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Social preference weights for treatments in Fabry disease in the UK: a discrete choice experiment

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Abstract

Objective:

Fabry disease is a rare inherited lysosomal storage disorder caused by deficiency of α -galactosidase A. Effective enzyme replacement therapies are available that are administered intravenously (IV). However, a new oral treatment is being developed as an alternative option for patients with amenable mutations. This study was designed to understand the value that people place on the different features of treatments for Fabry disease.

Research design and methods:

A discrete choice experiment (DCE) was designed to assess the importance of different aspects of treatments for Fabry disease. The attributes included overall survival, mode of administration, treatment related reactions, treatment related headaches and risk of antibody formation. Attributes were combined using a published orthogonal array into choice sets. A research panel was used to survey the UK general public. The mixed logit model was used to estimate strength of preference for the attributes and marginal rates of substitution (MRS). Disutilities were estimated from the DCE data for changes in each attribute.

Results:

The sample (n=506) were broadly representative of UK demographics. The logit model revealed that all attributes were significant predictors of choice. Participants were significantly more likely to choose a treatment which meant an increase in their life expectancy by 1 year (Odds Ratio = 1.574; 95%CI=1.504-1.647) and significantly less likely to choose self-administered IV

treatment compared to an every other day tablet (OR= 0.426 95%CI=0.384-0.474). Estimated disutilities were -0.0543 (self-administered infusion), treatment related headaches 12 times a year (-0.0361) and infusion reactions 6 times a year (-0.0202).

Conclusions:

The survey revealed a significant preference for oral treatment compared with IV even in the context of a treatment that can extend overall survival. MRS were used as a basis for estimating disutilities associated with changes in attribute levels which could be used to weight QALYs. It is possible that other important treatment attributes are missing from this research which may have provided further insights. It would also be useful to extend this research to include Fabry disease patients so their preferences can be assessed against the societal perspective.

Keywords

Fabry disease, health related quality of life, cost-utility analysis, discrete choice experiment

Short title: Social preference weights for treatments in Fabry disease

Introduction

Fabry disease is an inherited lysosomal storage disorder caused by deficiency of the enzyme α -galactosidase A, which leads to the accumulation of globotriaosylceramide and other products in the lysosomes of cells. Over time this leads to progressive and irreversible organ damage, typically involving the kidney, heart and nervous system^{1,2}. Fabry disease is a rare disease with a worldwide prevalence of approximately 1 in 40,000 to 1 in 117,000^{3,4} although new born screening suggests possible incidence rate of up to 1:2000. Current treatment consists of enzyme replacement therapies (ERT), administered intravenously (IV), which can be time consuming and disruptive for patients. In addition, patients can experience reactions to infusions such as rashes, tolerability, anaphylaxis and antibody formation. A new treatment based on small molecule technology has recently been licenced which offers a completely new mode of action and can be taken orally. Such treatments allow patients to avoid some problems with ERT, but may be associated with other side effects.

In the context of such a severe condition as Fabry disease, the mode of administration of a treatment and the avoidance of mild but bothersome side effects may seem inconsequential. However, it is worth considering that patients have to take the treatment for the rest of their lives and so issues of convenience and bother may become quite important for them. As more treatment options for Fabry disease patients emerge, physicians and other decision makers will start to consider the value of treatments beyond their efficacy. One way to consider this is if two treatments have equal efficacy then what other factors should be considered when making treatment decisions. This report describes

an attempt to capture the relative importance of these other factors using a stated preference survey.

Stated preference surveys such as discrete choice experiments (DCE) provide insight into the value that people place on different aspects of treatments or other health care interventions⁵. DCE surveys can provide information about the relative importance of different treatment attributes (such as treatment effectiveness, mode of administration or risk of side effects). A DCE survey typically asks participants to consider pairs (or triplets) of hypothetical treatment choices and simply indicate which they prefer. The treatment choices are defined in terms of specific attributes which are in turn characterized by distinct levels. The attributes and their levels are combined into choices using a statistical design which ensures that the combinations are orthogonal. The results provide information regarding the relative importance of the attributes and also the extent to which participants are willing to trade a worse level of one attribute to achieve a better level of another.

Recent work by a number of groups has employed these methods to explore whether people are willing to trade aspects of quality of life against length of life using DCE methods^{6,7}. DCE methods have also been used to provide health related quality of life (HRQL) weights for the widely used EQ-5D-5L^{6,8}. Similar methods were applied here in an attempt to estimate HRQL weights for Fabry disease which could be used in a cost-utility analysis.

