to, choosing between two populations or scenarios of health service provision. This allows the opportunity cost of the allocation choice to be transparent and unambiguous to facilitate estimation of distributive weighting (i.e. who to treat) [22]. DCEs describe hypothetical but realistic medicines for rare and common diseases by their characteristics (attributes) and associated levels [23]. Respondent choices are then modelled to reveal the importance of the attributes and the willingness of respondents to trade attributes and levels.

Ethical approval was obtained from the Health Care and Medical Sciences Academic Ethics Committee, Bangor University 2015-02-03.

PTO survey design

Four PTO scenarios were designed. Two represented a 'zero-sum' frame: (i) a scenario based on cost, of trading patients with a rare and common disease; and (ii) a scenario in which both treatment costs and benefits were varied; and two represented impacts of additional costs on the provision of

healthcare in terms of: (iii) an increased waiting list for an unspecified treatment; and (iv) leaving vacant NHS staff posts unfilled.

In the first two scenarios, the costs of rare disease medicines ranged between 1 and 20 times the cost of medicines for common diseases, to represent realistic values. In the waiting list scenario, we varied the benefits of both the rare disease medicine and the treatment for which patients are waiting, as well as their respective costs. Choices concerning staffing levels were based on the salaries of a health care assistant (1:5) or a nurse (1:3) relative to a doctor. The levels for this scenario were varied by staffing level standards; labelled as normal levels, overstaffed and understaffed.

A focus group of 8 members of the public was convened to examine the face validity of the PTO survey.

DCE survey design

We followed good practice guidelines to design the experiments [23,24]. Potential attributes of relevance to rare disease medicines were identified from a systematic review [25]. These were presented to four stakeholder groups using an online survey (Surveymonkey): patients with rare diseases, their carers, clinicians and allied health professionals, and NHS decision-makers. Each participant was also given an opportunity to suggest their own attribute, and then asked to rank all attributes they believed were important for the NHS to consider in funding decisions concerning orphan drugs. Aggregate ranking was summarised using Borda scores [26], calculated for each group and for all participants.

The identified attributes were presented to a separate focus group of 8 members of the public to decide on the final list of attributes and to refine the format and language used in the DCE. Members also discussed options for attribute levels and confirmed the final selection which was based on criteria for orphan drug designation [1], published evidence on the effectiveness and costs of orphan drugs [4], and change in health status, based on the EuroQol EQ-5D health outcome measure [27].

The DCE attributes and levels are presented in Table 1. A full factorial design would result in 108 profiles and 5,778 possible pairwise choice scenarios; hence, a fractional factorial design selected from a design catalogue [28] was selected to reduce burden on respondents.

Insert Table 1 here

Study sample

Patients and carers participating in the stakeholder survey were recruited via rare disease patient support groups. Clinicians and allied health professionals caring for patients with rare diseases were identified via Orphanet or their membership of NHS rare disease centres of excellence. NHS policy decision-makers were defined as members of NICE, AWMSG and SMC appraisal committees. Recruitment to the focus group was based on local advertising. Interested persons were included if they were a UK citizen, aged 18 years or over, had no diagnosis of a rare disease, or history of being refused funding for NHS treatment. Target sample size across all groups was 120 participants.

The population survey aimed to recruit 4,000 respondents representative of the general population in the UK, recruited by a market research company (Belindi). Participants were compensated by way of reward points which they can trade for goods.

Survey administration

In designing the questionnaires, we were cognisant of respondents' likely unfamiliarity of rare diseases, and the high cost of orphan drugs. We were also conscious that respondents may have limited motivation to participate in the research and that an online survey offered no opportunities for clarification and so may not be interpreted correctly. We therefore designed an animation to accompany the survey, with input from focus group members (available online from https://tinyurl.com/OrphansAnimation).

Both studies were piloted amongst a convenient sample of 12 staff and students at Bangor University. Piloting involved feedback on the instructions, layout and images used in the PTO and DCE, and resulted in some images being subsequently modified.

Participants in the main survey were required to view the animation before proceeding. They were reminded that there were no right or wrong answers, and that the research was to determine their views on how the NHS should prioritise treatments. They were directed at random to complete either the PTO or DCE questionnaire. Participants directed to the PTO survey were allocated at random to complete one of the four scenarios and asked to imagine that they were a decision maker for their local NHS health authority with a fixed budget. The final survey question asked whether or not respondents would prefer the NHS to fund patients with rare diseases knowing that if they chose to do

so, funding would be reduced in other areas. DCE participants were presented with a labelled choice of a treatment for a rare or common disease and asked which treatment they believe the NHS should fund. Respondents were blocked into 3 DCE surveys with 9 pairwise choice tasks in each.

An example of both the PTO and DCE is presented in figure 1.

