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ORIGINAL RESEARCH ARTICLE

Eliciting Preferences for Prioritizing Treatment of Rare Diseases: the Role of Opportunity Costs and Framing Effects

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Abstract
Background Understanding societal preferences regarding resource allocation in the health sector has gained importance as countries increasingly base reimbursement decisions on economic evaluations. Preference elicitation using surveys, a common practice in the health sector, is subject to a range of framing effects.
Objective This research investigates the importance of (theoretically relevant) opportunity costs and (theoretically irrelevant) framing effects on stated preferences for prioritizing treatment of rare (orphan) diseases.
Methods We elicited preferences from Norwegians, aged 40–67, using simple trade-off exercises. Respondents were randomised to different opportunity costs of the rare disease or to different framings of the trade-off exercises.
Results Respondents were quite sensitive to the visual presentation of the choice problem, and, to a lesser extent, to focusing and labelling effects. Elicited preferences varied little in response to large changes in opportunity costs, suggesting scope-insensitivity among respondents.
Conclusions Preferences for prioritizing treatment of rare diseases elicited using trade-off exercises are insensitive to (theoretically relevant) opportunity costs, but sensitive to (theoretically irrelevant) framing effects.

Key Points for Decision Makers

- Little support for the existence of consistent preferences for prioritizing rare diseases
- Survey respondents are insensitive to large differences in opportunity costs when allocating resources
- Survey respondents do, however, display great sensitivity to how choice exercises are framed

1 Introduction

Understanding societal preferences regarding resource allocation in the health sector has gained importance as countries increasingly base reimbursement decisions on economic evaluations. Surveys are an important tool for assessing preferences in the health sector because limited or non-existent markets make revealed preference methods inappropriate. An inherent problem with surveys is that a wide range of 'framing' effects can influence responses, clouding the interpretation of results. Traditionally, economists assume that stated preferences reflect a complete and well ordered set of underlying preferences over pairs of options. Framing effects allow for the possibility that stated preferences are an expression of attitudes and what Kahneman et al. [1] call 'valuations', that is, the sign (positive or negative) and intensity assigned to an attitude. A narrow definition of framing generally refers to Tversky

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and Kahneman's [2] finding that decision making under risk is sensitive to whether a problem is described in terms of gains or losses; individuals may express very different valuations for options that are identical from an objective standpoint but framed in terms of gains rather than losses. In this paper we employ a broader definition that includes instances in which presentation of the choice problem varies but outcomes "are equivalent from the perspective of economic theory" [3]. This definition of framing is consistent with what *Standards for Educational and Psychological Testing* [4] calls 'construct-irrelevance' and can capture the potential impact of heuristics and cognitive biases on choice. Given the impossibility of avoiding framing problems altogether, it is important to have a clear understanding of the extent to which alternate approaches to asking questions about preferences yield different results.

A growing body of literature provides evidence of framing effects (broadly defined) in preference elicitation related to health care. For example, Lloyd [5] reviewed selected articles documenting the role of heuristics in stated preference elicitations relying on willingness-to-pay (WTP) and discrete choice experiment (DCE) methodologies. How information is presented and how choices are made all have important effects on expressed preferences; for example, identified versus unidentified treatments, life expectancy versus cumulative probabilities, probabilities of living versus dying [6], accept versus reject treatment, presence versus absence of default option [7]. There is evidence that willingness-to-pay for a health intervention is unresponsive to the size of the health outcome but responsive to a variety of irrelevant information [8, 9].

This study examines the importance of framing effects in the context of eliciting preferences for prioritizing treatment of rare (orphan) diseases, typically defined as having prevalence between 0.18 and 7.5 per 10,000 [10]. Orphan diseases gained attention in the 1980s because of concerns that small patient populations provided few incentives for pharmaceutical companies to research and develop treatments. Legislation passed to address the problem, most notably the US Orphan Drug Act [11] and the EC regulation on orphan medicinal products [12], created grants, fast-track approval processes and extended patent periods for orphan drugs. While the growing number of treatments for orphan diseases speaks to the success of orphan drug regulations, it also poses challenges for healthcare systems. Because most orphan drugs are extremely costly, they typically fail to meet standard cost-effectiveness criteria for public reimbursement leading to a debate about exempting orphan drugs from the standard criteria [10, 13, 14]. McCabe et al. [10] suggested that a societal preference for prioritizing rarity could justify such an exemption.

The strength of potential preferences for rarity can be measured by eliciting one's willingness to forego the treatment of patients with a common disease. In one of the first surveys to examine preferences for rarity, Desser et al. [15] used simple trade-off exercises to gauge respondent preferences when faced with two patient groups who differed only in terms of disease prevalence and found little evidence of a general preference for rarity per se—a large majority (65 %) were indifferent between treating 100 rare versus 100 common disease patients when costs were identical, while 24 % favoured treating common disease patients and only 11 % favoured treating the rare disease group. Increasing the opportunity cost of the rare disease to four times that of the common disease; that is, 100 rare versus 400 common disease patients, resulted in an increase in support for prioritizing common disease patients, as would be predicted by economic theory, but an unexpectedly large number of respondents (45 %) continued to express indifference between the two patient groups, raising questions about the extent to which elicited preferences might have been sensitive to (theoretically irrelevant) framing issues.

