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A Discrete Choice Experiment Investigating Preferences for Funding Drugs Used to Treat Orphan Diseases

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Abstract

Policy debate about funding criteria for drugs used to treat rare, orphan diseases is gaining prominence. This study presents evidence from a discrete choice experiment investigating the preferences of the public regarding public funding for drugs used to treat rare diseases and common diseases using a convenient sample of university students. We find that: other things equal, the respondents do not prefer to have the government spend more for drugs used to treat rare diseases; that respondents are not willing to pay more per life year gained for a rare disease than a common disease; and that the public weighs relevant attributes of the coverage decisions (e.g., costs, disease severity, treatment effectiveness) similarly for both rare and common diseases. The results confirm the importance of severity and treatment effectiveness in preferences for public funding. Though the first study of its kind, the results send a cautionary message regarding the special treatment of orphan drugs in coverage decision making.

1.0 INTRODUCTION

Orphan disease and their treatments are currently the focus of considerable policy attention. This policy attention arises because those who suffer from an orphan disease are perceived to be disadvantaged under the prevailing model of development for medical treatments, especially drugs. A number of factors inhibit the development of treatments for rare disease and access to those treatments that are developed. Orphan diseases are by definition rare (Wastfelt et al., 2006): in Europe, an orphan disease is defined as serious, life-threatening and affecting fewer than 1 in 2,000 people (European Committee for Orphan Medicinal Products); Canada lacks an accepted definition, but the Canadian Organization for Rare Disorders (Canadian Organization for Rare Disorders, 2009) defines a rare disease as affecting fewer than 1 person per 2,000 people; and in the United States the Orphan Drug Act (1983) defined an orphan disease as affecting fewer than 200,000 persons in the US1 or more than 200,000 persons and the expectation that drug development costs will not be recovered from sales (Dear et al., 2006).

Because the diseases are rare the pharmaceutical industry has little financial incentive to develop new medicines. The small market size makes the return on investment insufficient to attract private capital. Treatments that are developed face a series of hurdles making it to market and getting placed on insurance formularies. Clinical evidence of safety and efficacy is often less strong because of small patient samples in randomized clinical studies and the reliance on surrogate markers of effectiveness that are not always well-linked to final outcomes (Drummond et al., 2007b). The high fixed costs of development and the small number of patients lead to high cost-per-patient (DiMasi et al., 1991; Medecins Sans Frontieres, 2001). Consequently, relatively high incremental cost-effectiveness ratios and the poor value for money, lead to denial of coverage (Drummond et al., 2007a).

Several governments (e.g., United States, Japan, the EU) have introduced special financial incentives such as tax credits to spur the development of treatments ("orphan drugs") for rare diseases (Dear et al., 2006; Cheung et al., 2004; Denis et al., 2009)2. Such incentives mitigate the industry's high risks and lower potential return on investments in treatments for rare diseases. These incentive

[1] Given the current US population, the implied incidence rate is less than 1.3 per 2000 persons.

[2] Such policies require that "orphan treatments" be defined. The Orphan Designation procedure at the EMEA, states that to qualify a medicine must meet two conditions: a) the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that either affects less than 1 in 2,000 individuals; or that without incentives is unlikely to generate sufficient return on investment to justify the expenditure and b) there is an absence of solution or the drug brings a significant benefit compared to the present situation (Denis *et al.*, 2009).

schemes have increased numbers of requests for the Orphan Designation of drugs by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) (Denis et al., 2009). However, such policies are of limited value if treatments developed ultimately fail to get covered by insurers because of their high cost-effectiveness ratios. In response to this latter problem, some have proposed that funders apply a different, higher, cost-effectiveness threshold for drugs used to treat rare diseases (see, e.g., discussion in (Drummond et al., 2007a). This policy recommendation, however, is controversial.

Arguments for setting a higher cost-effectiveness threshold for orphan drugs vary, but the two most commonly invoked are rights-based arguments and the rule-of-rescue. Rights-based arguments posit that all members of society are entitled to access to a minimum amount of health care. Given this premise, rare disease sufferers have a right to a basic level of quality health care even if treatment does not offer the largest health gain for its cost (Hughes et al., 2005). Secondly, the rule-of-rescue principle asserts that society should come to the aid of those facing immediate, often life-threatening danger. In the orphan drug debate, the underlying premise of this principle is used to argue that society should not abandon the most severely ill individuals with rare diseases who need highly specialized treatment and have no other treatments available (Hughes et al., 2005; Dolan and Olsen, 2002).

Opponents of such a policy offer a corresponding set of arguments. Hughes et al. (2005), argue that orphan diseases are not inherently life-threatening, although many are debilitating and reduce life-expectancy. McCabe et al. (2006) characterize arguments based on the rule-of-rescue as emotional reactions to identifiable individuals in catastrophic events, but that unknown patients will become identifiable in the future and hence it is an ethically invalid principle for policy-making. But perhaps the most common objection to setting higher cost-effectiveness thresholds for orphan drugs derive from the principle of maximizing the health gain achieved with society's limited health care resources (Schlander, 2008). The opportunity cost of such a policy is larger health losses among those who suffer from common, highly prevalent diseases (Dear et al., 2006; Hughes et al., 2005; McCabe et al., 2006).

This debate has proceeded in a virtual vacuum of evidence regarding the views of the public regarding such a special status for drugs used to treat orphan diseases. We know that members of the public are, in general, willing to sacrifice a reduction in the total amount of health gain generated to achieve a more equitable distribution of health or health gains and to respond to those suffering severe ill health (Nord, 1993; Ubel et al., 1998; Cookson and Dolan, 1999; Dolan et al., 2005). We do not know, however, if this holds for responding to the needs of those with rare diseases. The only direct evidence on this point offers partial support at best. The UK's Citizen's Council of the National Institute for Health and Clinical Excellence (NICE) recommended that the National Health Service pay higher

prices for ultra-orphan drugs (affecting fewer than 1000 people in the UK) provided that in addition to being very rare, the disease is severe, life-threatening, and there is evidence of health gain from treatment (NICE Citizens Council, 2004). So although rareness factors into their reasoning, rareness itself does not justify differential thresholds.

