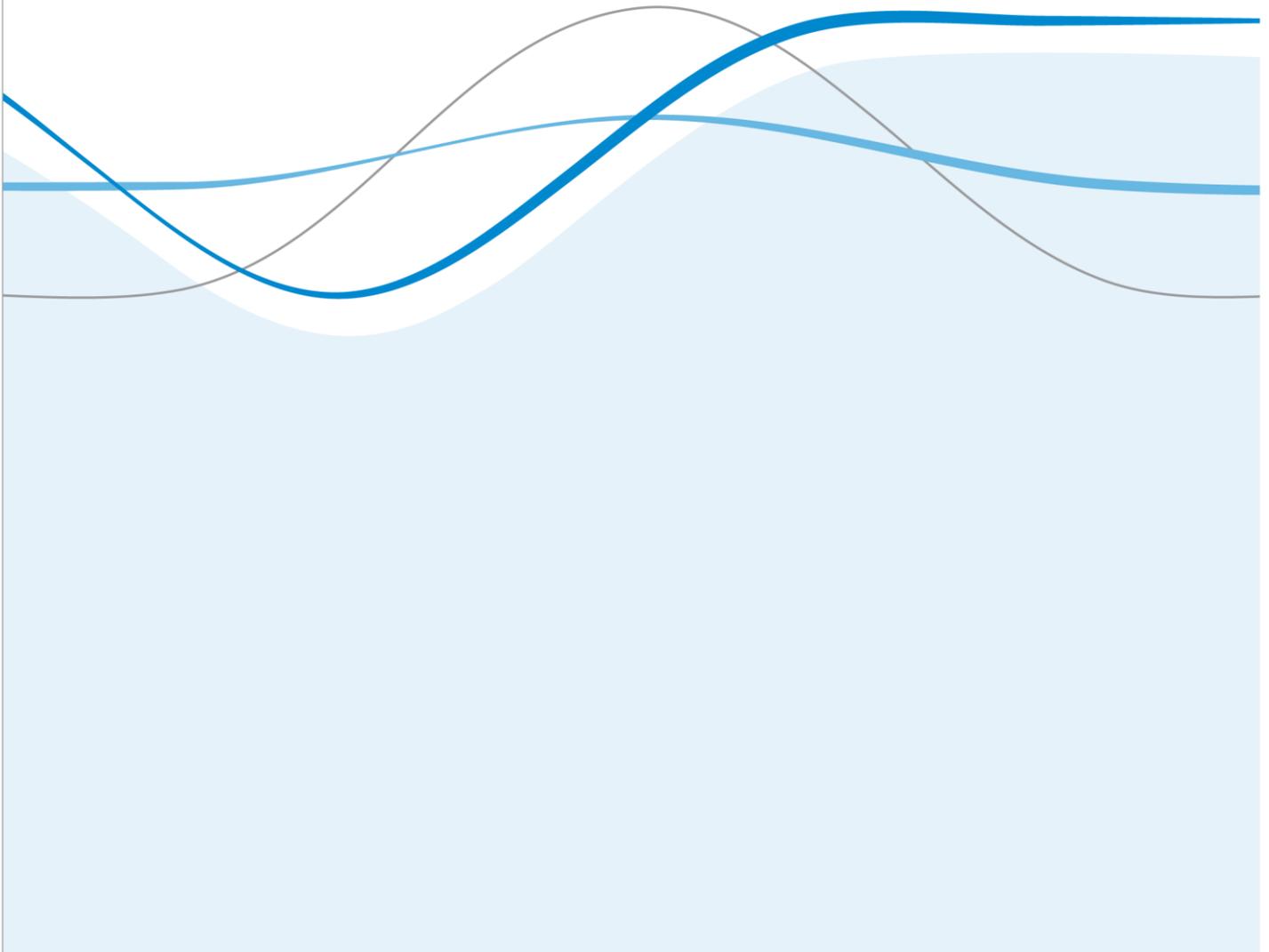# Public Preferences for Health Gains and Cures: A Discrete Choice Experiment

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EXECUTIVE SUMMARY

Background and aims: Curative therapies offer the potential of short "one-off" treatment regimens with lifelong benefits. Cures for Hepatitis C are now available, and cell and gene therapies – many of which also have the potential to offer large health gains and could also be curative – are emerging. Whether or not society values these types of therapies more highly (or less highly) than the sum of the iterative improvements that might come from conventional therapy has been highlighted as an important area for research. The aim of the research was thus to explore society's preferences across curative and non-curative therapies and large and small health gains.