Insert Figure 1 here

Analysis

PTO responses were analysed according to simple majority, and by the ratio of means (ROM) method [29], where a value of 1 is assigned to the most preferred choice, and $^{1}/_{N_i}$ assigned to the least, where N_i is the number of patients in the least preferred group that is equal to one patient in the most preferred group. Values of ROM>1 indicate higher social weights for populations receiving rare disease treatment. Respondents who chose an equal allocation of funds to both populations were excluded from the ROM analysis, to prevent over estimation of the weights.

Discrete choice experiment data were analysed using a random effects logit model that allowed for repeated observations from the same respondent [30, 31]. A linear utility function was defined according to:

$$Utility = \beta_1\, rare\ disease\ treatment + \beta_2\, cost + \beta_3\, debilitating\ or\ life\ threathening + \beta_4\, availability\ of\ other\ drugs + \beta_5\, improvements\ to\ everyday\ life + \beta_6\, cost \times rare\ disease\ treatment + e$$

An interaction term was included to account for cost levels being different for each drug treatment label. The size and significance of the coefficients indicate the relative importance of each attribute. The pre-defined sub-groups (age, sex, socioeconomic status and country) were analysed by comparison with the base-case model using log likelihood tests at 5% level of significance.

We assessed whether respondents' preferences were in agreement with NICE, SMC or AWMSG recommendations of orphan drugs approved by the European Medicines Agency (EMA) during 2014-16. This was done by implementing the DCE model using data specific to each drug to calculate total utility. Evidence on whether each drug was for a rare and life-threatening or chronically debilitating disease, as well as whether other drug treatments were available were based on information on the

EMA website. We sourced data on cost and incremental gains in life-years and QALYs from economic assessments included in submissions to each HTA organisation. QALY gains exceeding 1 were assumed to represent a return to everyday life activities. We defined a preference for NHS reimbursement of a given drug if the total utility was positive. The value-based price of the drug was determined as the price at which the utility of the drug is zero.

All data were analysed in STATA (version 13, StataCorp LP, College Station, TX).

RESULTS

Stakeholder survey

Forty-five patients, 14 informal carers, 16 healthcare professionals, and 24 policy makers participated in the stakeholder survey. Patients and carers were consistent in their selection of their most important attributes, with the debilitating or life threatening nature of the disease, therapeutic improvement to everyday life, magnitude of treatment benefit, and evidence of effectiveness featuring in their top 5. Healthcare professionals and policy makers each considered evidence of cost effectiveness in their top 5 attributes (Table 1). The overall ranking across groups was: evidence of effectiveness (=1), the debilitating or life threatening nature of the disease (=1), improvements to everyday life (2), magnitude of treatment benefit (3), cost effectiveness (4) and availability of alternative treatments (5). A decision was made to substitute the cost effectiveness attribute for a cost attribute to avoid double counting effectiveness and reduce cognitive burden on DCE respondents.

Focus group

The potential attribute concerning the evidence for effectiveness was not easily interpreted by focus group discussants, was given least priority and was therefore excluded from the final DCE design. The issue of cost dominated the discussion. Most participants argued that more information was needed to see the “whole picture of spending on the NHS” and that the figures presented may be “out of context”. Some focus group participants were reluctant to engage in a discussion they felt meant putting a cost on peoples’ lives but did feel that it was too important to be ignored. Consensus was

reached when an example DCE was presented to the group which included visual aids. This reduced participants' concerns about the context in which the survey would be presented.

Focus group participants stated that they had sufficient information on the differences between rare and common diseases and were able to complete the survey without assistance when presented with a mock version of both the DCE and PTO.

Survey of the general public

A total of 3,950 adults completed the questionnaires. Respondents to both surveys were broadly representative of the UK adult general population (Table 2).

Insert Table 2 here

Person trade off

Based on equal cost and treatment benefit, the majority of respondents (54%; 95% confidence interval, 50, 59) chose to allocate funds equally between the two groups (Table 3). Traders favoured treating patients with a rare disease (32%; 95% CI, 28, 36) over patients with a common disease (14%; 95% CI, 11, 17). Preference for treating rare disease patients reduced to 23% (95% CI, 20, 27) and 19% (95% CI, 16, 23), respectively, in the context of orphan drugs being 10- and 20- times more expensive. When the benefit of rare disease treatments reduced, there was more support for treating patients with common diseases.

Insert Table 3 here

ROM increased from 2.67 assuming equal cost and benefit, to 8.97 when a rare disease treatment costs the same but is more effective than a common disease treatment. However, the strength of respondents' preferences towards rare disease treatments reduced as their cost increased by 10- and 20-fold, with the social weight for a more effective treatment reducing to 1.60 and 1.42, respectively.

When we changed the framing of the question to reflect the opportunity cost of funding treatments for rare diseases in terms of increasing waiting lists, the majority of respondents prioritised either not increasing waiting list size (43%; 95% CI, 39, 48) or equal allocation of funds (23%; 95% CI, 19, 26) than treatment of rare disease patients (34%; 95% CI, 30, 38). More respondents favoured not to

increase waiting list as the cost of rare disease treatment increased, but this was reversed for rare disease treatments of higher effectiveness, even when cost increased 10- and 20-fold.