This study begins to fill the gap in evidence on public views regarding this issue by presenting results from a discrete-choice experiment investigating individual preferences regarding public funding for drugs used to treat rare diseases. The study investigated three specific questions: (a) other things equal, are individuals willing to have the government pay more for drugs used to treat rare diseases than drugs used to treat common diseases; (b) other things equal, are individuals willing to have government pay more per life-year gained for a rare disease than for a common disease; and (c) in making recommendations regarding public coverage, do individual place the same relative weights on attributes across rare and common diseases?

2.0 METHODS

2.1 Scenario for the Discrete-Choice Experiment

To put the experiment into context, respondents were told that specialised committees meet regularly to consider adding new drugs to public drug program formularies. However, the large number of potential drugs, the limited budgets and the high costs of such programs makes public funding of prescription drugs a challenge.

Participants were asked to imagine that they were a member of committee of the government of the province of Ontario, Canada that makes decisions regarding drugs to be listed drug formulary for the province's public drug plan (see Appendix 1 for the exact description). They were told that the drug budget is limited and there are more drugs available than can be funded with the budget, so choices must be made regarding which drugs to fund. They were then told that two drugs were being considered for listing on the formulary, presented with information on the two drugs and the conditions each drug is used to treat, and then asked which drug they would prefer to have the government fund under the public plan.

To reduce the chances that subjects might inject their own (erroneous) assumptions about the situation, the description explicitly stated that all patients were of similar age (mid-40s), marital status,

income, education, etc. and could expect to live for 10 years without treatment. It was, also, noted that if not treated patients with both conditions consumed the same dollar amount of miscellaneous health care services in an effort to alleviate their symptoms. Finally, it was stated that the two drugs were identical in every respect except those characteristics explicitly described and that neither drug was associated with adverse side-effects.

2.2 DCE Attributes and Attribute Levels

Potential attributes by which to describe the choice alternatives were identified by a review of the debate about coverage decisions for orphan drugs. This identified more potential attributes than could be included in the DCE. The full list was reduced to five attributes based on two main criteria: importance in the debate about orphan drugs (judged subjectively by frequency of mention and amount of attention given to the attribute) and ability to specify the attribute in DCE experiment. The five attributes were (Table 1):

- frequency of the disease;
- cost of treating a single patient with the drug;
- total cost of funding the drug (budget impact);
- severity of the disease without the treatment; and
- impact of drug treatment on a patient's health.

Frequency of the disease

Frequency of the disease treated by a drug is a primary attribute of interest. The frequency took on two levels: rare and common. The threshold incidence rate for distinguishing rare and common diseases was 1 case per 2000 people. To aid understanding, the information was presented for a reference population of 10 million people (the approximate population of Ontario), with rare diseases having an annual incidence of fewer than 5000 cases and common diseases having an annual incidence of more than 5000 cases.

Cost of treating a single patient

Cost-per-patient was included as an indicator of the costliness of the drug treatment and allowed us to identify respondents' views regarding the amount the government should be willing to pay at the margin for a drug treatment. To eliminate any potential confusion, the description emphasized that the cost of treating a single patient occurred over a three-month period and that no other costs were incurred after this treatment period. Cost-per-patient took on seven levels ranging from $1,000 to $100,000. A priori expectations were that, ceteris paribus, the lower the per-patient cost the higher the probability of choosing that particular alternative.

Total cost of funding the drug program

Formulary committees commonly consider not only cost-per-patient but also the total budget impact. This distinction can be particularly important for rare diseases, which can have a very high cost-per-patient but small budget impact because so few people have the disease. Total budget impact took on seven levels ranging from $5 million to $200 million. Other things equal, we expected subjects to prefer that government fund drugs with lower total budget impact.

Severity of the disease without treatment

Severity of disease is consistently identified as a factor individuals consider important for resource allocation in health care (Dolan and Olsen, 2002). Severity of disease if not treated could take on two values: serious and moderate impact. Severity was described in terms of the impact of the disease on a patient's quality of life and on the patient's self-assessed health status. The quality of life descriptions were drawn from the health state levels of the EQ-5D classification system corresponding to the Mobility, Usual Activities, and Pain/discomfort health states (Dolan, 1997), and emphasized a patient's functioning with respect to their mobility, activities of daily living, and pain levels. "Serious" severity corresponded to a utility health score of 0.24 and to a self-assessed health rating of "poor". Moderate severity corresponded to a utility health score of 0.877 and a self-assessed health rating of

"good" 3. Other things equal, we expected that respondents would prefer to fund a drug that treated those with a serious condition than those with a moderate condition.

Impact of drug treatment on a patient's health

The last attribute was the health gain due to the drug treatment. The health gain was specified in terms of life-years gained as a result of treatment. This attribute took on four levels ranging from 1 to 15 life years gained. In addition, respondents were told that, regardless of the baseline severity, each drug would return the patient to excellent health-related quality of life for their remaining lifetime. Ceteris paribus, we expected that respondents would prefer the drug that provided a larger number of life-years gained.

Interactions Among Attributes

The design allowed for interactions among attributes. In choice experiments interaction effects are expected to account for a small portion of the variation (between 5 and 15 percent of the variance) and hence selected two-way interactions are normally sufficient (Hensher et al., 2005). The design accounted for three interactions: that between cost-per-patient and total cost, between cost-per-patient and severity, and between severity and impact of treatment on health.

2.3 DCE design

Dependence among a subset of Attributes

[3] Using the EQ-5D scoring function based on econometric modeling of 0.0 dead to 1.0 perfect health value scale, with preference scores obtained from approx. 3000 UK individuals (Dolan *et al*., 1995). We get the following utilities: Serious: 1-(0.069+0.036+0.386+.269) = 0.24; Moderate: 1-(0.123) = 0.877. Note that these health states indicate that individuals face no problems with their usual activities or anxiety/depression.