Our objective in this paper is to examine the relative importance of potential framing effects in elicitation of preferences for rarity using trade-off exercises. We do so by first testing how responsive respondents are to a (theoretically relevant) economic incentive: the *opportunity cost* of treating rare disease patients measured in terms of the number of common disease patients that respondents are willing to forego. We hypothesise that the higher the opportunity cost, the lower the support for the rare disease.

We then turn our attention to the degree to which the following three different framings of the survey questions affect elicited preferences.

1. Visual presentation: The horizontal slide bar used by respondents to allocate resources between rare and common disease patients may lead to a *midpoint bias* in responses [16]. We hypothesise that a different visual presentation relying on randomly ordered vertical bars (where each bar indicates a different potential distribution of resources between the two patient groups) would reduce the number of respondents choosing to divide resources equally between the groups.
2. 'Focusing' with reference to general principles: Focusing respondents' attention on the broader implications of their choices by first asking them to select the principle they would like policy-makers to apply when allocating resources may influence their expressed preferences [17, 18]. We examine the extent to which this is true with respect to preferences for prioritizing rarity. From an economic theory standpoint, if an

individual's stated preferences are a reflection of a set of complete, well ordered preferences over pairs of options that have different implications for health maximisation (efficiency) versus fairness, a 'focusing' exercise should have no effect on choices. If, on the other hand, respondents' stated preferences are an expression of attitudes that can be influenced by the focusing exercise, the choice may depend on their attitudes regarding efficiency versus fairness. A general preference for efficiency would likely result in an increase in the share of resources devoted to the common disease group, while the share allocated to the rare disease group would probably increase given a preference for fairness.

3. 'Labelling' of disease groups: Are responses to the trade-off exercises purely reflective of preferences about prioritizing rarity per se or might they be indicative of more general distributive preferences? We hypothesise that similar responses would be obtained with *any* two groups of patients (with equally severe diseases and equal expectations of improved health), who could be differentiated by any chosen factor—no matter its relevance or importance.

2 Methods

2.1 Survey Design

To ensure comparability with results from Desser et al. [15], we used the same basic survey design. Respondents were asked to imagine that extra funds had become available in the health budget that could provide treatment of additional patients from two different patient groups, one with a rare disease, the other with a common disease. The two patient groups were characterised as having identical health problems, described along the mobility and pain dimensions in the EQ-5D instrument [19]: "patients experience some problems in walking about and have extreme pain". Expected treatment benefits were also described identically ("return to complete health"). Disease prevalence, however, differed with rare and common defined, respectively, as 100 and 10,000 cases in Norway (population 5 million). Respondents completed allocation exercises for two scenarios: an initial 'equal-cost' scenario, in which the opportunity cost of treating one rare disease patient was one common disease patient, and a 'costly-rare' scenario, in which the opportunity cost of treating one rare disease patient was a larger number of common disease patients. In all cases, respondents were instructed to choose the allocation that they *personally* preferred. Respondents were randomised to seven survey versions[1]. Table 1 provides a summary of the different survey versions. (Electronic Supplementary Material [ESM] 1 provides the text of the basic survey version.)

In the first four survey versions (V1–V4) we varied the opportunity cost (OC_R) of treating a rare disease patient, OC_R = 25:1, 8:1, 4:1 and 1:8, respectively, by varying the maximum number of common disease patients that could be treated instead. Because the 4:1 opportunity cost, which replicates the one used in Desser et al. [15], reflects a cost-effectiveness ratio below that associated with health technology assessments of even moderately priced orphan drugs, we included the 8:1 value to represent a more realistic 'moderately priced' orphan drug [20] and the 25:1 value as an even higher cost to test for price sensitivity. The 1:8 opportunity cost was intended to detect potential evidence of a preference for prioritizing treatment of common disease patients, should one exist.

The allocation exercise was completed using a horizontal slide bar (Fig. 1) marked with the number of patients in each disease group that would receive treatment under 11 possible allocations, ranging from 100 rare (0 common) disease patients at one end of the bar, to 0 rare ($OC_R \times 100$ common) at the other. The allocations varied in increments of 10 rare ($-OC_R \times 10$ common) disease patients as one moved along the bar.

In survey versions V5–V7 the opportunity cost of the rare disease treatment was held constant at 8:1, but other aspects of the survey were varied. V5 replaced the (horizontal) slide bar with a randomly ordered (vertical) bar chart, in which each bar represented a potential allocation of funds and indicated both total numbers treated and the division of resources between the rare and common disease groups (Fig. 2). Results from V5 are compared with V2, the basic 8:1 opportunity cost version with a horizontal slide bar.