Methods: A discrete choice experiment (DCE) was undertaken as part of an online stated preferences survey (n=1,000). Respondents were asked to take the role of a hypothetical social decision maker who must make funding choices in the face of limited resources. Each scenario consisted of two alternative groups of patients, of which only one group could be treated. Five attributes were included to describe the groups and the available treatments: life expectancy with current care, quality of life with current care, increase in life expectancy with new treatment, increase in quality of life with new treatment, and number of patients treated. A treatment was flagged to respondents as "a cure" if the combination of attributes restored patients to full life expectancy and quality of life. Respondents each completed 12 choice tasks and answered further demographic and attitudinal questions. Data were analysed via a mixed logit model with a full covariance matrix.

Results: Respondents were broadly representative of the UK population. 94% of respondents passed the dominance test (included as a data quality check) and only 10% reported that that the DCE was difficult to understand, indicating that overall the tasks were well understood. Respondents preferred larger health gains in terms of both quality of life and length of life, but evidence of diminishing marginal utility in health was identified. Health gains were the strongest factor driving the choice between groups, with a combined relative importance of 66%. Respondents were less likely to choose to treat groups with worse outlook under current care, but preferred to treat greater numbers of patients. Whether a treatment was a cure (i.e. the combination of attributes restored patients to normal length and full quality of life) or not did not appear to influence respondents' choices in the DCE task, above and beyond the influence of the health gains themselves.

Conclusions: This study adds to the priority setting literature that suggests that there is limited public support for the "QALY is a QALY" assumption, due to evidence of diminishing marginal utility in health gain. With respect to cures (defined in this study as treatments that restore patients to normal life expectancy and full quality of life), we find that respondents value health gains highly but do not appear to place additional value on the treatment being a "cure" *per se*. However, we use a very specific definition of a cure and therefore suggest that our results are taken with caution. Treatments that offer sizeable health gains, but do not necessarily restore health to that of a 'healthy' individual, would no doubt be of significant social value given the preferences of our respondents for larger health gains. This reflects the benefits offered by some advanced therapy medicinal products, which have the potential to result in substantial health benefits but may not entirely restore patients to the health of a disease-free individual.

1. INTRODUCTION

1.1. Curative therapies

Curative therapies offer the potential of short "one-off" treatment regimens with lifelong benefits. For example, cures for hepatitis C are now available (Horner and Naggie, 2015), and cell and gene therapies, many of which also have the potential to be curative, are emerging. However, various challenges must be overcome if these therapies are to reach patients[1]. One such challenge is that of demonstrating cost-effectiveness.

In 2016 the National Institute for Health and Care Excellence (NICE) undertook a review of their appraisal process to assess whether the process was appropriate for the assessment of regenerative medicines[2] and cell therapy products (Hettle et al., 2016; NICE 2016), in collaboration with the University of York. This review did not focus on cures specifically, but on whether regenerative medicines and cell therapy products (many of which also have the potential to be curative) could be assessed via the normal process. OHE Consulting conducted a review of this report, through which we found that "*Further research to explore whether society values "cures" more highly (or less highly) than the sum of the iterative improvements that might come from conventional therapy, would be useful to determine whether or not additional weight should be given to QALY gains that arise from curative therapies*" (Marsden and Towse, 2017).

Since then, the importance of appropriately valuing curative therapies has also been highlighted as one of the three key topics which need to be addressed for health technology assessment (HTA) in relation to advanced therapy medicinal products (ATMPs)[3] (Jönsson et al., 2018). The authors explain that the way in which potentially curative therapies are valued may need to be different from those which offer similar 'total' health gains but are not curative and highlight the need for research in this area.

The aim of this research was to build on and investigate these ideas by exploring society's preferences across curative and non-curative therapies and large and small health gains. The results may have implications for innovative new treatments coming to market and the way that HTA bodies, such as NICE, evaluate them. In turn, there may also be important implications for patients, and knock-on implications for further drug development.

1.2. What is a cure?

The definition of a cure is central to this research. However, there is no clear consensus in the literature on the definition of a cure. Two key papers are available which discuss the definition of a cure in general terms (Husereau 2015; Tapestry Networks, 2016), and further research considers possible definitions of cures in relation to specific diseases (Chacińska et al. 2017; Levrero et al. 2016; Saikia, 2018; Zoulim and Durantel, 2015).