In the present study we aimed to understand the views of the general public regarding treatments for Fabry disease and also the value that they place on innovations in treatment.

The study had three main objectives:

1. Understand participants' strength of preference for different attributes of treatments for Fabry disease.
2. Explore the extent to which people are willing to trade between the different attributes of treatment
3. Estimate HRQL weights for Fabry disease which could be used in a cost-utility analysis.

Patients and methods

Survey development

Attributes for inclusion in the DCE survey were identified from the profiles of existing treatments for Fabry disease as well as the target profile for a new treatment for Fabry disease. This was captured from the published Summary of Product Characteristics from the European Medicines Authority (EMA). At the time the project was undertaken two treatments had marketing authorization from the EMA – Fabrazyme⁹ and Replagal¹⁰. A third treatment, Migalastat was under review for marketing approval (and has now been approved by the EMA). What were perceived to be the most important treatment attributes were identified by the clinical expert (DH) for inclusion in the survey. A decision

was made to focus on attributes of treatments for which there was evidence of a difference between the three treatments. So general issues which affect people with Fabry disease such as pain or the risk of dialysis in the future were not included because there was no evidence that any treatment was more beneficial in that regard. The attributes selected for inclusion in the survey included 1) hypothetical effects on survival, 2) treatment effectiveness, 3) route of administration (tablet or infusion), 4) side effects, and 5) hypothetical risks associated with long-term use of treatment (e.g. risk of antibody formation).

Treatment effectiveness was described in terms of overall life expectancy. Fabry disease shortens patients' overall survival and the enzyme replacement therapies have been shown to be effective in improving overall survival¹¹. Although there is no clear evidence that any one treatment in Fabry disease is more effective than others for reducing mortality and morbidity¹², including hypothetical effects on survival in the survey allowed exploration of the importance of the relative importance of survival compared to the other attributes. This was also done to estimate HRQL weights.

The route of administration attribute described actual differences between the treatments. The attributes regarding treatment reactions and headache reflect side effects that people may experience with these treatments. Treatment reactions are primarily associated with IV therapies in Fabry disease. Headaches have been reported as a very common adverse reaction following treatment with migalastat¹³. The attribute which described the risk of antibody formation is based on research which indicates that this is a risk for recombinant enzyme replacement therapies (ERT), but further work is underway¹⁴. Neutralising antibody formation could theoretically lower the overall effectiveness of ERT¹⁴. The potential risk for

developing antibodies is substantially reduced or even eliminated for small molecule treatments. The DCE methodology is well suited to exploring hypothetical or theoretical prospects as well as outcomes that are more concrete (such as route of administration). Therefore, it was included to provide some insight into this possible risk.

The five attributes and associated levels were discussed with the clinical expert in Fabry disease. Through this discussion there was a clear conclusion that the survey should include some description of treatment effectiveness in terms of overall survival (even though available treatments don't differ in this regard). Differences in overall survival between treatments helps to emphasise the importance of the treatment for maintaining people's health. The overall survival attribute was described in terms of 6 levels in order to provide as much sensitivity as possible to participants' preference functions. The attributes and levels were combined into choice sets using a published orthogonal fractional factorial array which had been folded over. The survey consisted of 36 pairs of choice sets, however in order to not overly burden participants, the choice sets were divided into two sets of 18 choices, and participants were randomly assigned to one of the surveys. See Figure 1 for an example choice question.

The survey included some background details regarding Fabry disease and how it affects people and how uncommon or rare the disease is. This was designed to provide a frame of reference for when the participants subsequently were asked the choice questions. A description was provided for each attribute as well, to help participants understand the attributes.

In addition to the choice questions, the survey was designed query participants using a series of background questions such as their age, sex and health status. The survey also included a series of questions designed to capture participants attitudes regarding the risks and benefits of the treatment options and the extent to which cost should be considered as a factor when making decisions about the approval of drugs. These questions were included to provide background information regarding the diversity of views in the general public.

The draft survey was piloted with five members of the public. Participants were asked to complete the survey and then take part in a cognitive debriefing interview. During the interview, participants were asked about their understanding of the attributes and questions, and about how they decided on their answers on the treatment questions. Following the interviews some minor formatting and wording changes were made.

Ethics, consent and permissions

The study protocol was reviewed and approved by an independent review board: Salus IRB (date of approval: 10th February 2016) prior to commencing the recruitment process. Study procedures were in accordance with the Declaration of Helsinki, all participants gave informed consent using an IRB approved consent form prior to taking part in the study.