In V6 respondents first selected one allocation principle, from among four options (Fig. 3), which they felt health authorities should apply when allocating resources between patient groups and then completed the allocation exercise using the randomly ordered bar chart. Results from V6 are compared with V5, which also used the randomly ordered bar chart for the allocation exercise, but made no mention of allocation principles.

[1] We exclude from the current discussion two additional survey versions: The first tested whether a slight modification to the wording of the survey used in Desser [15] had an effect on responses. The second served as a bridge between survey versions V2 and V5 by explicitly providing *total numbers of patients treated* on the slide bar used for allocation choices in V2, as this information was provided in the random bar chart used in V5 (see below). There were no significant differences in the responses in either case. A complete set of all versions of the current survey is available upon request.

Table 1 Overview of survey versions (V1–V7), which differ in terms of opportunity costs and framing (allocation mechanism and other information)

Version	*n*	OC[a]	Allocation mechanism	Other information
V1	314	25:1	Slide bar	
V2	315	8:1	Slide bar	
V3	312	4:1	Slide bar	
V4	253[b]	1:8	Slide bar	
V5	316	8:1	Random bars	
V6	315	8:1	Random bars	Allocation principles
V7	312	8:1	Slide bar	Labelled with cancer info rather than rarity

[a] Opportunity cost (*OC*) of treating the rare disease (common patients : rare patients)

[b] V4 an error in the original randomisation led to a smaller number of respondents for this survey version. This had no impact on our ability to detect relevant differences in responses

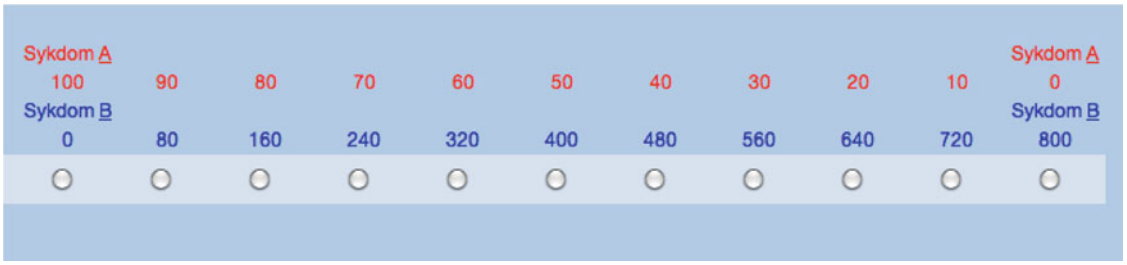

Fig. 1 Slide bar mechanism used to allocate resources between rare and common disease patients for basic survey versions, shown with opportunity cost (common patients : rare patients) of 8:1. Text introducing slide bar in the survey (translated from Norwegian): *If it is possible to divide the extra funds so that some patients with Disease A (rare) and some with Disease B (common) can be treated, how would you recommend that the funds be divided? Allocate the extra funds between the patient groups by clicking and sliding the green and white pointer* (not shown in the figure). Note: The 'radio buttons' were not visible to respondents, but the pointer could only be placed at those points

Finally, V7 presented alternate descriptions of the patient groups: instead of being described as having a rare disease, one patient group was said to have a variant of colon cancer that responded to a new treatment. The other patient group was said to have a variant of colon cancer that only responded to an existing treatment rather than being described as having a common disease (Fig. 4). The 'cancer' wordings were used in all V7 questions. The results of V7 are compared with V2.

2.2 Methods of Analysis

Because the maximum number of rare disease patients that can be treated is fixed at 100 across survey versions, a respondent's preferred combination of number of patients treated from each group will reflect both the preferred number of rare disease patients treated and the preferred share of the extra funding to be allocated to the rare disease group. The preferred share of funding to be allocated to the common disease group is simply the complement of that provided to the rare disease, but the number of common patients treated will depend on the specified opportunity cost. (See Sect. 2.1).

To facilitate comparison and interpretation of these responses, we characterised the distribution of choices in each survey version by examining: (i) the mean response, which represents the average share of the extra funds that respondents devote to treatment of the rare disease and can be thought of as the 'demand' for treating the rare disease group at a given opportunity cost, and (ii) the percent of respondents who allocated $\leq$20 %, 50 % (i.e., equal distribution) or $\geq$80 % of funds to rare disease patients. We tested for differences in means across survey versions using *t* tests if the responses were normally distributed or a Wilcoxon rank-sum test if not. To test for differences between survey versions in the share of respondents allocating a specified share of resources to the rare disease group, we performed *Z* tests of proportions. All statistical analyses were performed using STATA.