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[1] A discussion of challenges likely to be faced by advanced therapies is provided by Abou-El-Enein et al. (2016)
[2] "[A group of] methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function" (Science and Technology Committee, 2013)
[3] "Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells." (EMA, 2018)

1.2.1. General definitions

Husereau (2015) provides a commentary on the challenges of valuing cures, including a discussion of different potential definitions. The paper discusses issues such as whether curing symptoms is enough, whether the definition should include an element of permanency and/or the treatment being a 'one off', or whether the term 'cure' should be reserved for interventions that correct the underlying cause of a disease (such as cell and gene therapies). No conclusion is reached, but the paper serves to highlight the difficulties in, and the importance of, defining this term.

Tapestry Networks (2016) present a report based on discussions held by a US-based consortium of manufacturers, payers, patient advocates, economists and other experts. The report highlights the difficulties in defining a cure, stating that some attendees felt that disease-modifying therapies could be considered curative, whilst others felt that the term 'curative' was actually misleading, because proving such an effect is incredibly challenging. Indeed, therapies may appear curative during relatively short-term trials, but real-world effectiveness and durability are typically highly uncertain.

For the purpose of their discussions and report, Tapestry define curative therapy as:

- "*an innovative one-time (or short-term) treatment,*
- *delivered via an irreversible process (or procedure or drug), and*
- *followed by a significant (multiyear) disease-free interval (i.e., long-term durable effect)."* (Tapestry Networks, 2016)

1.2.2. Disease specific definitions

Various definitions of 'cure' have been suggested for individual diseases:

- Chacińska et al. (2017) conducted a survey of 180 patients with multiple sclerosis, in which they asked what patients would perceive as a cure. The majority of patients (51%) cited current symptoms relief, but this was closely followed by removal of the cause of the disease (49%).
- In the context of chronic hepatitis B, Zoulim and Durantel (2015) suggest that a 'functional cure' could be defined as control of infection, without the need for eradication of the virus (or cccDNA clearance). However, Levrero et al. (2016) state that a 'complete cure' would require cccDNA clearance from all infected hepatocytes.
- In oncology, 5-year survival with no detectable disease following treatment is considered to demonstrate a cure (Saikia, 2018).

1.2.3. Definition for this research

Based on the information gathered from the literature, OHE's internal expertise and discussions with experts (see section 3.2 below), we adopted the following strict definition of a cure to allow clear differentiation between cures and therapies that offer large clinical gains but do not eradicate disease:

A cure:

- leads to the absence of disease or condition following the completion of treatment, and
- restores the health of the individual to the same as that of an individual without the disease or condition.

2. CONCEPTUAL MODEL AND HYPOTHESES

The general assumption for NICE's assessments of cost-effectiveness within its technology appraisal assessment programme is that "a QALY is a QALY" – i.e. that all health gains (measured in quality adjusted life years [QALYs]) are valued equally, regardless of who they accrue to and in what circumstances. This means that, for example, the 5th QALY gained by an individual is valued the same as the 1st QALY gained. This is illustrated in Figure 1, in which Total Utility$_1$ (TU$_1$) represents linear increases in utility with increases in health. In this case, the marginal utility (MU) of an increase in health is constant, i.e. for every additional unit of health, total utility increases at a steady rate.

Alternative assumptions TU$_2$ and TU$_3$, which show decreasing and increasing marginal utility in health respectively, are also shown for comparison. In these scenarios, utility increases by decreasing amounts (TU$_2$) or by increasing amounts (TU$_3$) with every additional unit of health (or QALY) as the health stock increases.

TU$_4$ is of particular interest for this research. TU$_4$ shows a sharp discontinuity in total utility when the health gain represents a cure[4]. That is, marginal utility becomes very large when the improvement in health constitutes a cure. If this utility function reflects societal preferences *in reality*, then there is a case for including a 'premium' for cures in cost-effectiveness analysis. Establishing whether or not this 'jump' exists is the purpose of this research.

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[4] In the figure, this sharp increase in utility associated with an improvement in health which is a cure is shown as occurring from an otherwise linear TU function. However, that same increase in TU associated with a cure could, in principle, also be associated with increasing or decreasing MU.