Participant recruitment

The study was designed to recruit a representative sample of the general public in the UK. The general public (rather than people with Fabry disease) were recruited because this study was done from a societal perspective. Decision makers such as National Institute of Health and Care Excellence (NICE) in the UK state that decisions should reflect the preferences of the general public because of the central role of taxation in funding health care. Outcome measures like the widely used EQ-5D are based on societal preferences (rather than weights derived from patients).

Survey participants were recruited through a specialist recruitment panel in the UK. Potential participants were contacted by e-mail with a link to the survey and screened for eligibility; participants were eligible if they were at least 18 years of age and lived in the UK. Participants completed the online survey themselves. Recruitment was designed to produce a representative sample of approximately 500 people from the general public in the UK.

Procedures

Prior to the survey, all participants gave informed consent online, participants were then directed to the survey. The survey design consisted of three parts: the first part of the survey collected participants' socio-demographics; the second part of the survey assessed participants' preferences for different attributes of Fabry disease medication (the DCE); the third part of the survey asked participants to indicate their level of agreement with a series of statements about treatments.

Statistical Analysis Plan

Demographic and attitudinal data were analysed using descriptive statistics. Discrete choice data were analysed using regression models which accommodated the nature of the data. Analysis was conducted using a mixed effects logit regression model. The mixed effects logit model extends the standard conditional logit model by allowing one or more of the parameters in the model to be randomly distributed. The limitation of a conditional logit model is that it assumes respondents have the same preferences and therefore makes the assumption of independence of irrelevant alternatives which may not be true. The mixed effects logit model overcomes this limitation by allowing the coefficients in the model to vary across respondents. By doing this, it accounts for preference heterogeneity between respondents, i.e. respondents are allowed to have different preferences. Mixed logit models adjust the standard errors of utility estimates to account for repeated choices by the same individual. The model is estimated using the maximum simulated likelihood approach.

In the analyses, all attributes were specified as random coefficients, and choice scenarios were identified using a grouping variable. Then a higher level grouping was specified at the level of respondent to account for multiple choice scenarios per respondents and to account for preference heterogeneity. The life expectancy variable was specified as a continuous variable in terms of additional years of survival which took into account both the individuals' current age and their conditional life expectancy given their age¹⁵.

In this model, the preference strength associated with each attribute level was measured with respect to a reference level. Odds ratios and 95% confidence intervals were calculated

from the results of the logit analyses. Odds ratios were used to interpret the importance of each attribute. Significant odds ratios below 1 imply that the participants were less likely to choose treatments with this attribute level (compared to the reference); and values above 1 imply that they are more likely to. Significance of each OR was assessed using a type 1 error cut-off of $p < 0.05$ with two-tailed tests.

Marginal rates of substitution (MRS) reflect the extent to which participants are willing to trade between treatment attributes, in turn reflecting the value of each attribute to the participant. They were calculated using the ratio of coefficients for two attributes. MRS indicates the extent to which participants are willing to forego a unit of one attribute to gain a unit in a different attribute.

The MRS estimates were used to estimate HRQL weights for changes in treatment profiles which could be used to estimate Quality adjusted life years (QALYs). The extent to which participants were willing to trade overall survival against the other attributes (in the DCE survey) was hypothesised to be analogous to a time trade off exercise. Based on this assumption it was hypothesised that the MRS indicates the extent to which people are willing to trade some duration of overall survival in order to achieve a gain on another attribute such as avoiding 12 headaches a year for the rest of their life.

Results

A total of, 506 participants completed the survey. Demographics of the sample are summarised in Table 1. The sample approximately reflects the UK population demographics

in terms of gender, age and ethnicity¹⁶. Just over half the participants indicated that they are normally healthy and do not require prescription medicine. Thirty percent indicated that they took prescription medicine despite being fit and well and almost 20% indicated that they had a long-term illness that required prescription medication. Just over 3% also indicated that they had some personal experience with a rare disease.

Table 1

Table 2 shows a summary of the extent to which people agreed or disagreed with a series of statements about NHS treatments. There is a diversity of opinion regarding most questions. However, over 80% of participants recognised that treatments for rare diseases will inevitably be more expensive and generally people believed quite strongly in equitable access to treatments. There was also a recognition that the NHS cannot afford to pay for all treatments and must prioritise. Levels of agreement that treatments come with risks of side effects, and this risk may be higher for rare diseases were high.