2.3 Survey Methods and Sample Description

TNS Gallup Norway surveyed a random sample of Norwegians, aged 40–67 years, via the Internet in June 2010. To ensure rapid survey completion, Gallup invited

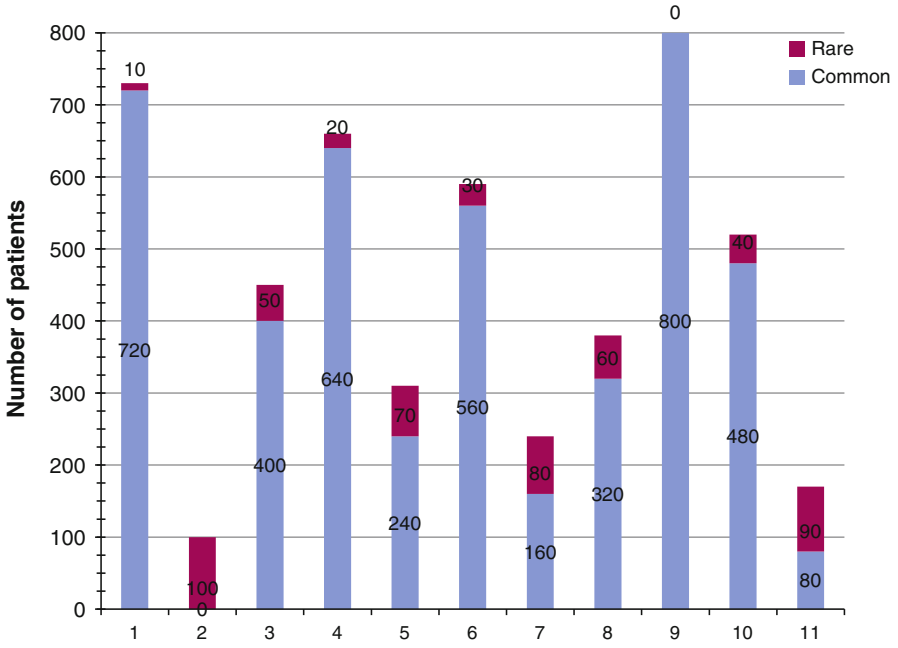

Fig. 2 Random bar mechanism used to allocate resources between rare and common disease patients for survey version V5, with opportunity cost (common patients : rare patients) of 8:1

Instructions to respondents: *Each bar in this figure represents a different division of patents with the two diseases. The red area shows the number of rare disease patients while the blue area shows the number of common disease patients. Divide the extra funding between the to patient groups by clicking on the green and white pointer* (not shown here) *and moving it to the number below your preferred distribution.*

Fig. 3 Allocation principle options for survey version V6

Which of the following principles would you like health authorities to apply when they must decide how resources should be divided between different patient groups? Assume that the diseases are equally severe and the expected benefits of treatment are equal for individual patients.

Divide the budget so that the largest possible number of patients receive treatment, regardless of whether they are suffering from a rare or a common disease

Divide the budget so that equal numbers of patients within each patient group receive treatment even though this will result in a smaller total number of patients treated

Give some of the budget to rare disease patient group, which is expensive to treat, but give the largest share of the budget to the patient group that is least expensive to treat even though this will result in a somewhat smaller total number of patients treated.

Give the largest share of the budget to the rare disease patient group, which is expensive to treat, but give some of the budget to the patient group that is least expensive to treat even though this will result in a much smaller number of total patients treated.

5,593 individuals from its active, randomly recruited panel of 60,000 to participate in the survey. Of the 3,359 people who responded to the invitation, 167 opened the survey but didn't respond to any questions, 119 returned partially completed surveys and 306 were unable to answer because the desired number of respondents had already been reached. The resulting group of 2,767[2] respondents represents 49 % of those who were invited to participate[3] and 82 % of those who accepted the invitation. The sample was representative of the target age group in the Norwegian population for gender (48 % female) and personal income (44 % with income ≥400,000 Norwegian kroner [≈€50,000, June 2010]), had a slightly higher level of education and was relatively balanced for these characteristics across survey versions (ESM 2).

[2] This represents the total number of respondents for the nine survey versions to which individuals were actually randomized. Because we exclude two survey versions from our discussion here, we report on a total sample of 2,137.

[3] TNS Gallup is unable to track how many of the 5,593 individuals who were invited to participate actually received the email invitation.

Version V2 (rare/common version)
Now imagine that it is less expensive to treat Disease B than Disease A. With the extra funds it is now possible to treat 100 patients with Disease A or 800 patients with Disease B. Otherwise, everything is as described before. Disease A is a rare disease (100 cases in Norway) and Disease B is a more common disease (10,000 cases in Norway). The two diseases are equally serious (limited mobility and extreme pain). For both patient groups, treatment will lead to complete recovery.

Version V7 (cancer version)
Now imagine that it is less expensive to treat Disease B than Disease A. With the extra funds it is now possible to treat 100 patients with Disease A or 800 patients with Disease B. Otherwise is everything as described before. Disease A is a specific type of colon cancer that can be treated with a new type of medication and Disease B is a slightly different type of colon cancer that can't be treated with the new medication, but can be treated with the old medication. The two diseases are equally serious (limited mobility and extreme pain). For both patient groups, treatment will lead to complete recovery.