Figure 1: Total utility in health
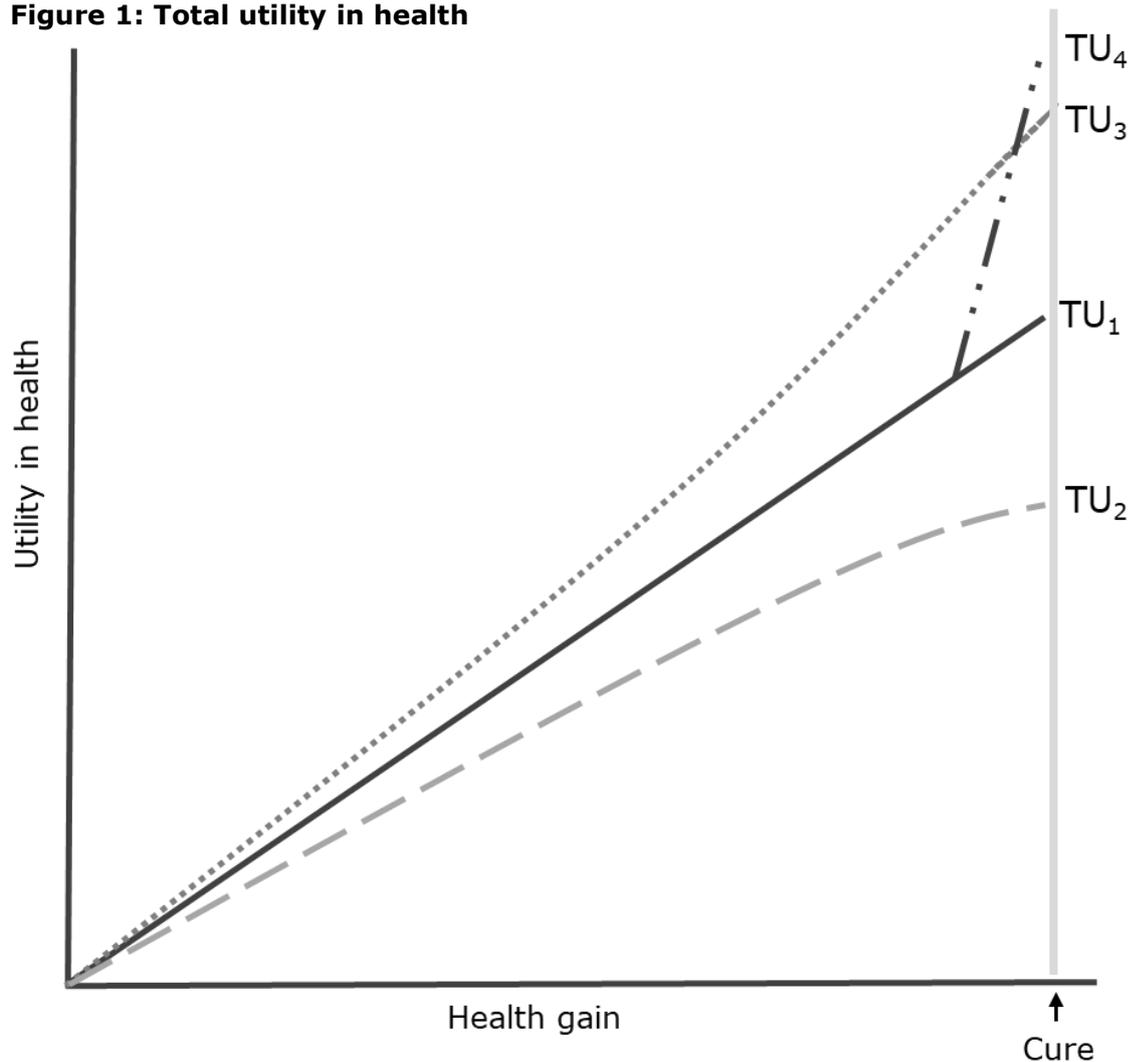
The null hypothesis is that utility is a linear function of health gain (QALYs), as shown by TU_1. In addition, people are indifferent about the distribution of health gains, meaning that a cure that results in a gain of 40 QALYs for a single patient would be equally preferred to a set of treatments each offering one QALY gain to 40 different patients.

This hypothesis would not hold if people's preferences indicate diminishing or increasing marginal utility with respect to health gains (TU_2 or TU_3 in Figure 1). In such cases, two QALYs for a given individual may increase welfare by more or less than twice what one QALY for that individual is worth. The hypothesis may also not hold if people's preferences indicate that they are inequality-preferring or inequality-averse. In such cases, 40 QALYs to one individual may be worth more or less than 40 QALYs spread across 40 individuals.

The case for a 'cure premium' is stronger if people disproportionately prefer larger gains over smaller gains, and if they are not inequality-averse.

In the UK Government's (now abandoned) proposals for the value-based pricing of branded medicines (Department of Health, 2010), it was proposed that treatments generating 'significant' improvements in health ought to be given a premium, on the basis that society may prefer to concentrate sizeable QALY gains amongst a few individuals rather than to distribute smaller QALY gains to a larger number of individuals.