Table 2

Preference data

The results presented in Table 3 show that all of the attributes are significant predictors of choice and therefore each of the attributes was considered by respondents when they were making their decisions. The odds ratios provide some indication of the importance of each attribute. Table 3 shows that participants were significantly more likely to choose a treatment which meant an increase in their life expectancy by 1 year (Odds Ratio = 1.574; 95%CI=1.504-1.647). Participants expressed a strong preference for an every other day tablet compared to the infusion treatment. Participants also preferred to avoid treatments

with headaches and treatments with some form of treatment reaction (such as flu like symptoms). Participants were perhaps least concerned about the risk of antibody formation.

Table 3

From this analysis the MRS were estimated so that it is possible to determine the extent to which participants were willing to trade years of life for avoidance of headaches, reactions, antibodies and treatment by infusion (compared to tablet). The MRS are displayed in Table 4, these represent the number of units of attributes that is equivalent to one year of additional life.

Table 4

To estimate utilities we proposed the following argument: If we have 2 treatments and one causes 12 headaches a year while the other has none and the treatments are the same in all other regards then the MRS tells us how many years of additional life participants will consider equivalent to having to also endure 12 headaches a year (for the rest of their life). The MRS data (Table 4), indicate that the difference between 0 and 12 headaches a year has the same weight as $1/0.61$ years of life. In the study sample with a mean age of 46.9 years and based on UK life expectancy it was estimated participants would have approximately 34.6 years of life left [11]. Therefore, the utility loss associated with experiencing 12 headaches a year is $(1/0.61)/34.6 = 0.047$.

Stated another way: the MRS of $1/0.61 = 1.64$ for 12 episodes of headache implies that a participant is willing to trade 1.64 years of life to avoid 12 episodes of headache every year for the rest of their lives. Over a 34.6 year life span, assuming life in full health, this is

$1.64/34.6 = 0.047$ loss of QALYs per year. Respondents are indifferent between (a) 34.6 years of life with 12 episodes of headache per year and (b) 32.96 years of life in full health (i.e. 34.6 years - 1.64). Applying this rationale we have estimated utility weights for differences in attribute levels (Table 4).

Discussion

This report describes a stated preference survey designed to understand the value of innovations in treatment for Fabry disease. The study suggests that the general public was willing to engage in this task and provided values with good face validity. The DCE results show the importance of the attributes of treatment. Overall survival is a very important attribute for participants, but the underlying DCE design and analysis allowed it to be concluded that participants still value improvements in the other attributes. Participants placed significant value on moving to an oral therapy from regular infusions. This perhaps reflects the bother or inconvenience of regular infusions which take up a lot of time, and are administered by needle (which many people prefer to avoid). Regular infusions are also a significant on-going reminder that the person has Fabry disease. A tablet taken every other day at bedtime has much less impact on people's lives and is considerably easier to take. One way to consider these results is that if two treatments with equal efficacy differ according to the route of administration then our participants would strongly prefer the oral treatment. Furthermore the participants would prefer to avoid infusion reactions and any headaches associated with treatment.

In addition to route of administration, participants recognised the impact of treatment related reactions which can be experienced following an infusion. Participants had a strong preference to avoid infusion reactions. Participants also had a strong preference to avoid treatment related headaches even though it was noted that they could be treated with pain killers. The effect of headaches and infusion reactions was considered broadly similar by the participants in this study. Lastly, participants placed less weight on the risk of developing antibodies. It was stated in the questionnaire that the actual risk of this is very unclear at the moment and its probable the valuations reflect that.

The survey also included questions regarding people's attitudes to treatments in the health service. Most people in the sample agreed that treatments for rare diseases will inevitably be more expensive. There was overall agreement that the NHS needs to consider cost when making decisions. Interestingly the public also agreed with the theoretical statement that treatments for rare disease probably have more risk of side effects associated with them. These data provide some interesting context when considering the patient preference data.

In the UK, the benefits of treatments are considered in terms of how they affect health-related quality of life (HRQL) as well as length of life, which are combined into the quality adjusted life year (QALY) metric [13]. The HRQL data is often obtained from participants in clinical trials completing standardised measures such as the EQ-5D. However in trials in rare diseases, adequate data are often not available due to the small sample sizes, making it difficult to aggregate the data and claim it is representative of patients with the disease in question. Despite this, decision makers still request HRQL outcomes data to estimate QALYs to support economic evaluations. This study tried to avoid the difficulties of estimating the

HRQL associated with side effects and mode of administration using a measure like EQ-5D by using the DCE data directly. The data were used to explore the extent to which participants were willing to trade overall survival against other benefits of treatments. This was hypothesised was analogous to the time trade off method and we applied that logic to estimate disutilities. Preferences from a representative sample of the UK general public rather than people with Fabry disease were captured to provide a societal perspective. In the UK, NICE state that they wish to see health outcomes data used in models which has been weighted by preferences from the general public¹⁷. It is believed that this approach could be applied in other disease areas to understand the value of new treatments in rare disease.