Opportunity cost represented in terms of staffing implications followed a similar trend. Only when a hospital was already overstaffed did respondents' preferences switch to treating a patient with a rare disease over filling vacant staff posts.

Statement on resource allocation

Responses to the supplementary question indicated that the majority 61% (95% CI, 58, 64) would prefer for the NHS not to reduce funding in other areas in order for money to be available to pay for drugs for rare diseases.

Discrete choice experiment

Treatment for a rare disease was preferred in 37% of choice tasks. Each of the five attributes significantly influenced respondents' choice between treatments for a rare versus common disease (Table 4). All else being equal, the odds of preferring funding to be allocated towards rare disease treatments increased by 2.35 (95% CI, 2.24, 2.47) for survival advantages of 1 or more years, and 1.19 (95% CI, 1.12, 1.27) for a disease which is debilitating or life threatening. Respondents indicated they would not want to prioritise NHS funding based on: whether the disease was rare, no availability of other drug treatment, or on the basis of cost. There was a preference to fund medicines that provide large benefit and which improve quality of life.

Insert Table 4 here

Analysis of sub-groups did not show any statistically significant difference from the base case (Supplementary data).

Twenty-two orphan drugs were approved in 2014-16, of which 2 were subsequently withdrawn from the register of orphan medicinal products and 7 had not been appraised by NICE, SMC or AWMSG. All remaining 13 orphan drugs were for a rare and life-threatening or chronically debilitating disease and, with the exception of ataluren for Duchenne muscular dystrophy, were for a disease where an alternative drug treatment was available. Based on public preferences for NHS funding, a positive utility was estimated for 5 of the 12 orphan drugs which received a positive recommendation by NICE, SMC or AWMSG (Table 5). Respondents' preferences indicated that the NHS should consider each

of these acceptable at annual prices exceeding £250,000 per patient per year or more, which represents up to a 5-fold increase on their list prices. Eliglustat for Gaucher disease type 1 was associated with a negative utility at its list price of £250,000 per patient per year, but a 9-fold reduction in price to £27,705 would make this an acceptable option for NHS funding. The remaining recommended drugs were each associated with a negative utility and were not preferred at any price (value-based price <£0 per patient per year). A negative utility was determined for the only orphan drug (daratumumab) which was not recommended by SMC (but has yet to be appraised by NICE or AWMSG).

Insert Table 5 here

DISCUSSION

This study shows that the UK general public does not consider rarity in itself as being sufficient to justify special preferential NHS funding. Respondents were willing for the NHS to pay more per year of treatment for those affected by a common disease than those with a rare disease. They also showed a large preference for attributes that are independent of disease prevalence, specifically, whether a treatment improves everyday life or prolongs survival. However, both methods of preference elicitation suggest that the general public is willing for the NHS to preferentially fund treatments for patients with rare diseases when treatment benefit is greater than that of its common disease counterpart. But posed with more realistic scenarios of NHS opportunity cost, respondents preferred funding to be directed towards not increasing waiting lists and tackling staff shortages. The utility model indicated a preference for funding of only one NHS approved orphan drug that received market authorisation during 2014-16. There was no price at which treatments that were associated with a negative utility would be preferred.

The finding of a lack of preference towards NHS funding being allocated to treatments for rare diseases on the basis of rarity alone is aligned with previous research. Five large PTOs of the UK [16], Norwegian [17], Canadian [18], Australian [19], and Swedish [20] general public each failed to demonstrate evidence for societal preference if funding decisions were at the expense of treatment being available to patients with common diseases. Similar findings were found among doctors [32], in a convenience sample of university students [33], as well as by the NICE citizens' council [15].

Responses to preference elicitation studies, however, are sensitive to the framing effects of how choices are presented [21]. Offering respondents the choice between two competing populations, the 'zero-sum' frame, may not represent the opportunity cost in terms which are easily understood by the general public [32] or which reflect reality. In order to make the PTO exercise more familiar to those surveyed, and more closely aligned with NHS decisions, we included two scenarios relating to waiting lists and staffing levels. We further included a discrete choice experiment as an alternative method of preference elicitation, and obtained results that were consistent across all scenarios and methods.

To our knowledge, our study is the first to elicit preferences from the general population on prioritising orphan drugs using DCE, and to use systematic methods to select attributes that were relevant and meaningful to the general public. However, as with other revealed preference studies, a number of simplifying assumptions were made to reduce the burden on respondents. To convey the concept of treatment benefit, the PTO presented the rare disease treatment to be more or less beneficial than the treatment for common disease. The DCE considered treatment benefit in terms of achievement of 1 or more years of extended survival and improvement in everyday life activities. While both approaches are simplified representations of benefit that are easily understood, they capture limited aspects of treatment effect, and were dependent on assumptions relating to QALY gains. Neither survey accounted for the uncertainty of treatment benefit; and the scenario of returning a patient to normal everyday life may be unrealistic and overstate the effectiveness of orphan drugs, considering the serious and debilitating nature of these diseases.