A systematic review of the literature on priority setting preferences (Gu et al., 2015) reported that while large gains are universally preferred over small gains, many studies have found evidence of reduced strength of preferences for larger gains as the size of gain increases. The majority of studies investigating the topic of concentration versus dispersion have concluded that people prefer giving small gains to many rather than large gains to a few (in contrast to the hypothesis behind the value-based pricing proposals). However, some studies note that this preference is observed only when the size of gain exceeds a certain threshold (e.g. Abel Olsen, 2000). Other studies report that people value the prevention of rare cases of severe disease more highly than that of frequent cases of mild disease (Prosser et al., 2004; Christensen et al., 2014).

The literature on preferences for 'curative therapies' typically focuses on choices between preventive interventions and treatments that improve the health of patients with health problems but do not necessarily restore their health to the level of a disease-free individual. This literature is therefore of limited relevance to our study, given our definition of a cure as presented in section 1.2.3. See Hernandez-Villafuerte et al. (forthcoming) for a summary.

3. METHODS

3.1. Eliciting preferences

In the context of valuing health effects, NICE recommends the elicitation of public preferences using a choice-based method (NICE, 2013). Preference elicitation was therefore based on a discrete choice experiment (DCE). DCEs offer a quantitative means of eliciting respondents' preferences over a defined set of attributes by asking them to make trade-offs. DCE has a strong theoretical basis and is a widely accepted choice-based method in the fields of applied health economics and health care priority setting[5]. Indeed, DCEs have been used in a number of studies of preferences regarding priority setting funded by public agencies such as the National Institute for Health Research, NICE and the Department of Health (Baker et al., 2010; Shah et al., 2015; Rowen et al., 2016).

DCEs involve presenting a series of choice tasks that require the respondent to choose between different options, each described in terms of their characteristics (or attributes). DCEs therefore require respondents to make trade-offs between different characteristics of hypothetical options (in this case the options are different treatment options). By analysing how the different combinations of attributes affect respondents' choices between the options, researchers can estimate respondents' relative preferences over the attributes.

In this case, respondents were asked to take the role of a hypothetical social decision maker who has to make funding choices in the face of limited resources. The choices consisted of two groups of patients, with the respondent being told that only one group could be treated.

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[5] For an overview of the use of DCEs in healthcare see Clark et al. (2014), Whitty et al. (2014) and Soekhai et al. (2018).

3.2. Defining attributes and levels for the DCE

The DCE requires that the different groups of patients and treatments that the respondent is presented with are described in terms of their attributes. The attributes (and the levels that each attribute could take) were identified via a literature review, combined with OHE's internal expertise and interviews with experts.

As noted above, the existing literature on societal preferences for curative therapies was of limited relevance for this study. As such, we consulted literature on preferences around: 1) size of health gain, often in the context of equity/distribution of gain (Gu et al., 2015), and 2) treatment of rare diseases (for example: Bourke et al., 2018). The purpose of the review was to identify candidate attributes and levels for the DCE.

Candidate attributes included: disease severity, unmet need, health (length and quality of life) gains from treatment, number of patients treated, age, cost, and uncertainty in the evidence base. These attributes were refined by the research team for use in the context of cures, and a sub-list of those deemed to be the most relevant were taken forward to the interviews.

Interviews were undertaken with three experts in this field: one industry representative from a company with potentially curative products in their pipeline; one representative from NICE, and; one representative from the Cell and Gene Therapy Catapult[6]. The attributes and levels were further refined in the light of these interviews. The experts also contributed to the development of the definition of a cure presented in section 1.2.

The final attributes and levels are presented in Table 1. The life expectancy and quality of life with current care attributes provide an indication of disease severity with current care (i.e. without the new treatment on offer).

The choice of levels for the increase in life expectancy and increase in quality of life with new treatment attributes allowed the possibility of the new treatment offering a full, partial or no restoration of life expectancy or quality of life to normal levels.

Given that the definition of a cure presented in section 1.2 is based on the combination of other attribute levels, it was not included as an attribute in its own right. Instead, treatments that restored individuals to normal life expectancy and full quality of life (based on a combination of the included attributes) were labelled as cures in the scenarios (see section 3.3).