The design of the choice experiment was complicated by the fact that three of the attributes are linearly dependent. By definition, total budget impact (or total cost, TC) equals the product of the disease frequency (F) and cost-per-patient (CP): TC=F*CP. Hence, assigning values to two of them automatically determines the third. Yet we judged it important to specify quantitative values for cost attributes rather than qualitative categories (e.g., “high cost” vs. “low cost” or “good value for money” vs. “poor value for money”). To resolve this problem implied incidence rates (frequency levels) were allowed vary in the background within pre-specified ranges: following conventional definitions, incidence rates of fewer than 1 case in 2000 people were classified as a rare disease and incidence rates of more than 1 case in 2000 were classified as a common disease. As presented to respondents, disease frequency still took on only two possible values: rare and common.

We further chose a labelled, forced-choice experimental design. Unlike generic experiments, labelled experiments brand each alternative, which subsequently carries information and meaning that is likely to influence the choice outcomes. Moreover, such designs allow for different attribute levels across the different alternatives. Hence, for every decision, respondents faced a choice between: a drug used to treat a rare disease with specified attribute levels for each of cost-per-patient, total budget impact, severity of disease and life-years gained by treatment; and a drug used to treat a common disease with correspondingly specified attribute levels.

Forced experiments constrain respondents to express a preference (i.e., make a trade-off among attributes) even when both alternatives are unattractive. Hensher et al. (2005) argue that such a design is preferred when the objective of the study is to examine “the impact of the relationships different attribute levels have upon choice” (p. 176), such as is the case in our setting.

2.4 Experimental design

A full-factorial, labelled design with three four-level attributes and one two-level attributes generates 16,384 possible combinations (LMA = 42*3 * 22=16,384), hence a fractional factorial design was used. Allowing for two-way interactions a D-efficient (D-efficiency = 0.817) fractional factorial design was produced with 64 pairwise choices (Zwerina et al., 1996), which we blocked into 4 blocks of 16 choices each. All aspects of the experimental design were performed using SAS 9.1.3 built-in capabilities (Kuhfeld, 2005).

2.5 Cut-offs elicitation

By definition, discrete choice experiments are based on trades-offs between attributes. More of one attribute is assumed to compensate for less of another (Louviere et al., 2000). However, individuals sometimes simplify the decisions they face by using decision heuristics that violate such compensatory behavior. Such heuristics can include, elimination-by-aspects (Tversky, 1972) and conjunctive rules (Dawes, 1964) in which subjects follow cut-offs when making choices. A cut-off is a decision rule that sets limits beyond which the subject would never choose an alternative (e.g. a 'rule' that one would never buy a house without a swimming pool or they would never pay more than $X for a specific product). However, even when individuals exhibit such cut-off rules, the evidence shows that they do not follow them strictly (Huber and Klein, 1991; Swait, 2001). Rather than follow hard cut-offs individuals might employ soft cut-offs, or thresholds, at which the marginal utility of a change in an attribute level varies. This possibility is important because standard discrete-choice experiments assume no such non-linearities in the marginal utility of attributes.

The difficult nature of the decision problems we presented subjects regarding coverage for orphan drugs suggested to us that they might employ non-compensatory decision heuristics in decision-making. We therefore included in our study a component that would enable us to test for non-linear utility with respect to attributes. In implementing this we followed Swait (2001), who proposed a penalising utility function that allows for cut-off violation and approximates/simulates a number of non-compensatory behaviours. In this framework, decision cut-offs are not "hard" in the sense that a person never violates them; rather, it assumes that subjects suffer a greater loss in utility at the margin the further one is from the threshold (i.e., there is a utility penalty for such a choice).

Implementing this approach required that we collect from respondents information on the value of individuals' cut-offs (below or above which they would never choose an alternative) with respect to each attribute included in our study. For example, if a subject agreed that "the government should not fund drug treatments that extend life less than 5 years", this would provide information regarding the lower threshold (minimum) the subject placed on the life years gained attribute.

Following Swait (2001), for choice i and k attributes

$$U_i = \sum_k \beta_k X_{ik} + \sum_k w_k \cdot \max(0, c_k - X_{ik}) + \sum_k v_k \cdot \max(0, X_{ik} - d_k) \qquad \text{(eq. 1)}$$

Where U_i is the derived utility of choice i and X_{ik} is the choice attributes, c_k and d_k are the lower and upper cut-offs as stated by the respondent, $\max(0, c_k - X_{ik})$ identifies the magnitude of the violation of the lower bound cut-off and $\max(0, X_{ik} - d_k)$ identifies the corresponding violation for the upper bound cut-off. For an attribute with a negative effect on utility (e.g., cost) the impact of cut-off violation will be as in Fig 1. If a subject were to choose an alternative with a cost over "d" (the upper threshold), marginal utility will decrease by v_k; if they choose an alternative with cost below "c", marginal utility will increase by w_k. That is, if a person's choice violates their self-stated cuff-off, their utility suffers a penalty (though this effect could be offset by highly valued levels of other attributes, causing the person to eventually choose the alternative).

As, Swait (2001) further shows, cut-off violation is possible even for binary indicators, where a violation becomes itself a dummy variable indicating a case where the level of the attribute differs from that stated in the cut-off elicitation exercise. The subjects completed the cut-off elicitation questions before completing the choice experiment. The elicitation method itself comprised asking subjects a series of questions formulated as "I would never pay more than $X to fund this drug" (see Appendix 2).

The cut-off information is integrated into the analysis by including in the regression the second and third terms of eq. 1, with their coefficients estimated along with the rest of the parameters. The magnitude and statistical significance of the associated coefficient estimates provides a test of the importance of non-linearities4 in the subjects' decisions (compared to a model that assumes cut-offs are not present) (Danielis and Marcucci, 2007). Non-significant coefficients on the cut-off variables imply that such cut-off values play no role in decision-making.