The value-based pricing model is driven primarily by attributes capturing treatment benefit in terms of quality of life and survival, but as variables representing these are dichotomous, the model may overestimate the value of a drug in relation to its benefits. Nevertheless it provides a basis for capturing societal preferences to inform decisions on orphan drug funding allocation, and what constitutes a fair price.

Since April 2017, NICE has new arrangements for evaluating orphan drugs that fall within the Highly Specialised Technologies programme. These include increasing the threshold value to £100,000 per QALY (and where transformational improvements to health, to £300,000 per QALY) [6]. This would place the value of health gains in rare diseases up 15 times higher than equivalent gains in common diseases. Our results – confirming those of others [16-20] – indicate that there is no societal

preference for higher valuation of orphan drugs, whose sole distinctive attribute is rarity [10]. Policymakers should therefore be cautious when determining special funding status for orphan drugs especially given the increase in their numbers, cost [34], and the profitability of their manufacturers [35].

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Table 1. Discrete choice experiment attributes and levels

Attribute	Attribute description	Ranking by patients (P), carers (C), healthcare professionals (HCP), policy makers (PM); overall rank (OR)	Levels	Rationale for level
Debilitating or life threatening	The disease affects patients' everyday life OR the patient could die if they do not receive treatment	P: 2 C: 1 HCP: 3 PM: 5 OR: 1	Yes No	Focus group members identified a wide range of symptoms that could be used for this attribute. However, to simplify the task, we adopted the EC definition for orphan drug designation (1), which requires the condition to be life-threatening or chronically debilitating.
Improvements to everyday life	The drug improves the well-being of patients and their	P: 1 C: 2 HCP: 4	Returns patient to normal everyday life	Based on the usual activities domain of the EQ-5D-3L.

	families e.g. school/ work social activities	PM: >5 OR: 2	Some improvement to everyday life No improvement to everyday life	
Treatment benefit	Extent to which the drug increase survival	P: 3 C: 3 HCP: 2 PM: 4 OR: 3	Increases survival by <1 year Increases survival by ≥1 year	Based on the evidence of effectiveness of orphan drugs (4). One year was chosen to represent a transformational health benefit.
Cost per patient per year*	Cost of treatment on the NHS per patient per year	P: >5 C: >5 HCP: 5 PM: 2 OR: 4	Rare: £5,000, £60,000, £200,000	Low-cost orphan drugs (e.g. ibuprofen, caffeine, sildenafil) Middle-cost is the average annual, per-patient cost of orphan drugs (4) High cost ultra-orphan drug (e.g. enzyme replacement therapies for lysosomal storage diseases)
			Common: £500, £2,000, £9,000	Low-cost representative of the annual cost of branded treatments (e.g. direct oral anticoagulants)

				Middle-cost (e.g. pregabalin) High cost representative of commonly used biologics (e.g. adalimumab)
Availability of other drug treatments	Other drug treatments are available to treat the disease	P: >5 C: 5 HCP: >5 PM: 3 OR: 5	Yes- a drug is available to treat the cause of the disease No, but patients' symptoms are treated	Many orphan drugs fulfil the EC regulation (1) on orphan medicinal products of there being no satisfactory alternative treatment. Treatment of symptoms reflects the NHS provision of best supportive care if no other alternative treatment exists. Drugs available to treat the cause of diseases capture targeted therapies such as ivacaftor for cystic fibrosis.

*Described as cost-effectiveness in the ranking exercise

Table 2. Sociodemographic characteristics

	DCE number (%)	PTO number (%)	United Kingdom (%)
Number of responses	1940	2000	
Female[1]	970 (49.7)	1036 (51.8)	50.8
Age[1]			
18-24	106 (5.4)	131 (6.5)	7.2
25-34	311 (15.9)	338 (16.9)	13.5
35-44	381 (19.5)	385 (19.2)	12.9
45-54	399 (20.4)	385 (19.2)	14.1
55-64	313 (16.0)	320 (16.9)	11.3
65+	440 (22.5)	441 (22.0)	23.0
Household income (£ per annum)[2]			
Under 19,999	546 (28.0)	522 (26.1)	29.1
20,000-39,000	641 (32.9)	670 (33.5)	31.3
40,000-59,000	285 (14.3)	308 (15.4)	12.2
60,000-79,000	133 (6.8)	133 (6.6)	8.4
80,000-99,000	53 (2.7)	56 (2.8)	6.6
100,000-119,000	28 (1.4)	22 (1.1)	5.5
120,000-149,999	9 (0.5)	14 (0.7)	7.0
150,000+	6 (0.3)	11 (0.6)	
Don't know	39 (2.0)	47 (2.4)	
Prefer not to say	210 (10.7)	217 (10.8)	
Social Grade[3]			
AB, C1	1166 (60.0)	1028 (51.0)	53.0
C2, DE	784 (40.0)	792 (48.0)	47.0
Household composition[4]			
With children	610 (31.0)	668 (33.3)	28.0
Without children	1340 (69.0)	1332 (66.7)	72.0