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[6] https://ct.catapult.org.uk/about-us

Table 1: Final attributes and levels

Attribute	Definition	Levels	Analysis Coding	Expected Sign
Life Expectancy with Current Care	The number of years that the patients are expected to have left to live with their current care (i.e. without the new treatment).	▪ Normal life expectancy ▪ Die 10 years early ▪ Die 20 years early ▪ Die 40 years early	▪ (Base) ▪ LE_{10} ▪ LE_{20} ▪ LE_{40}	?
Quality of Life with Current Care	The level of quality of life that the patients are expected to experience for the rest of their lives with their current care (i.e. without the new treatment).	▪ Mild problems (75%) ▪ Moderate problems (50%) ▪ Severe problems (25%)	▪ (Base) ▪ QOL_{50} ▪ QOL_{25}	?
Increase in Life Expectancy with New Treatment	The increase in the number of years left to live that the patients are expected to receive with the new treatment.	▪ No gain ▪ 5 year gain ▪ 10 year gain ▪ 20 year gain ▪ 40 year gain	▪ (Base) ▪ $LEGAIN_{5}$ ▪ $LEGAIN_{10}$ ▪ $LEGAIN_{20}$ ▪ $LEGAIN_{40}$	+
Increase in Quality of Life with New Treatment	The increase in the level of quality of life that the patients are expected to experience for the rest of their lives after receiving the new treatment.	▪ No gain ▪ Small improvement (25% gain) ▪ Large improvement (50% gain) ▪ Very large improvement (75% gain)	▪ (Base) ▪ $QOLGAIN_{25}$ ▪ $QOLGAIN_{50}$ ▪ $QOLGAIN_{75}$	+
Number of Patients Treated	The number of patients that would be treated with the new treatment.	▪ 100 ▪ 200 ▪ 400 ▪ 800	▪ (Base) ▪ $NUMBER_{200}$ ▪ $NUMBER_{400}$ ▪ $NUMBER_{800}$	+

Note: For the purpose of this study, a cure is a treatment which leads to normal life expectancy and full (100%) quality of life. This is therefore a combination of the first four attributes.

Note from Table 1 that uncertainty was not included as an attribute. Whilst this is a relevant consideration for analyses of clinical and cost-effectiveness, it was considered that uncertainty was captured elsewhere in the appraisal process. The purpose of this research is to explore societal preferences over curative therapies and health gains, rather than the impacts of uncertainty.

Age was not included as an attribute, despite also being relevant, as a full analysis of the value of a cure at different stages was outside the scope of this study. Instead, respondents were informed of the age of the patients facing treatment, which was held constant throughout the tasks in order to avoid introducing age-related preferences and to minimise cognitive burden. The age specified was 35 years, which was discussed and agreed with the interviewees to represent a realistic adult patient age for which curative treatments are likely to emerge.

Finally, cost was also omitted. Instead, the respondents were informed that the two treatment options cost the same amount of money, but that it is not possible to fund both due to limited resources. Respondents were then asked to trade between different numbers of people receiving the treatments, assuming that the total cost is the same. This provides an indication of the strength of preference for each choice. This approach was chosen because members of the UK public are not typically exposed to health care costs, and as such may struggle to answer questions related to the cost of health care. Further, the choices presented to respondents can be argued to reflect scenarios faced by health care decision makers whereby a trade-off needs to be made between providing a relatively cheap or routine therapy to a larger number of patients or a new, more expensive therapy to a smaller number of patients.

3.3. DCE design

Respondents were required to choose between two 'unlabelled' alternatives, with no opt out option. An opt out was not required as it was assumed that the decision maker would always want to treat at least one group of patients should the resources be available, since both treatments provided at least some health benefit and could therefore be assumed to be utility-enhancing.

Given the number of alternative choices that can be constructed from the various attribute levels in Table 1, it was not feasible to present respondents with the full range of possible alternatives. In addition, not every combination of attribute levels makes logical sense. Due to the need to create a design that was capable of estimating the effect of the different attribute levels, whilst also being constrained to avoid implausible combinations, a D-efficient experimental design was created using Ngene v1.2.0 (ChoiceMetrics, 2018). Such designs are routinely used for choice experiments due to their flexibility, and their use improves the likelihood that the parameters of interest can be estimated (Johnson et al., 2013).

The constraint command in Ngene was used in order to ensure that:

1. Every new treatment offered some health gain.
2. Overall quality of life after the new treatment did not exceed 100%.
3. Overall life expectancy after the new treatment did not exceed a 'normal' life expectancy.
4. No alternative dominated with respect to quality of life gain, life expectancy gain *and* number of patients treated, within a given scenario.