2.6 Survey Development and Administration

Development of the survey instrument was guided by two pilot tests. The first pilot was conducted among a convenience sample of colleagues, research staff and graduate students very early in the development of the instrument. This pilot focused on basic aspects of the design such as the instructions, design of the choice scenario, and specification of the attributes. The second pilot was

[4] Note that attributes in standard choice model are assumed to have constant marginal effect on utility across the whole range of attribute values presented.

conducted among a sample of 50 individuals drawn from the subject pool and focused on final refinement of the survey, clarity and understanding by respondents, and testing the procedures for administering the survey. As part of this pilot, respondents also completed open-ended questions regarding the clarity and difficulty of the content and length of time required to complete the survey. In addition, five in-depth interviews provided further insight into points of ambiguity or other problems. Revisions were made in light of the feedback.

For the main survey, a random sample of individuals drawn from the experimental economics registration database was invited to partake in the study. Following recommendations on sample size (Hensher et al., 2005; Lancsar and Louviere, 2008), 20 to 50 participants per block was deemed adequate for robust estimation, suggesting a target a sample of 200 individuals. The vast majority of subjects were students. Past experimental valuation studies (Maguire et al., 2003; Depositario et al., 2009) have concluded that the views of students often closely represent those of the broader community of non-students. All participants were compensated $8 for their participation.

The full survey was administered electronically in the McMaster University Experimental Economics Laboratory. Ethics approval for the study was obtained from the Hamilton Health Sciences/McMaster University Research Ethics Board.

2.7 Econometric methods

Based on Lancaster's idea that utility is derived from the attributes of a good and not by the good per se (Lancaster, 1966), a DCE presents respondents with hypothetical choice sets that include alternatives with varying levels of defined attributes and asks them to choose their most preferred option among the alternatives. Including a cost or some other numeraire as an attribute, one can estimate individuals' marginal rates of substitution between attributes (for more on DCEs see Hensher et al., 2005).

Assuming an additive deterministic component to utility, $V_{iq} = \sum_{k=1}^{K} \beta_k X_{ikq}$, where k denotes the attributes, and a stochastic component to utility, ε_{iq}, the utility of an individual q choosing alternative i is

$$U_{iq} = V_{iq} + \varepsilon_{iq} \qquad \text{(eq. 2)}$$

Where β_k are the utility parameters to be estimated, which are assumed to be homogeneous across the population.

Conditional Logit versus Latent Class Models

Taking ε_{iq} to be independent and identically distributed (iid) extreme value type I (EV1), $F(\varepsilon) = \exp(-\exp(-\varepsilon))$ gives rise to the McFadden's (1974) conditional logit (CL), with the probability for individual q choosing alternative i being

$$P_{iq} = \frac{\exp(V_{iq})}{\sum_{j=1}^{J} \exp(V_{jq})} \qquad \text{(eq. 3)}$$

The conditional logit model has a number of attractive features and is the standard approach to analyzing data from choice experiments, but it does impose some restrictive assumptions that often fail to hold (Hensher et al., 2005). In particular, the assumption of independence of irrelevant alternatives assumption (IIA) and the failure to incorporate preferences heterogeneity in the utility parameters and to account for the panel structure of the data has led researchers to identify models with more flexible structures. One such specification is the semi-parametric latent-class model (LCM) (Greene and Hensher, 2003), which some argue performs equally well or better than models such as the mixed logit (Greene and Hensher, 2003; Hole, 2008).

In the LCM, parameter heterogeneity across individuals is modeled with a discrete distribution or a set of classes. "Individuals are implicitly sorted into a set of C classes, but which class contains any particular individual, whether known or not to that individual, is unknown to the analyst" (Greene and Hensher, 2003, p.682). The IIA is imposed only within classes and not on the observed unconditional probabilities. The probability that individual q chooses alternative i in choice set t conditional on falling within class c is

$$P_{iqt|c} = \frac{\exp(X_{iqt}\beta_c)}{\sum_{j=1}^{J} \exp(X_{jqt}\beta_c)} \qquad \text{(eq. 4)}$$

Following Greene and Hensher (2003) let y_{qt} denote a specific choice made such that $P_{qt|c} = \Pr ob(y_{qt} = i \mid class = c)$. Hence, given a specific class assignment

$$P_{q|c} = \prod_{t=1}^{T} P_{qt|c} \qquad \text{(eq. 5)}$$

Additionally, let H_{qc} be the probability for class c for individual q

$$H_{qc} = \frac{\exp(z_q \theta_c)}{\sum_{c=1}^{C} \exp(z_q \theta_c)} \qquad \text{(eq. 6)}$$

where z_q is a set of variables that characterize the probability for class membership.

Following from eq. 5 and eq. 6, for c classes the likelihood for individual q is

$$P_q = \sum_{c=1}^{C} H_{qc} \cdot P_{q|c} \qquad \text{(eq. 7)}$$

The number of latent classes is not determined endogenously but is determined a priori, based on the performance of alternative models with respect to information criteria measures such as the Akaike (AIC), the Bayesian (BIC) and the Hannan-Quinn (HQIC) (Hole, 2008; Swait and Adamowicz, 2001; Hannan and Quinn, 1979). Both conditional logit and latent-class models were estimated and compared.

Variable Specification

In addition to variables representing each of our attributes, our specification of V_{iqt} includes, as noted above, three two-way interactions (total cost cost -per-patient; cost-per-patient · severity; severity · life years gained) and the cut-off information elicited. Because of the labeled design, all attributes are specified as alternative-specific; a Wald test for the equality of attribute coefficients across alternatives was performed.

In addition to presenting the estimated model coefficients, we present marginal rates of substitution among attributes (Bennett and Adamowicz, 2001) along with their standard errors (computed using the delta method). We are particularly interested in marginal rates of substitution

between attributes and cost (which conveys marginal willingness to pay for an attribute). The figures are computed for changes in the means of the attributes; for the LCM they are (along with the estimated coefficients), class specific. Additionally, we calculate changes in the predicted probabilities of choosing an alternative associated with changes in the attributes. Probabilities are computed for unitary changes at the mean of the regressors for total budget, cost-per-patient and life-years gained and for discrete changes for frequency and severity. All estimation and calculations were performed using Nlogit 4.0.