Country [1]			
Northern Ireland	27 (1.3)	26 (1.3)	2.8
Wales	96 (4.9)	101 (5.0)	4.8
Scotland	127 (6.5)	142 (7.1)	8.2
England	1700 (87.2)	1731 (87.0)	84.0

[1]UK data from the Office for National Statistics Population Estimates Summary for the UK, mid-2014

[2]UK data estimated from the Office for National Statistics UK household income and wealth, 2013/14

[3]UK data from the Office for National Statistics UK census 2011,

[4]UK data from the Office for National Statistics General Lifestyle Survey, 2011

Table 3. Results of the person trade off experiment

	Proportion preference to rare (95% CI)	Equal allocation of funds (95% CI)	Proportion preference to alternative (95% CI)	ROM (number in analysis)
Scenarios for common disease treatment, based on the rare disease treatment being:				
Equal cost	0.32 (0.28, 0.36)	0.54 (0.50, 0.59)	0.14 (0.11, 0.17)	2.11 (228)
5x higher cost	0.31 (0.27, 0.35)	0.31 (0.27, 0.35)	0.39 (0.34, 0.43)	0.68 (346)
10x higher cost	0.23 (0.20, 0.27)	0.25 (0.21, 0.29)	0.51 (0.46, 0.55)	0.43 (375)
20x higher cost	0.19 (0.16, 0.23)	0.25 (0.21, 0.29)	0.56 (0.51, 0.60)	0.35 (375)
Scenarios for common disease treatment, based on the rare disease treatment being:				
Equal cost, and less effective	0.23 (0.20, 0.27)	0.26 (0.22, 0.30)	0.51 (0.46, 0.55)	0.75 (370)
Equal cost, and equally effective	0.29 (0.25, 0.33)	0.59 (0.54, 0.63)	0.12 (0.10, 0.15)	2.67 (206)

Equal cost, and more effective	0.71 (0.67, 0.75)	0.20 (0.17, 0.24)	0.08 (0.06, 0.11)	8.97 (399)
10x higher cost and less effective	0.17 (0.14, 0.21)	0.18 (0.15, 0.21)	0.65 (0.61, 0.69)	0.27 (410)
10x higher cost and equally effective	0.23 (0.20, 0.27)	0.33 (0.29, 0.37)	0.44 (0.39, 0.48)	0.51 (335)
10x higher cost and more effective	0.50 (0.46, 0.54)	0.28 (0.24, 0.32)	0.22 (0.18, 0.25)	1.60 (358)
20x higher cost and less effective	0.18 (0.14, 0.21)	0.17 (0.14, 0.20)	0.65 (0.61, 0.69)	0.27 (415)
20x higher cost and equally effective	0.19 (0.16, 0.23)	0.27 (0.23, 0.30)	0.54 (0.50, 0.58)	0.36 (367)
20x higher cost and more effective	0.44 (0.39, 0.48)	0.30 (0.26, 0.34)	0.26 (0.23, 0.30)	1.42 (351)
Waiting list scenarios, based on the rare disease treatment being:				
Equal cost, and less effective than treatment being waited for	0.34 (0.30, 0.38)	0.23 (0.19, 0.26)	0.43 (0.39, 0.48)	5.11 (272)
Equal cost, and equally effective as treatment being waited for	0. 45 (0.41, 0.49)	0.46 (0.41, 0.50)	0.09 (0.07, 0.12)	1.09 (387)

Equal cost, and more effective than treatment being waited for	0.68 (0.64, 0.72)	0.22 (0.19, 0.26)	0.10 (0.07, 0.13)	7.19 (389)
10x higher cost, and less effective than treatment being waited for	0.33 (0.29, 0.37)	0.26 (0.23, 0.30)	0.41 (0.36, 0.45)	0.72 (386)
10x higher cost, and equally effective than treatment being waited for	0.30 (0.26, 0.34)	0.17 (0.14, 0.21)	0.53 (0.48, 0.57)	0.53 (414)
10x higher cost, and more effective than treatment being waited for	0.51 (0.47, 0.56)	0.27 (0.23, 0.31)	0.22 (0.18, 0.25)	1.63 (365)
20x higher cost, and less effective than treatment being waited for	0.25 (0.22, 0.29)	0.15 (0.12, 0.18)	0.59 (0.55, 0.64)	0.64 (424)
20x higher cost, and equally effective than treatment being waited for	0.32 (0.28, 0.36)	0.22 (0.18, 0.25)	0.48 (0.43, 0.52)	0.42 (398)
20x higher cost, and more effective than treatment being waited for	0.43 (0.38, 0.47)	0.25 (0.21, 0.29)	0.32 (0.28, 0.36)	1.19 (374)
Staffing scenarios, based on the cost of rare disease treatment being equivalent to:				
3 nurses (understaffed)	0.29 (0.25, 0.33)	0.28 (0.24, 0.32)	0.44 (0.39, 0.48)	0.63 (362)
3 nurses (normal staffing)	0.31 (0.27, 0.35)	0.34 (0.30, 0.39)	0.34 (0.30, 0.39)	0.83 (328)