Fig. 4 Differences in descriptive language used in survey versions V2 (rare/common version) and V7 (cancer version)

3 Results

3.1 General Observations

In this section, we report detailed results only for the allocation question in the costly-rare disease scenario, in which respondents were asked to divide funds between 100 rare disease patients and a larger number (usually 800) of common disease patients, since these results speak most directly to the research questions raised in this research. Responses to the equal-cost scenario questions, asked mainly for consistency and to validate results from Desser et al. [15], followed a similar pattern to the earlier paper. A large majority of respondents divided resources evenly between rare and common disease patients, but more of the remaining respondents favoured treating the common disease group, a result that may reflect the much larger probability of suffering from a common disease. For questions requiring respondents to select only one patient group for treatment (or express indifference), results for both the equal-cost and costly-rare scenarios were consistent with but provided less nuanced information than when respondents allocated resources between the two patient groups. Detailed results are presented in ESM 3.

3.2 The Effect of Varying Opportunity Cost

In Table 2, we present results indicating the extent to which varying the opportunity cost of the rare disease in survey versions V1–V4 (25:1, 8:1, 4:1 and 1:8) affected the share of funds allocated to treating the rare patient group. Starting with the 1:8 opportunity cost (V4), we found statistically significant *decreases* in the mean allocation to the rare disease group as 'price' (common disease patients forgone/rare disease patient treated) increased in all but one case. A price increase from 1:8 (V4) to 4:1 (V3) yielded a decrease in mean allocation to the rare disease from 49.1 to 45.3 % ($p = 0.04$); from 4:1 (V3) to 8:1 (V2) decreased the mean allocation from 45.3 to 40.5 % ($p = 0.003$); while from 8:1 (V2) to 25:1 (V1) there was no significant change in mean allocation, 40.5–41.7 % ($p = 0.48$). Although these results imply some sensitivity to opportunity cost, the variation in the share of funds allocated to the rare disease group was tiny: Moving from an opportunity cost of 4:1 to 25:1 reduced the share allocated to the rare disease by only 3.6 % points.

We also examined the *number* of rare patients treated as a percentage of total number of patients treated at the mean allocation of funds for each price. There was a uniform decrease in this percentage as the opportunity cost of the rare disease rose. However, these figures need to be normalised to account for the fact that an increase in the opportunity cost of treating the rare disease is equivalent to increasing the potential maximum number of patients treated, thereby automatically reducing the number of rare disease patients treated as a percentage of total patients treated for any *given* share of funds allocated to the rare disease. By assuming that the share of resources devoted to the rare disease was 45 % at every price (the actual allocation at $OC_R = 1{:}1$)[4] and examining the difference between the resulting number of rare patients treated as a percentage of total treated and the actual percentage of rare to total patients treated (see last two columns in Table 2) we found that the component attributable to the change in price was negligible. As with the share of funds allocated to the rare disease, there is very little variation in the normalised number of rare disease patients treated with respect to changes in price.

3.3 Effects of Framing

3.3.1 Visual Effects of Alternate Allocation Mechanisms: Slide Bar versus Random Bars

To test the second hypothesis, that respondents using the horizontal slide bar allocation mechanism would be more

[4] This information is available because all respondents completed the allocation question for the 'equal-cost' scenario. See ESM 3.

Table 2 The effect of varying opportunity cost (*OC*) on allocations to the rare disease: mean percentage of funds allocated to rare disease; percentage of respondents allocating ≤20, 50 or ≥80 % of funds to rare disease; and rare treated (*RT*) as percentage of total treated (*TT*) (actual and normalised)

Version	OC[a]	*n*	Mean[b] (SD)	≤20 %	50 %	≥80 %	RT/TT[c] (%)	RT/TT normalised[d] (%)
V1	25:1	314	41.7 (21.1)	22.9	38.9	4.8	2.8	3.2
V2	8:1	315	40.5[e] (20.5)	25.7	45.1	4.5	7.8	9.3
V3	4:1	312	45.3[f] (20.7)	16.0	48.4	8.7	17.2	17.0
V4	1:8	253	49.1 (21.9)	14.2	52.2	12.7	88.5	86.7

[a] Opportunity cost (*OC*) [common patients : rare patients]

[b] % Funds allocated to rare disease, which is equivalent to rare patients treated (*RT*)

[c] Total patients treated (*TT*) = RT + (100 × OC − OC × RT). Note that TT will increase with the opportunity cost unless all funds are allocated to the rare disease so RT/TT will decline as OC increases even if RT does not change

[d] RT/TT when OC is 1:1 (equal treatment costs) and TT = 100. We used RT = 45.0, the mean share allocated by V1–V4 respondents to the rare disease in the equal opportunity cost (OC 1:1) question answered by all respondents, to compute the normalised RT/TT for each version. The difference between the actual and normalised RT/TT represents the change in allocation to rare disease patients that is directly attributable to the change in OC of treating the rare disease

[e] Significantly different from mean V3 (*t* test, $p < 0.01$)

[f] Significantly different from mean V4 (*t* test, $p < 0.05$)

likely to divide funds equally between the two patient groups than those using a more visually neutral allocation mechanism, we created a different selection mechanism (Fig. 2) using 11 randomly arranged bars, each indicating a possible combination of numbers of rare and common disease patients to be treated. The height of each bar reflected total number treated for a particular division of resources, with the red and blue areas showing the rare and common patient groups, respectively. Figure 5 provides a comparison of the choices of respondents to V2 (slide bar), V5 (random bars) and V6 (principles, see Sect. 3.3.2).