3.0 RESULTS

3.1 Sample descriptive statistics

213 respondents completed the survey. The sample characteristics are as follows (Table 2): 59% was female; mean age was approximately 22 years; 80% reported excellent or very good health status; about 30% had a part-time job; for 6.5% and 17.4% the father or the mother, respectively, was unemployed; for approximately 87%, their parents owned their house; and 32% financed their education at least partly through a registered education savings plan (RESP), which are generally used by those with above-average income.

3.2 Multivariate Results

Model Selection

Information criteria (AIC, BIC, HQIC) indicated that the 2-class LCM performed better than the traditional conditional logit (CL: AIC = 1.027, HQIC = 1.039; LCM: AIC = 0.982 & HQIC = 1.015). Within the LCM, specifying more than 2 classes often resulted in convergence problems and singularities in the variance matrices. However, in all specifications that converged, the specification with 2 classes was preferred to the specification with more than two classes. A test of the joint statistical significance of the alternative-specific attributes indicated that they were preferred to the generic model (χ^2 = 33.6; p-value = 0.002). We therefore present results from the 2-class LCM with alternative-specific

coefficients. Finally, an LR-test (χ^2 = 45.1; p-value = 0.000) implied the joint significance of the cut-offs and, hence they were kept in the estimated model.

Coefficient Estimates

Table 3(a) presents the results of the logit model regarding the probability each individual falls into each of the two latent classes, with assignment being based on a set of personal characteristics. Among the characteristics included in the model only sex, father's employment status and whether the respondent's university education is at least partly financed by a registered education savings plan are statistically significant predictors of class membership. The table presents the logit coefficients, so the results imply that the odds that a female is in class 1 are 0.41 times those of than a male; the odds that a subject whose father is unemployed is in class 1 are 0.11 and the odds that a subject who finances their education at least partly through a RESP is 2.92, respectively.[5] The two classes are of approximately equal size with the average probability that a respondent falls into class 1 being 47% and the average probability for class 2 being 53%.

Table 3(b) presents the alternative-specific attribute coefficients for each class. We discuss the estimates separately for each class and then compare them. For class 1, the insignificant common disease intercept indicates that, all else equal, frequency of disease (common vs. rare) did not influence respondents' preferences for government funding of a drug. Similarly, the coefficients on both total budget impact and cost-per-patient are not statistically significant for either common or rare diseases, implying that neither cost aspect had a role in decisions over funding a drug. Nor are the interaction terms involving these two cost attributes (TC*CP and CP*SEV) statistically significant. The coefficients for baseline severity and life years gained by treatment are significant and positive for both common and rare disease. As expected, respondents prefer that government fund a drug to treat a serious condition rather than a moderate condition, and a drug that produces more life years gained. Table 4 presents the impact of a one-unit change (or discrete change) in each attribute on the probability that subjects prefer funding a drug. The change from rare to common disease increases this probability by about 10 percentage points, but recall that this effect is imprecisely estimated and is not statistically different from zero. The same is true for the two cost attributes. For severity, the probability that a subject chose to have government fund a drug used to treat severe condition was 33 percentage

[5] Odds ratios are obtained by exponentiating the coefficients, i.e. exp(-0.8991)=0.41; exp(-2.313)=0.11; exp(1.0711)=2.92.

points higher for a common disease and 22 percentage points higher for a rare disease. For life-years gained by treatment, an increase of 1 life-year gained increases the probability that a subject would choose to have government fund a drug by 5.5 percentage points for a common disease and a 4.0 percentage points for a rare disease.

For class 2, the common disease intercept is again not statistically significant, indicating that frequency of disease exerted little influence on subjects choices. The coefficient estimates on total budget impact (TC) is negative and statistically significant for both common and rare diseases. Similarly, the coefficient estimates for cost-per-patient (CP) are also negative for both diseases, though it is statistically significant for a rare disease. Overall, therefore, it appears that costs influence choice in the expected direction (greater cost reduces the probability of funding a drug) for class 2. The coefficient on the interaction term TC*CP is statistically significant only for the rare alternative and possesses an unexpected positive sign. However, the aggregate effect (TC+CP+TC*CP) is negative over values of CP and TC that appear in our design.[6] The implied magnitudes of these cost effects are as follows: a $1 million dollar increase in the total budget impact is predicted to decrease the probability that a drug is chosen by 0.17 percentage points for a common disease and 0.25 percentage points for a rare disease; for cost-per-patient, an $1 thousand increase in cost-per-patient is predicted to decrease the probability that a drug is chose by 0.23 percentage points for a rare disease. As we saw for class 1, the coefficient estimates for both baseline severity of illness and life-years gained are positive and statistically significant for both common and rare diseases, and the estimates again imply large effects on choice. The probability that a drug used is chosen for government funding is 16.0 percentage points higher if it is used to treat a severe condition than a moderate condition for a common disease and 30.0 percentage points higher for a rare disease. A drug that provides one additional life year is 4.3 and 5.0 percentage points more likely to be chosen for government funding for common and rare diseases respectively. Looking at the interactions terms we find that CP*SEV has an unexpected negative sign, implying that for cases involving a serious common disease an increase in CP makes the alternative more attractive. However, as expected, a significant positive interaction effect is observed for severity and life years.

The coefficients estimates associated with the cut-off analysis are presented at the bottom of Table 3. None of the estimates approach statistical significance for class 1, while for class 2 there is evidence of non-linearities with respect to two attributes: severity and life-years gained by treatment. For severity, the estimate implies that the “penalty” for choosing an alternative for which the condition is

[6] The aggregate effect becomes positive only when the three highest TC values (100, 150, 200) are interacted with the highest CP value (100), which does not appear in our design (see attribute levels definition, Table 1)

only moderate (-0.1685) results in an associated utility weight of -0.1685 for both common and rare diseases (the coefficient for choosing a moderate condition is 0, i.e. baseline of a binary indicator, and hence, penalty is: 0 + (-0.1685) in each case). Similarly, choosing a drug that generates fewer than 5 additional life-years results in a negative impact on utility. The magnitude of the penalty is larger than that the effect of the attribute itself and implies that for cases below the cut-off (5 years) the actual utility obtained from life years is negative (0.174513- 0.515134 = -0.340621).