3 nurses (overstaffed)	0.44 (0.40, 0.49)	0.31 (0.27, 0.35)	0.25 (0.21, 0.29)	1.42 (346)
5 healthcare assistants (understaffed)	0.25 (0.21, 0.29)	0.24 (0.20, 0.28)	0.51 (0.47, 0.56)	0.48 (381)
5 healthcare assistants (normal staffing)	0.33 (0.29, 0.37)	0.30 (0.26, 0.34)	0.38 (0.33, 0.42)	0.76 (352)
5 healthcare assistants (overstaffed)	0.52 (0.48, 0.56)	0.21 (0.17, 0.25)	0.27 (0.23, 0.31)	1.35 (395)
1 doctor (understaffed)	0.24 (0.20, 0.28)	0.23 (0.20, 0.27)	0.53 (0.49, 0.57)	0.73 (384)
1 doctor (normal staffing)	0.33 (0.29, 0.37)	0.27 (0.23, 0.31)	0.40 (0.35, 0.44)	1.12 (363)
1 doctor (overstaffed)	0.50 (0.46, 0.55)	0.21 (0.18, 0.25)	0.28 (0.24, 0.32)	2.09 (393)

Table 4. Results of the discrete choice experiment

Attribute	**Coefficient (95% confidence interval)**	**Odds ratio (95% confidence interval)**
Rare disease treatment	-0.52 (-0.57, -0.47)	0.59 (0.56, 0.62)
Cost of treatment (thousands)	-0.022 (-0.028, -0.017)	1.00 (1.00, 1.00)
Debilitating or life threatening disease	0.18 (0.11, 0.24)	1.19 (1.12, 1.27)
Availability of other drug treatment	-0.075 (-0.123, -0.025)	0.93 (0.88, 0.97)
Treatment benefit	0.86 (0.81, 0.91)	2.35 (2.24, 2.47)
Improvements to everyday life None	-0.052 (-0.076, -0.027)	0.95 (0.93, 0.97)
Some	0.39	
Returns patients to normal activities	0.66 (0.63, 0.70)	1.94 (1.87, 2.00)
Interaction term cost x rare disease treatment	0.019 (0.015, 0.023)	1.00 (1.00, 1.00)
Constant	-0.14 (-0.19, -0.09)	
Number of observations	35100	
AIC	42720.09	
BIC	42804.75	
Model χ^2	0.0000	

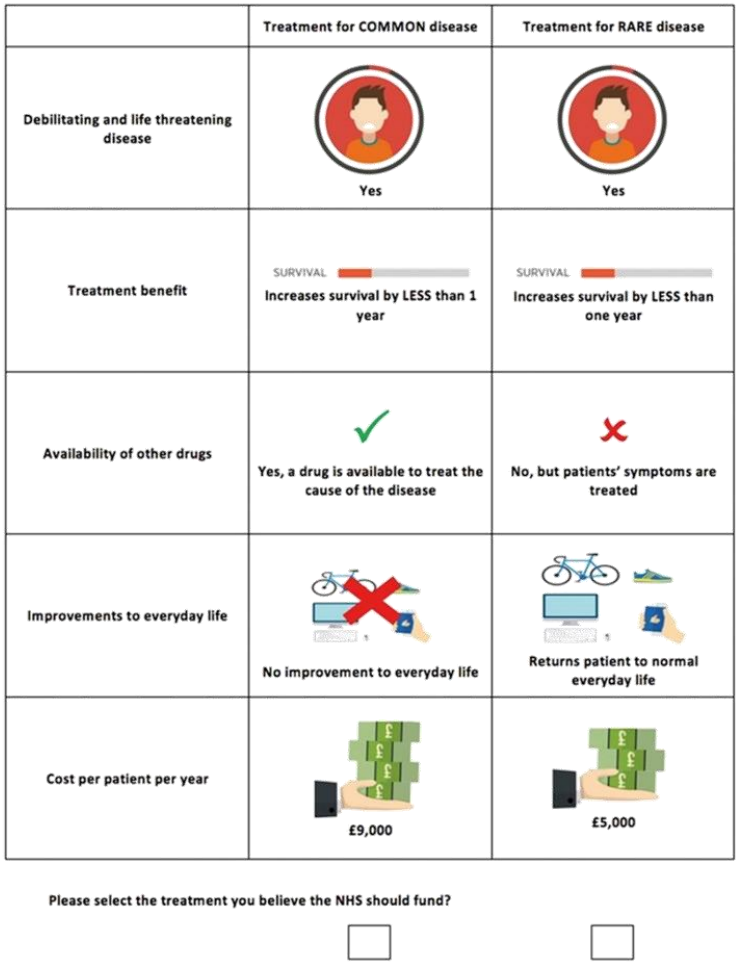
Table 5. Total utility and value-based pricing estimates for orphan drugs