The full design consisted of 40 rows (choice scenarios), which were split into four blocks (using Ngene) as part of the design process, such that respondents would see 10 choices each from the main experimental design. As the classification of whether the new treatment constitutes a cure was determined by the combination of other attribute levels, potential designs were examined post-hoc to ensure that cures featured in every block. The final experimental design met this criterion and 25% of the scenarios overall featured at least one cure.

In addition to the 10 choices from the main experimental design, respondents were also asked to complete an additional two choice scenarios: a dominance test, and an 'equal QALY' test. The dominance test included one alternative that clearly dominated the other alternative; these are often used in DCEs as a test of 'rationality' or respondent focus (Tervonen et al., 2018). The 'equal QALY' test consisted of two alternatives that provided an identical amount of total QALY gains across the two patient populations, but where only one of the new treatments was curative. The intention was to directly examine whether respondents preferred cures over non-cures, whilst controlling for differences in the size of overall health gains. The two tests did not differ between respondents.

Therefore, respondents completing the DCE would face a total of 12 choice scenarios, which fits well within the range that is generally considered to be feasible and appropriate for a general population sample (Clark et al., 2014). Blocks were randomly assigned in the survey, and the order of the ten scenarios from the main experimental design and the 'equal QALY' test were randomised. The dominance test was always the last scenario to appear in the task. An example choice task is shown in Appendix 1, the dominance test is shown in Appendix 2 and the 'equal QALY' test is shown in Appendix 3. Note that treatments that restore individuals to normal length of life and full quality of life (based on a combination of the attributes) were considered to be cures, and were labelled as such in the scenarios, despite not being an attribute within the experimental design. Our data analysis approach allowed us to examine whether a treatment being a cure (as defined in this study) *per se* influenced respondents' preferences above and beyond the influence of the attributes and levels included in the experimental design. Section 3.5 details how we included a cure variable in our data modelling.

3.4. Online survey

The DCE was delivered as part of an online survey. The survey began with study information pages and required respondents to provide consent for their participation. This was followed by a small number of demographic questions, which were used to screen respondents in order to obtain a representative sample. The DCE task was then introduced, including a series of information pages, and was followed by debrief questions asking whether the respondent found the tasks difficult. Following the DCE, respondents were asked a series of attitudinal questions asking for their opinions regarding the priorities of the health service. This was followed by some final demographic questions.

The online survey was coded by a company called SurveyEngine (http://www.surveyengine.com) who were also responsible for recruiting the general population sample. Once the initial survey was coded, the survey was piloted with a convenience sample comprising small number of lay respondents (family members and non-researcher colleagues of the study authors) in a 'think-aloud' fashion (Ryan et al., 2009) to test comprehension and to gain feedback on the wording of the questions. Following this, the survey was updated and recruitment began. Sample size

requirements for DCEs are challenging to determine, with no clear consensus at present (de Bekker-Grob et al., 2015). For the avoidance of doubt, and to allow for potential subgroup analyses at a later date, a large sample size of 1,000 respondents was chosen for this study.

A soft launch was undertaken with an initial 100 respondents. The purpose was to check for any problems and check that the survey was functioning correctly. Based on the responses received in the soft launch we added a practice question, immediately prior to the choice tasks. Having completed the practice question the respondent was shown a summary and brief explanation of their choice (see Appendix 4) and asked if they wished to stick with this choice. A summary was shown regardless of which option was selected. The inclusion of the practice question was informed by Rowen et al. (2016), who used a similar approach in an effort to ensure that respondents were well-informed about the implications of their choices. The initial 100 respondents that completed the survey before this change were not included as part of the final sample.

Prior to the delivery of the survey, the study team sought ethical approval from an independent expert in research ethics, acting under the auspices of the Association of Research Managers and Administrators (ARMA). Following some minor adjustments to the survey, ethical approval was granted on 13th June 2018.

3.5. Data analysis

Data from DCEs are typically modelled using a random utility framework, where the utility a decision-maker derives from choosing an alternative is made up of an observable component and a random component. The attribute levels of the alternatives are assumed to influence the observable component. Thus, the function that is estimated in the choice models consists of the attribute levels from the DCE. In this case, we estimate a utility function that is linear in parameters and use dummy coding for all variables due to the interest in testing for diminishing marginal utility (section 2). This is shown by Equation 1 below.