Marginal rates of substitution

Tables 5 and 6 present marginal rates of substitution (MRS) among selected attributes. The calculated MRSs are meaningful only when both attribute coefficients are statistically significant. Hence, for class 1 (Table 5) we present MRSs only with respect to life years gained by treatment. On average, individuals of class 1 are willing to forgo 5.9 and 5.5 life years respectively to fund a drug that treats a serious condition rather than a moderate one. This implies that for a common disease individuals are equally willing to have government fund a drug that treats a serious condition as a drug that treats a moderate condition and produces an additional 5.9 life years gained for recipients.

Individuals in the second class (Table 6) are willing to forgo slightly more life-years gained (6.6 and 6.9 respectively for common and rare diseases) to treat a serious condition rather than a moderate one. The significance of the cost attributes in class 2 allows for the calculation of monetary willingness-to-pay. For a rare disease, individuals are willing to have government spend an extra $148,490 to fund a drug used to treat a serious condition rather than a moderate condition. Furthermore, they are willing to have government incur an additional total cost of $135 million to treat a serious rather than moderate condition; for a common disease, they are willing to have the government incur an additional total cost of $144 million to treat a serious rather than moderate condition.

Finally, all else equal, for a common disease individuals are willing to have the government spend an additional $18,470 cost-per-patient for an extra life-year gained by treatment; with a corresponding figure of $21, 350 for a rare disease. For a common disease they are willing to have the government spend an additional $27.62 million in total to fund a drug that provides an extra life year gained for all those who receive treatment; for a rare disease the corresponding figure is $19.48 million.

4.0 DISCUSSION

This study is a first attempt to present empirical evidence on public preferences into the debate about funding for drugs used to treat orphan diseases. The frequency of a disease in a population is only one feature of a disease relevant to funding coverage decisions, making discrete-choice methodology well-suited for investigating how and to what extent disease frequency influences peoples' judgments regarding public funding for a drug.

Our study was designed to answer three specific questions with regard to coverage decisions: (a) other things equal, are individuals willing to have the government pay more for drugs used to treat rare diseases than drugs used to treat common diseases; (b) other things equal, are individuals willing to have government pay more per life-year gained for a rare disease than for a common disease; and (c) in making recommendations regarding public coverage, do individual place the same relative weights on attributes across rare and common diseases. Our results indicate that the answer to the first question is no: other things equal, people do not appear willing to have government pay more for drugs used to treat rare diseases. In both of the latent classes, the common disease intercept was not statistically different from zero (not close to conventional levels of significance). In fact, for both classes the non-significant trend favors funding for common diseases over funding for rare diseases.

Our results indicate that the answer for the second question is also no: people do not appear willing to pay more per life-year gained for those who suffer from a rare disease than those who suffer from a common disease. For those who fall in latent class 1, costs did not exert a meaningful influence on costs; for those who fall in latent class 2 and for whom costs do exert an important influence on decisions, the willingness-to-pay for an additional life year gained by treatment were very similar for common and rare diseases ($18,470 and $21,250 respectively).

Finally, the results indicate that respondents did not weight attributes in a meaningfully different way across common and rare diseases. Although the Wald test did reject the null hypothesis of no difference, so that coefficient estimates are statistically different from each other, inspection of coefficients and their associated MRS reveal that the relative weights among attributes are not meaningfully different. Indeed, the similarity of the estimated MRS (Tables 5 and 6) and their plausible magnitudes gives us greater confidence in our overall results. Had subjects been confused, answered randomly, or otherwise not genuinely engaged in the decision-making exercise, we would have expected greater inexplicable variation in the willingness-to-pay estimates across the cells.

Furthermore, we do find large effects for those attributes that the literature on priority-setting suggests we should: severity of disease and treatment effectiveness. For both classes, the influence of these two attributes outweighs all other influences. These findings are also consistent with the findings of NICE's Citizens Council — the only other evidence available regarding the public's views on coverage for drugs used to treat orphan diseases — that rareness itself does not justify special consideration, but rather than severity, established evidence of effectiveness and the life-threatening character of the disease weighed more heavily (NICE Citizens Council, 2004).

The striking difference in choice behavior across the two classes may reflect the broader divisions in the debate about coverage decision-making. There is no such thing as the "view" of the public; rather, there is systematic heterogeneity that the LCM was able to identify. Specifically, one approach to coverage decision-making (Class 1) put little weight on cost considerations, focusing almost exclusively on severity and treatment effect; in contrast, the second (Class 2) considered costs in addition to severity and treatment effect. Note that an individual's class cannot be identified (i.e. latent) but overall, across the whole sample, the two tendencies are almost of equal frequency. Hence, in debates about coverage decision-making, one would expect differing positions, one of which emphasizes the importance of considering costs and one who which downplays such considerations. Interestingly, our results also suggest that the decisions of males and those of higher socio-economic status (father employed and finances education through registered savings accounts) have a stronger tendency to downplay considerations of costs. The ability to accommodate such heterogeneity is a strength of the LCM and the likely reason why both in this and previous studies (Greene and Hensher, 2003; Hole, 2008) it performed better than the more commonly applied CL model.

Our results find some evidence of non-linearities for two attributes in Class 2, indicating that the marginal utilities of severity and life-years gained are not constant over the whole range of values presented. However, the forced-choice nature of our design may have compromised our ability to accurately identify such effects and in fact exaggerate their presence (even with such potential exaggeration raw averages present little cut-off is violation, see Table 2). For instance, an individual may have faced two alternatives, each of which violated a decision cut-off (e.g., life-years gained for each alternative was below the respondent's self-declared cut-off), but still was forced to choose one as the preferred alternative. It should be noted that the results discussed above for all other attributes are the same whether the LCM includes or omits the cut-offs' information.