The mean share of funds allocated to the rare disease using the slide bar mechanism (V2) was 40.5 % (Table 3A) versus 44.7 % using the random bar (V5), (Wilcoxon rank-sum: $W = 95{,}111$, $z = -1.965$, $p = 0.049$). There is also a clear difference in the proportion of respondents opting to divide the funds *equally* between the patient groups under the two allocation mechanisms: 39.4 % of those using the slide bar versus 13.6 % of those using the random bars (*Z* test: $p < 0.001$). Among slide bar respondents (V2), 25.7 and 4.5 % allocated ≤20 and ≥80 % of funds to the rare disease, respectively, while for random bar respondents the comparable results were 30.1 and 20.3 %.

3.3.2 Focusing Effect of Defining Allocation Principles

Survey V6 examined the effect of asking respondents to choose how, *in principle*, they would want health authorities to prioritise rare versus common disease patient groups, given limited resources and a very costly treatment for the rare disease, *before* answering the allocation question. The allocation question made use of the same random bar mechanism used in survey version V5 (see Sect. 3.3.1). Comparing the mean share allocated to the rare disease in V6 (40.5 %) (Table 3B) and V5 (44.7 %), we found a marginally significant difference (Wilcoxon rank-sum: $W = 103{,}796$, $z = 1.734$, $p = 0.08$). There was a significant difference in the percentage of respondents opting to divide the funds *equally* between patient groups for V6 and V5, 7.6 versus 13.6 % ($p = 0.01$). The percentage of respondents allocating ≤20 and ≥80 % to rare disease patients was 35.6, and 16.8, respectively for V6 and 30.1, and 20.3 for V5.

Responses to the principles question indicated that 76.8 % of respondents favoured treating the greatest number of patients, 4.8 % favoured treating equal numbers of rare and common disease patients, 17.5 % recommended reserving some funds for the rare disease patients, but using most for treatment of the common disease, and 1.0 % favoured giving most of the funds to the rare disease patients. The actual choices regarding allocation of funds in V6 only partially reflected the beliefs respondents expressed in their choice of preferred allocation principle. For example, among those who favoured treating the greatest number of patients (which would entail treating only common disease patients), only 6.2 % allocated all funds to the common disease, while 38.4 % allocated more than 80 % of funds to common disease patients. The 17.7 % in this group who chose to allocate 80 % of funds to the rare disease patients are clearly inconsistent.

3.3.3 Labelling Effects: The 'Cancer Version'

Finally, we examined the extent to which the inclination to divide resources evenly between diseases might indicate a

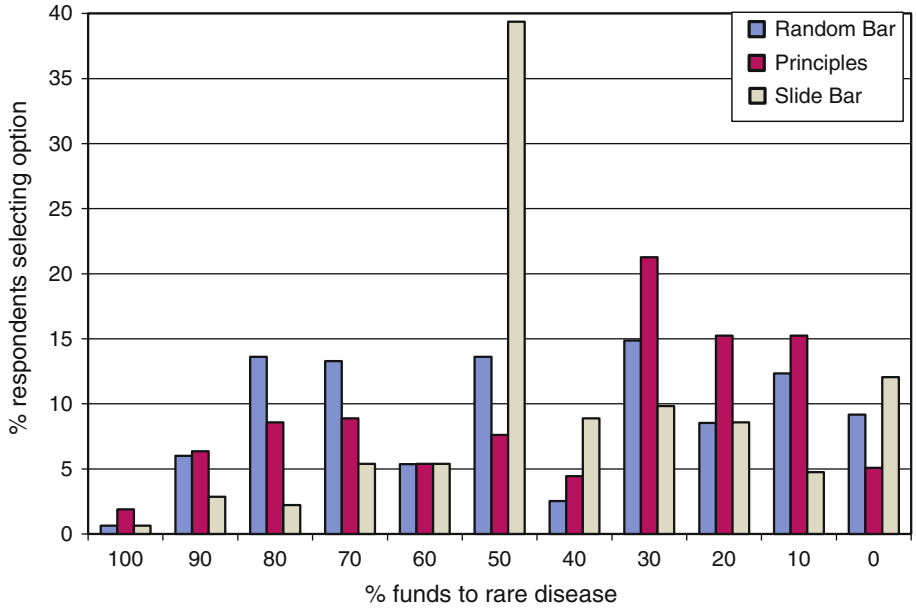

Fig. 5 Allocations of funds to rare disease for survey versions V2 (slide bar), V5 (random bars) and V6 (random bars and allocation principles)