The resulting disutilities from this exercise appear to have some face validity. But testing whether they are truly valid or accurate is difficult to achieve. It would be possible to try to validate the results by estimating the same effects on HRQL using the EQ-5D. However as already stated, being able to recruit a sufficiently large sample of Fabry patients to verify these effects would be very difficult. Further work in other disease areas which are easier to verify would be a useful next step. There are several issues to consider which may affect the accuracy of our estimates. The DCE method may lead the participants to overly focus on some very specific issues. Other important features of the different treatments for Fabry disease could have been included. For example, existing intravenous treatments for Fabry disease have a much longer history of use compared with the new oral treatment and so greater real world data regarding efficacy and toxicity are available for the drugs. History of use data or other treatment attributes may be important to patients making treatment decisions but these attributes are missing from this study. It would be interesting to verify

the weights given to our study attributes in a subsequent survey that also included other aspects of the disease such as history of use. It would also be interesting to verify these findings in a study with Fabry patients. This methodology does necessitate quite large samples of participants which would make it difficult to conduct in Fabry patients. But leaving aside the practical problems, the preference weights from patients who have experienced intravenous (IV) therapy for many months or years would be a very interesting contrast to the public preference data here. Such a study may provide some insight into whether people would prefer to remain on their current IV treatment even though they perhaps preferred oral therapy in the survey.

The survey recruited the general public and we can only assume that prior to this study most were not aware of Fabry disease. To provide context for the decisions they were asked to make, we provided a quite detailed background document about the disease. However it is unclear if the sample fully understood the nature of the questions they were being asked or indeed the nature of the condition. The cognitive debrief data indicated good levels of understanding. But in an online survey we cannot be certain that everyone read all of the information received or understand the information to the level of the participants in pilot study. The DCE results have some face validity which suggests that people did understand what they were asked to do. It is also worth commenting that even if people did not understand all of the complications of Fabry disease, they probably did understand the more tangible concepts such as headaches, treatment reactions and switching from an infusion treatment to a tablet. We asked participants to define the relative importance of these factors so that we can better understand and determine whether these key issues and limitations can be addressed. The other main limitation

perhaps relates to the calculation of weights for QALY estimation. The logic that was applied is outlined in the methods, which notwithstanding certain assumptions we believe are reasonably robust. At the current time it is not been possible to test these assumptions, but future studies could do that quite usefully.

Conclusions

This stated preference survey shows the value that the general public place on innovations in treatments for Fabry disease. The results show that overall survival, treatment effectiveness, route of administration, side effects, and risks of treatment related antibody formation are all significant drivers of choice. The survey data was also used to estimate QALY weights for these attributes.

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Table 1 Sample demographics

		N=506	
Gender	Female n (%)	257 (50.8%)	
Age	Mean (SD)	46.93 (16.15)	
Ethnicity	White British n (%)	416 (82.2%)	
Education	No formal qualifications n (%)	31 (6.1%)	
	GCSE/O levels n (%)	87 (17.2%)	
	A levels or equivalent n (%)	86 (17.0%)	
	Vocational qualifications n (%)	72 (14.2%)	
	University degree n (%)	218 (43.1%)	
	Other n (%)	12 (2.4%)	
	Employment	Employed full time n (%)	238 (47.0%)
		Employed part time n (%)	72 (14.2%)
Looking after family n (%)		28 (5.5%)	
Retired n (%)		112 (22.1%)	
Seeking work/unemployed n (%)		14 (2.8%)	
Disabled n (%)		18 (3.6%)	
Student n (%)		18 (3.6%)	
Other n (%)		5 (1.0%)	
Prefer not to answer n (%)		1 (0.2%)	
General health		Normally fit and well and do not take prescription medication n (%)	268 (53.0%)
	Normally fit and well but do take prescription medication n (%)	147 (29.1%)	
	Long term illness that requires prescription medication n (%)	96 (19.0%)	
	Diagnosed with a rare disease n (%)	8 (1.6%)	
	Member of close family has a rare disease n (%)	9 (1.8%)	