Overall, our results indicate that the public (in this case, represented by a university-affiliated sample from Ontario, Canada) does not support differential consideration of orphan diseases for coverage decision-making. They therefore send a cautionary message about implementing special

coverage rules for drugs to treat orphan diseases. Two considerations, however, should determine the role of this evidence in the debate. First, even assuming we have accurately elicited the views of the public, such preferences are not necessarily determinative in resolving difficult ethical problems such as funding treatments for orphan diseases. The resolution of such issues normally requires consideration of both sound ethical reasoning from principles and the preferences and attitudes of members of society. Second, as the first empirical results on this question, these findings should be seen as tentative and subject to further research both in different populations (i.e. generalizability of student samples is hard to advocate) and using modified designs (i.e. more comprehensive utility functions) to validate any conclusions. Although it is reasonable to observe differences in views across populations, such research can help identify potential framing effects associated with any single study and those aspects of the results that are robust across studies.

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Table 1: Attributes definitions and levels

Attributes	Levels	Coding
The frequency of the disease in the population (Common)	Common disease Rare disease	Common=1 Rare=0
The cost of treating a single patient for Common alternative (CP)	$1,000 $5,000 $10,000 $12,000	1 5 10 12
The cost of treating a single patient for Rare alternative (CP)	$12,000 $15,000 $50,000 $100,000	12 15 50 100
The total cost of funding the drug program for Common alternative (TC)	$50 million total cost $100 million total cost $150 million total cost $200 million total cost	50 100 150 200
The total cost of funding the drug program for Rare alternative (TC)	$5 million total cost $10 million total cost $20 million total cost $50 million total cost	5 10 20 50
The severity of the disease without treatment (SEV) for both alternatives	Serious Impact Moderate Impact	Serious Impact=1 Moderate Impact=0
The impact of drug treatment on a patient's health/life years gained (LYG) for both alternatives	15 years 10 years 5 years 1 year	15 10 5 1

Table 2: Sample descriptive statistics

Total # participants	*213 (100%)*
Individual characteristics	
Mean age (sd; min, max)	21.6 (4.9; 18, 60)
Sex	
Female	125 (58.7%)
Self-assessed Health Status	
Excellent/Very Good	171 (80.3%)
Know someone with chronic disease (Base = No)	
Yes-Rare disease (Dis_Rare)	35 (16.4%)
Yes-Common disease (Dis_Com)	87 (40.9%)
McMaster University Status	
Graduate	10 (4.7%)
Faculty/Staff	9 (4.3%)
Work Status	
Working part-time	63 (29.6%)
Working full-time	10 (4.7%)
Part of your university education paid with funds from a Registered Education Savings Plan (RESP)	
Yes	69 (32.4%)
Family characteristics	
Parent's housing tenure	
Owner	185 (86.9%)
Father's employment status	
Unemployed/Not applicable	18 (6.5%)
Mother's employment status	
Unemployed/Not applicable	37 (17.4%)
Stated cut-offs (% of choices that violated the cut-off)	
TC140: Cut-off violated when an individual chooses alternative with TC higher than 140mil, when initially s/he had identified it as the maximum TC they would be willing to incur.	11.4%
CP80: Cut-off violated when an individual chooses alternative with CP higher than 80 thousand, when initially s/he had identified it as the maximum CP they would be willing to incur.	4.7%
LYG5: Cut-off violated when individual chooses alternative with LY gained of less than 5 years, where initially s/he had identified it the minimum amount they would require.	7.6%
SevSer: Cut-off violated when individual chooses alternative with moderate severity, while initially s/he had stated that government should only fund diseases with serious impact.	19.7%

Table 3. Latent Class Model Results (2 Classes)

(a) Logistic Regression Results for Class Assignment

Constant	1.6469	--
	(2.2373)	
Sex (female)	-0.8991 **	--
	(0.4259)	
Age	-0.0283	--
	(0.0846)	
Dis_Rare	-0.2494	--
	(0.596)	
Dis_Com	0.5599	--
	(0.4437)	
Health	0.3489	--
	(0.6251)	
Faculty/Staff	0.8259	--
	(1.8075)	
Graduate student	0.808	--
	(1.0824)	
Part-time employed	0.0067	--
	(0.4294)	
Full-time employed	-1.5809	--
	(1.5495)	
Parents own house	0.1571	--
	(0.5463)	
Father unemployed	-2.313 ***	--
	(0.8492)	
Mother unemployed	0.643	--
	(0.4715)	
RESP	1.0711 **	--
	(0.4965)	
Average class probabilities	0.470	0.530

(b) Alternative-specific Attribute Estimates, by Class

	Class1		Class 2	
	Common	Rare	Common	Rare
Common disease (intercept)	0.4101		0.2469	
	(0.5427)		(0.1824)	
Total Budget (TC)	0.0024	0.004	-0.0067 ***	-0.0102 ***
	(0.0039)	(0.0096)	(0.0011)	(0.003)
Cost-per-patient (CP)	0.0742	0.0038	-0.0101	-0.0093 ***
	(0.0527)	(0.005)	(0.0182)	(0.0019)
Severity of Disease (SEV)	1.5752 ***	0.9349 ***	0.6657 ***	1.382 ***
	(0.4263)	(0.3533)	(0.1737)	(0.1415)
Life-years Gained (LYG)	0.2237 ***	0.1599 ***	0.1745 ***	0.1988 ***