Drug	Orphan indication	Modelled evidence LYG	Modelled evidence ΔQALY*	Cost per patient per year (£)**	Total utility (95% confidence interval)	Value-based price (£)
Obeticholic acid	Primary biliary cholangitis	4.43	5.83	29,005	0.78 (0.76, 0.79)	265,212
Ibrutinib	Mantle cell lymphoma	1.01	0.94	85,848	0.75 (0.73, 0.83)	265,212
Blinatumomab	Neuroblastoma	1.75	1.5	104,884	0.58 (0.55, 0.59)	265,212
Trametinib	Melanoma	1.65	1.30	110,880	0.56 (0.53, 0.57)	265,212
Ataluren	Duchenne muscular dystrophy	>1	5.17	246,448	0.14 (0.14, 0.19)	285,947
Olaparib	Epithelial ovarian cancer	1.17	0.89	51,350	-0.50 (-0.52, -0.47)	<0
Eliglustat	Gaucher disease type 1	0	1.05	249,999	-0.80 (-0.87, -0.70)	27,705
Lenvatinib	Thyroid cancer	0.79	N/A	52,307	-0.80 (-0.83, -0.73)	<0
Ibrutinib	Chronic lymphocytic leukaemia	>1	>2	55,955	-0.92 (-0.98, -0.86)	<0
Nintedanib	Idiopathic pulmonary fibrosis	0.03	0.05	26,100	-1.27 (-1.28, -1.22)	<0
Panobinostat	Multiple myeloma	0.21	0.12	111,840	-1.57 (-1.59, -1.57)	<0
Migalastat	Fabry disease	0	0.34	210,000	-1.93 (-1.95, -1.89)	<0
Daratumumab	Multiple myeloma	>0.25	0.58	103,680	-1.54 (-1.56, -1.54)	<0

*QALY gains >0 but <1 were assumed to reflect an improvement in everyday activities; QALY gains >1 (or if no data available, N/A) were assumed to reflect a return to usual activities

**Based on list price; a confidential discounted price based on a patient-access scheme is available for many of the drugs listed

Figure 1. An example of a discrete choice experiment choice (left) and patient trade off exercise (right) presented to those surveyed.



	Treatment for COMMON disease	Treatment for RARE disease
Debilitating and life threatening disease	Yes	Yes
Treatment benefit	SURVIVAL Increases survival by LESS than 1 year	SURVIVAL Increases survival by LESS than one year
Availability of other drugs	Yes, a drug is available to treat the cause of the disease	No, but patients' symptoms are treated
Improvements to everyday life	No improvement to everyday life	Returns patient to normal everyday life
Cost per patient per year	£9,000	£5,000

Please select the treatment you believe the NHS should fund?

Your local NHS Trust has a fixed annual budget. A new drug has been launched that can treat 10 patients who have a particular rare disease. To treat all 10 patients, the Trust has to divert funds from elsewhere, meaning that 100 patients with a common disease would **NOT** receive treatment.

The **common disease** treatment is **more beneficial** than the drug for rare diseases.

	Patients with the common disease	Patients with the rare disease
Numbers of patients	100	10
Cost per patient	LESS expensive	MORE expensive
Treatment benefit	MORE beneficial	LESS beneficial

The NHS must now decide how to divide the budget between the two groups. Using the information in the table above how do you think the NHS should divide it's budget?

Please use the slider to indicate your choice.