Table 3 Effects of framing on distribution of funds to rare versus common disease treatment: mean percentage of funds allocated to rare disease; percentage of respondents allocating ≤20, 50 or ≥80 % of funds to rare disease

Framing Effect	OC[a]	*n*	Mean[b] (SD)	≤20 %	50 %	≥80 %
A. Visual effect of (horizontal) slide bar vs. (vertical) random bar chart on allocation choices						
V2: slide bar	8:1	315	40.5 (20.5)	25.7	45.1	4.5
V5: random bars	8:1	316	44.7 (28.9)[§§]	30.1	13.6***	20.3
B. Effect of stating allocation principles before making allocation choices						
V5: random bars	8:1	316	44.7 (28.9)	30.1	13.6	20.3
V6: principles, random bars	8:1	315	40.5 (27.9)[§]	35.6	7.6**	16.8
C. Effect of naming: cancer vs. rare and common disease description						
V2: slide bar	8:1	315	40.5 (20.5)	25.7	45.1	4.5
V7: cancer[c]	8:1	312	43.6 (22.3)[+]	19.6	52.9*	7.7

[a] Opportunity cost (*OC*) [common patients : rare patients]

[b] *Mean* mean budget share to rare disease patients

[c] In this version, 'rare' disease is the variant of colon cancer described as responsive to a new medication, while 'common' disease is the variant of colon cancer described as responsive only to existing medication

[§] Significantly different from mean V5 at $p < 0.10$, [§§] significantly different from mean V2 at $p < 0.05$ (Wilcoxon rank-sum)

* Significantly different from proportion V2 at $p < 0.05$, ** significantly different from proportion V5 at $p < 0.05$, *** significantly different from proportion V2 at $p < 0.001$ (Z test)

[+] Significantly different from mean V2 at $p < 0.10$ (t test)

general preference for 'fairness' rather than a preference for rarity per se by replacing the labels 'rare' and 'common' with other distinctions that had no effect on disease severity or treatment effectiveness. To test this relationship we compared results from survey V7, in which patient groups were labelled as having different genetic variants of colon cancer, with those from survey V2, which used the standard 'rare' and 'common' labels. (See Fig. 4 for wording differences between the versions.)

Response patterns varied somewhat between the two versions (Table 3C). The mean budget share allocated to the expensive disease group was 43.6 % for the cancer survey version and 40.5 % for the standard rare/common description (Wilcox rank-sum: $p = 0.075$). A larger share of respondents chose to divide resources equally between the patient groups in the cancer version than with the standard labels, 52.9 versus 45.1 %, respectively ($p = 0.05$). The percentage of respondents preferring to allocate ≤20 and ≥80 % to the expensive disease group was 19.6 and 7.7, respectively, when the expensive disease was labelled as 'the variant of colon cancer treatable with

the new medication' compared with 25.7 and 4.5 when the expensive disease was 'rare'.

4 Discussion

In this survey we applied a person trade-off exercise to examine how the preferred allocation of hypothetical extra funds between rare and common disease patients varied in response to changes in economic incentives (opportunity costs) and in the framing of survey questions. In general, our findings indicate that framing effects can be important while evidence of price responses was more equivocal.

4.1 Response to Different Opportunity Costs

Although we find some support for the hypothesis that the share of funds allocated to the rare disease would be responsive to changes in the opportunity cost of treating the rare disease, the limited variation in respondents' mean allocation of funds to the rare disease as price varied substantially leads us to question whether this, in fact, reflects a preference-based price response. We suspect, instead, that it may be evidence of 'scope insensitivity', a term normally used in contingent valuation studies to indicate that willingness-to-pay is insensitive to differences in the size of health outcome [8, 9]. There are several explanations for scope insensitivity, including purchase of moral satisfaction—the 'warm glow' one experiences in giving [21] and the impact of affect heuristics—shortcut emotional responses (as opposed to stated economic preferences) evoked by the framing of a choice [1] that could easily apply when individuals are asked to decide how many rare versus common disease patients to treat.

A final point of interest regarding price concerns the allocation of funds between the rare and common disease groups when the common disease had the *higher* opportunity cost. At an opportunity cost of the rare disease of 8:1, 4.5 % of respondents allocated more than 80 % of funds to the rare disease group, however at a rare disease opportunity cost of 1:8, 14.2 % of respondents allocated more than 80 % of funds to the more expensive (common) disease group. This is consistent with our earlier findings that, among those who were not indifferent between rare and common disease patients, there was a stronger preference for treating the common disease.

4.2 Framing Effects

We were not surprised to find that relying on the chart of randomly arranged bars rather than the horizontal slide bar in the allocation exercise resulted in a significant reduction in the proportion of respondents that divided funds equally between the groups. The result is consistent with the documented central tendency bias in responses to Likert-scale questions, particularly those arranged horizontally [16]. It may reflect both a desire to avoid extreme positions and the visual ease of selecting the midpoint if one is uncertain about how to answer, both of which are relevant concerns for our allocation exercise using the slide bar. A choice mechanism relying on randomly arranged bars presenting the same information breaks the visual basis for a central tendency bias, but it may also have introduced a high degree of complexity to the exercise, making it more difficult to interpret the results. Our finding in this case should therefore be viewed with some caution.