	(0.0285)	(0.029)	(0.0086)	(0.0098)
TC*CP	-0.0005	-0.0001	0.0001	0.0002 ***
	(0.0004)	(0.0002)	(0.0001)	(0.0001)
CP*SEV	-0.0409	-0.001	0.0346 **	0.0003
	(0.0329)	(0.0043)	(0.0156)	(0.0018)
SEV*LYG	-0.0286	-0.0079	0.0481 ***	-0.0024
	(0.0437)	(0.0284)	(0.0128)	(0.0144)
TC140	-0.0085		-0.0015	
	(0.0061)		(0.0018)	
CP80	0.011		0.0009	
	(0.0169)		(0.006)	
SevSer	0.0929		-0.1685 *	
	(0.3713)		(0.0953)	
LYG5	-0.076		-0.5151 ***	
	(0.1075)		(0.0466)	
# of individuals	213			
# of obs.	6816			
Log-L	-2362.246			

Standard errors in parentheses; * significant at 10%; ** significant at 5%; *** significant at 1%

Table 4. Change in the Probability of Choosing a Drug Associated with a One-Unit Change in an Attribute

	Class1		Class 2	
	Common	Rare	Common	Rare
Common disease (intercept)	0.1011	--	0.0614	--
Total Budget (TC)	0.0006	0.001	-0.0017	-0.0025
Cost-per-patient (CP)	0.0185	0.0009	-0.0025	-0.0023
Severity of Disease (SEV)	0.3285	0.2181	0.1605	0.2993
Life-years Gained (LYG)	0.0557	0.0399	0.0435	0.0495

Note: see Table 1 for a definition of what a one-unit change in the value of an attribute means.

Table 5. Marginal rates of substitution in monetary and life years for Class 1

	Common disease			Rare disease		
	WTP in 1000$ of CP	WTP in millions of $ TC	Willingness to forego life years	WTP in 1000$ of CP	WTP in millions of $ TC	Willingness to forego life years
Moderate to Serious	--	--	5.9	--		5.52
			(1.36)			(1.57)
A life year gained	--	--	--	--		--

Standard errors in parentheses computed through the delta method

Table 6. Marginal rates of substitution in monetary and life years for Class 2

	Common disease			Rare disease		
	WTP in 1000$ of CP	WTP in millions of TC	Willingness to forego life years	WTP in 1000$ of CP	WTP in millions of TC	Willingness to forego life years
Moderate to Serious	--	144.39	6.57	148.49	135.55	6.93
		(29.60)	(0.569)	(32.25)	(38.95)	(0.455)
A life year gained	18.47	27.62	--	21.35	19.48	--
	(33.41)	(4.67)		(4.3)	(5.68)	

Standard errors in parentheses computed through the delta method

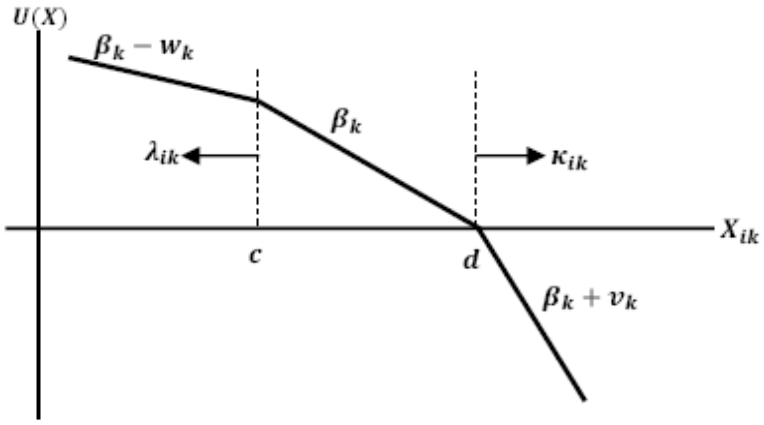

Fig. 1. The impact of cutoff violation on a negatively sloped attribute (e.g. cost) (from Swait, 2001, p. 912).

Appendix 1

Exact description and wording of discrete choice experiment exercise.

In this part of the questionnaire we are interested in your preferences with respect to funding drugs. Each scenario will present information about two health conditions, a drug used to treat each of them, the effect of each drug on a patient's health, and the cost of each drug. For each scenario you will be asked to choose which drug you would prefer that the government include within its public drug plan. If a drug is funded by the public plan patients with the condition can obtain the drug free of charge. The two drugs, the diseases they treat, and the individuals who suffer from the diseases differ only with respect to the attributes listed in the scenario. All other aspects of the decision problem should be assumed identical across the two choice options.

Example Scenario

Imagine that you are a health care decision maker on an Ontario government committee that has been asked to decide which of two drugs will be included within the public drug insurance program. Both drugs are used to treat conditions that arise in the general population. When answering the question below, assume that the characteristics of patients who develop the respective diseases are identical in all respects (e.g., age, marital status, income, education, etc.) except those explicitly mentioned. The two drugs are also identical except with respect to attributes described below; neither drug is associated with adverse side-effects. The money used to fund the chosen drug will come from the provincial public health care budget, which in 2008 was $46 billion. Only one drug can be funded. Please indicate whether you prefer to fund drug A or drug B by placing a tick on one of the boxes below. There are no right or wrong answers.

Example choice problem:

	Drug A used to treat a Common disease	**Drug B used to treat a Rare disease**
The cost of treating a single patient	$10,000 per patient	$12,000 per patient
The total cost of funding the drug program	$20 million to fund	$100 million to fund
The severity of the disease without treatment	Serious Impact	Moderate Impact
The impact of drug treatment on a patient's health	Gain of 1 year	Gain of 10 years

Which drug program would you prefer?	Prefer to fund drug A	Prefer to fund drug B
(*tick one box only*)	☐	☐

Appendix 2

In this part of the questionnaire we ask you to indicate your agreement or disagreement with each of a series of statements listed below. Please read each statement carefully before responding, as differences between some statements are small but important. For each statement, please indicate whether you agree or disagree by placing a tick in the appropriate box.

	I Agree	I Disagree
1. The government should not fund drug treatments for conditions with total cost higher than $140 million.	☐	☐
2. The government should not fund drug treatments for conditions with cost per patient higher than $80,000.	☐	☐
3. The government should not choose to fund drug treatments that extend life less than 5 years.	☐	☐
4. The government should only fund drug treatments that have a serious impact on the health status of the patient.	☐	☐