SUPPLEMENTARY DATA

S1 Table. Sub-group analysis by region

Attribute	**Coefficient (95% confidence interval)**		
	Scotland	**England**	**Northern Ireland & Wales**
Rare disease	-0.4473* (0.6383, 0.2563)	-0.5322* (-0.5866, -0.4778)	-0.4617* (-0.6674, -0.2560)
Cost of treatment	-1.78x-05* (-3.36e-05, -2.11e-06)	-2.34e-05* (-2.77e-05, -1.91e-05)	-1.51e-05 (-2.99e-05, -3.74e-07)
Debilitating and life threatening disease	0.1561 (-0.0765, 0.3888)	0.1713* (0.1021, 0.2405)	0.2975 (0.0179, 0.5771)
Availability of other drug treatment	-0.2346* (-0.4177, -0.0515)	-0.0537 (-0.1061, -0.0013)	-0.2060 (-0.3956, -0.0164)
Treatment benefit	0.9747* (0.7707, 1.1786)	0.8618* (0.8084, 0.9151)	0.6523* (0.4544, 0.8502)
Improvements to everyday life			
No improvements to everyday activities	-0.096 (-0.1930, 0.0007)	-0.0449 (-0.0721, -0.0177)	-0.1093* (-0.2009, -0.0177)
Returns patient to everyday life	0.8166* (0.6850, 0.9481)	0.6499 (0.6137, 0.6860)	0.6757* (0.5437, 0.8077)
Interaction Cost*Label	1.48e-05 (-4.56e-07, 3.01e-05)	1.98e-05 (1.56e-05, 2.4e-05)	1.15e-05 (-2.66e-06, 2.56e-05)
Constant	-0.1462 (-0.3302, 0.0378)	-0.1437 (-0.1980, -0.0893)	-0.1341 (-0.3428, 0.0747)

*significant at the 95% level

S2 Table. Sub-group analysis by socioeconomic status

Attribute	**Coefficient (95% confidence interval)**	
	Socioeconomic status ABC1	**Socioeconomic status C2DE**
Rare disease	-0.5766* (-0.6426, -0.5106)	-0.4454* (-0.5248, -0.3661)
Cost of treatment	-2.59e-05* (-3.12e-05, -2.05e-05)	-1.76e-05* (-2.36e-05, -1.16e-05)
Debilitating and life threatening disease	0.2379* (0.1543, 0.3214)	0.0957 (-0.0059, 0.1972)
Availability of other drug treatment	-0.0523 (-0.1160, 0.0114)	-0.1064* (-0.1821, -0.0307)
Treatment benefit	0.9081* (0.8414, 0.9747)	0.7830* (0.7077, 0.8582)
Improvements to every day life		
No improvements to everyday activities	-0.0366* (-0.0686, -0.0047)	-0.0753* (-0.1160, -0.0346)
Returns patients to everyday life	0.7017* (0.6581, 0.7453)	0.6081* (0.5555, 0.6608)
Interaction Cost*Label	2.21e-05* (1.69e-05, 2.72e-05)	1.44e-05* (8.61e-06, 2.02e-05)
Constant	-0.1849* (-0.2504, -0.1194)	-0.0862* (-0.1659, -0.0066)

S3 Table. Sub-group analysis by gender

Attribute	**Coefficient (95% confidence interval)**	
	Male	**Female**
Rare disease	-0.5350* (-0.6095, -0.4605)	-0.5090* (-0.5778, -0.4401)
Cost of treatment	-2.16e-05* (-2.73e-05, -1.60e-05)	-2.33e-05* (-2.89e-05, -1.76e-05)
Debilitating and life threatening disease	0.1684* (0.0731, 0.2637)	0.1851* (0.0982, 0.2720)
Availability of other drug treatment	-0.0982 (-0.1675, -0.0289)	-0.0483 (-0.1165, 0.0199)
Treatment benefit	0.8185* (0.7487, 0.8883)	0.8928* (0.8213, 0.9644)
Improvements to every day life		
No improvements to everyday activities	-0.0637* (-0.0985, -0.0289)	-0.0415* (-0.0780, -0.0050)
Returns patients to everyday life		
Interaction Cost*Label	0.6108* (0.5632, 0.6584)	0.7149* (0.6673, 0.7626)
Constant	1.75e-05* (1.21e-05, 2.29e-05)	2.04e-05* (1.49e-05, 2.59e-05)

S4 Table. Sub-group analysis by age

Attribute	**Coefficient (95% confidence interval)**	
	<50 years	**≥50 years**
Rare disease	-0.4767* (-0.5483, -0.4052)	-0.5742* (-0.6461, -0.5023)
Cost of treatment	-2.14e-05* (-2.68e-05, -1.59e-05)	-2.36e-05* (-2.95e-05, -1.78e-05)
Debilitating and life threatening disease	0.2225* (0.1341, 0.3109)	0.1332* (0.0388, 0.2276)
Availability of other drug treatment	-0.0661 (-0.1328, 0.0007)	-0.0847 (-0.1564, -0.0131)
Treatment benefit	0.8073* (0.7386, 0.8760)	0.9159* (0.8429, 0.9889)
Improvements to every day life		
No improvements to everyday activities	-0.0474* (-0.0833, -0.0115)	-0.0588* (-0.0940, -0.0237)
Returns patients to everyday life		
Interaction Cost*Label	0.5616* (0.5165, 0.6066)	0.7795* (0.7297, 0.8293)
Constant	1.86e-05* (1.33e-05, 2.39e-05)	1.93e-05* (1.36e-05, 2.49e-05)