We also examined the impact of focusing respondent attention more explicitly on the allocation trade-offs required when the opportunity costs of treating rare versus common disease patients differ substantially by having respondents select an allocation *principle* before dividing resources between the two patient groups. This led to a small, marginally significant decrease in the mean allocation to the more costly rare disease and a significantly different distribution of responses, with a significant increase in the share of respondents who would devote 80 % or more of the resources to the common disease group. Our results are consistent with findings by Aguilar et al. [17] that creating psychological distance from a moral dilemma (in this case by asking respondents which principles they would like *health authorities* to use in making difficult allocation decisions) favours choices that are more "uncompromisingly consequentialist", i.e. utilitarian, in nature.

Examining the effect on allocation preferences of changing the labels attached to the two treatment groups was motivated by a desire to determine if the result in Desser et al. [15], where a large proportion of respondents divided resources relatively evenly between rare and common disease patients despite the high opportunity cost of the rare disease, was related to rarity, per se, or might have reflected a more general concern for distributive fairness. The distinction is not trivial since a specific preference for prioritizing rare disease patients could justify special exemptions for this group from the standard cost-effectiveness criteria used in the approval process for new treatments. Our results indicated that labelling did have some effect on expressed preferences—there was a different distribution of resources between the patient groups in the 'cancer' survey version than in the rare versus common disease version, with a smaller share of 'cancer' version respondents favouring the less expensive treatment group and a higher percentage choosing to divide resources equally—but it is a bit unclear how to interpret this result. We can imagine several interpretations. Identifying both patient groups as having cancer may have caused

respondents to view them as more equivalent than with the rare versus common disease labelling, resulting in a larger share of respondents choosing to divide resources equally between the groups. Alternatively, fears associated with the term *cancer* might have made respondents more reluctant to choose between the patient groups. Finally, the shift towards devoting an increased share of resources to the group with the higher opportunity cost of treatment, that is, towards the cancer variant that was responsive to the new medication, might have been a reaction to the stated 'newness' of the medication. The main message here is that choice of wording in surveys remains a critical issue.

4.3 Limitations and Future Research

Our survey has several limitations. There are two changes in design that we would advise for anyone wishing to repeat this research: (i) the slide bar rather the random bar chart in the allocation principles version (V6) would provide a more direct comparison to the basic survey version; and (ii) in the cancer version (V7), avoid using the term 'new' to refer to the cancer drug that is available for one of the cancer variants; we suspect that it might confound the results. Another potential survey limitation is that the random bar chart used in V5 is more cognitively demanding than the horizontal slide bar as a mechanism for indicating the preferred allocation of funds between rare and common disease patients. It is possible that the extra thought needed to locate the preferred option encouraged respondents to think more carefully about their choice and thus indicate their 'true' preference; however, it is also possible that some respondents may have selected randomly because of difficulty finding the allocation that they actually preferred. Additional tests with other visual arrangements would be useful to confirm our finding that a visual midpoint bias could be the reason for the large percentage of respondents that divided resources equally between the rare and common disease groups.

Research into society preferences for prioritizing the treatment of rare diseases is quite new and this work is, to the best of our knowledge, the first to investigate the importance of framing effects in eliciting preferences about rarity. As such, all of the results about specific framing issues would benefit from additional verification in future research. Our finding that (theoretically irrelevant) framing issues appear to have a more substantial impact on preferences than (theoretically relevant) opportunity costs is, however, consistent with a wide range of similar findings of scope insensitivity in other arenas. An important topic for further consideration is how (or whether) the knowledge that elicited preferences can be sensitive to framing effects should influence the use of such preferences among policy-makers responsible for decisions about resource allocation.

5 Conclusions

In the context of prioritizing treatment of equally severe rare and common diseases, we examined the extent to which preferences elicited using trade-off exercises are responsive to opportunity costs and the extent to which they display sensitivity to alternative framing issues. We found evidence of framing effects, but less conclusive indications of preference-based price response. Respondents were particularly sensitive to the type of allocation mechanism employed; a horizontal slide bar is significantly more likely to result in an equal division of funds than a more visually neutral mechanism. Requiring that respondents indicate the principle they would prefer policy-makers to apply in setting treatment priorities had small but significant effects on the way in which they distributed funds between the rare and common disease treatment groups in a subsequent allocation exercise. Preferences were also sensitive to the labelling of the two treatment groups. Indications that responses were responsive to opportunity costs were less clear-cut. While an increase in the opportunity cost of treating the rare disease resulted in a smaller share of funds allocated to rare disease patients, the effect was quite insensitive to the size of the price change, potentially indicating scope insensitivity in the survey responses.

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