N=number; SD=standard deviation

Table 2 Statements about NHS treatments

	STRONGLY AGREE	SLIGHTLY AGREE	NOT SURE	SLIGHTLY DISAGREE	STRONGLY DISAGREE
<i>Treatments should only be used in the NHS if they are completely safe</i>	170 (33.6%)	190 (37.5%)	86 (17.0%)	56 (11.1%)	4 (0.8%)
<i>For all treatments we have to accept that there is always some risk of side effects</i>	229 (45.3%)	228 (45.1%)	43 (8.5%)	5 (1.0%)	1 (0.2%)
<i>I agree that treatments for rare diseases will inevitably be more expensive for the NHS</i>	231 (45.7%)	187 (37.0%)	74 (14.6%)	10 (2.0%)	4 (0.8%)
<i>When the NHS decides which treatments to buy they should consider the cost of the treatment as well as how effective it is.</i>	115 (22.7%)	193 (38.1%)	105 (20.8%)	65 (12.8%)	28 (5.5%)
<i>The NHS cannot afford to pay for all drugs and so should prioritise</i>	75 (14.8%)	179 (35.4%)	141 (27.9%)	68 (13.4%)	43 (8.5%)
<i>Decisions about treatment should be agreed between the doctor and the patient</i>	336 (66.4%)	125 (24.7%)	38 (7.5%)	5 (1.0%)	2 (0.4%)
<i>I accept that treatments for rare diseases probably have more risks of side effects</i>	198 (39.1%)	209 (41.3%)	79 (15.6%)	17 (3.4%)	3 (0.6%)
<i>Many people will be less likely to accept treatment by injection than a tablet</i>	120 (23.7%)	227 (44.9%)	115 (22.7%)	37 (7.3%)	7 (1.4%)
<i>Decisions taken by the NHS to fund a drug should be fair for all patients.</i>	288 (56.9%)	143 (28.3%)	64 (12.6%)	8 (1.6%)	3 (0.6%)

Table 3 Results of mixed logit but with transformed survival attribute which considers the value of an additional year of life with respect to each participants' age and their predicted overall survival

<i>Variables</i>	<i>Coefficients</i>	<i>P> z </i>	<i>Odds ratios</i>	<i>95% CI</i>	
Remaining life expectancy in years (continuous variable)					
<i>Increase in remaining life expectancy by one year</i>	0.454	0.000	1.574	1.504	1.647
Mode of administration (reference category: tablet)					
<i>Nurse-administered infusion</i>	-0.816	0.000	0.442	0.406	0.482
<i>Self-administered infusion</i>	-0.853	0.000	0.426	0.384	0.474
Reaction to the treatment (reference category: never experience a reaction to your treatment)					
<i>Reaction to your treatment about 6 times a year</i>	-0.318	0.000	0.728	0.669	0.792
<i>Reaction to your treatment about 12 times a year</i>	-0.567	0.000	0.567	0.520	0.619
Side effects: headache (reference category: No headaches from treatment)					
<i>Headaches 6 times a year treatable with painkillers</i>	-0.448	0.000	0.639	0.587	0.696
<i>Headaches 12 times a year treatable with painkillers</i>	-0.742	0.000	0.476	0.435	0.522
Long term use of treatment (reference category: no known risk of developing antibodies)					
<i>15% or under 1 in 7 people will develop antibodies in a few years</i>	-0.149	0.000	0.862	0.795	0.935
<i>25% or under 1 in 4 people will develop antibodies in a few years</i>	-0.437	0.000	0.646	0.573	0.730

Table 4 Estimated marginal rates of substitution and associated disutilities for differences in attribute levels

	<i>MRS</i>	<i>Disutility</i>
<i>Nurse-administered infusion (compared to oral tablet)</i>	0.56	0.0520
<i>Self-administered infusion (compared to oral tablet)</i>	0.53	0.0543
<i>Reaction to your treatment about 6 times a year (compared to no reaction)</i>	1.43	0.0202
<i>Reaction to your treatment about 12 times a year (compared to no reaction)</i>	0.80	0.0361
<i>Headaches 6 times a year treatable with painkillers (compared to no headache)</i>	1.01	0.0285
<i>Headaches 12 times a year treatable with painkillers (compared to no headache)</i>	0.61	0.0473
<i>15% or under 1 in 7 people will develop antibodies in a few years (compared to no antibodies)</i>	3.05	0.0095
<i>25% or under 1 in 4 people will develop antibodies in a few years (compared to no antibodies)</i>	1.04	0.0278