$$
\begin{aligned}
V = \ & \beta_1 LE_{10} + \beta_2 LE_{20} + \beta_3 LE_{40} + \beta_4 QOL_{50} + \beta_5 QOL_{25} + \beta_6 LEGAIN_5 \\
& + \beta_7 LEGAIN_{10} + \beta_8 LEGAIN_{20} + \beta_9 LEGAIN_{40} + \beta_{10} QOLGAIN_{25} \\
& + \beta_{11} QOLGAIN_{50} + \beta_{12} QOLGAIN_{75} + \beta_{13} NUMBER_{200} \\
& + \beta_{14} NUMBER_{400} + \beta_{15} NUMBER_{800} + \beta_{16} CURE
\end{aligned}
\tag{1}
$$

The *β*s represent the coefficients and the attribute levels are as defined in Table 1, with the exception of 'CURE', which does not feature in Table 1 because it is not part of the experimental design. 'CURE' is an interaction term that is equal to one only if the new treatment brings life expectancy and quality of life to the level expected for a healthy individual i.e. normal life expectancy and no health problems (100% quality of life). The coefficient for 'CURE' was key to testing one of our main research questions and our *a priori* expectation was that *β₁₆* would be no different from zero.

Other linear specifications were tested, such as: using continuous variables rather than dummy variables; combining (continuous) attributes to look at QALYs with current care and QALY gains; and splitting the health gain into three (continuous) variables using the approach by Shah et al. (2015). A range of interaction terms were also included in the continuous models, such as interactions between health (either life expectancy or quality of life) with current care and health with the new treatment. However, given the focus on marginal utility to test our hypotheses and the fact that combining attributes could

result in a loss of useful information, the specification in Equation 1 was preferred for this analysis.

The standard model used for choice analysis is the multinomial logit model (McFadden, 1973), which assumes that the random component is independent and identically distributed (IID). The model also assumes that preferences are homogenous across individuals. Given that this may not be the case, more flexible choice models have been suggested for consideration by researchers (Hauber et al., 2016; Lancsar et al., 2017). One such alternative is the mixed logit model, which relaxes the preference homogeneity assumption and allows for random preference heterogeneity to be incorporated.

We prioritise the use of the mixed logit model for our analyses on a theoretical basis. We estimate the mixed logit model with all parameters set as random and normally distributed, as well as with a full covariance matrix. The latter allows for all possible parameter correlations to be accounted for within the model. This is beneficial given the links between different parameters in our design and the fact that differences in scale, another form of random heterogeneity, are essentially correlations between parameters (Hess & Train, 2017). Thus, our preferred model allows for *both* random preference heterogeneity and scale heterogeneity.

We began our analyses using the multinomial logit model initially before moving on to the more flexible mixed logit model. Alongside these models, other models were considered for use in our analyses. The generalised multinomial logit model was considered (Fiebig et al., 2009), but deemed less flexible and harder to compute relative to the mixed logit model (Hess & Train, 2017). In addition, the latent class model was also considered (Zhou et al., 2017). However, it was felt that, despite the potential for insightful results, a single set of results based on aggregated preferences was most appropriate for this particular analysis.

One way to interpret the results from the regression analysis is compute the relative importance (%) of each attribute. This is done by determining the utility range for each attribute and dividing this figure by the overall utility range (i.e. for all attributes). In addition to the regression analysis, it is also possible to examine the probability of any given alternative being chosen based on the model estimates. In this study we follow the approach by Green and Gerard (2009) and Shah et al. (2015). We calculated the relative predicted probabilities for all of the 80 alternatives included in the experimental design, and compared the alternatives with higher probabilities to those with lower probabilities. For simplicity, we focused on QALYs with current care and QALY gains as a result of new treatment for this analysis.

4. RESULTS

4.1. Demographics

A total of 1,000 respondents completed the survey; their characteristics are described in Table 2. By design, the sample was intended to reflect the characteristics of the UK general population. Comparisons with UK general population figures indicate that the sample is largely representative, though older individuals and those with socioeconomic grade ABC1 are slightly overrepresented in our sample. Over three-quarters (75%) of the sample remained in education beyond the minimum leaving age, while 68% of the sample are not limited in their day-to-day activities due to a long-term (12 months minimum) health problem or disability.

Table 2: Characteristics of the sample

	Sample		General Population
	n	**%**	**%**
Gender			
Female	524	52%	51%
Male	476	48%	49%
Age			
18-29	178	18%	20%
30-44	241	24%	25%
45-59	261	26%	26%
60+	320	32%	30%
Socioeconomic Grade			
ABC1	570	57%	55%
C2DE	430	43%	45%
Country			
England	839	84%	84%
Scotland	90	9%	8%
Wales	52	5%	5%
Northern Ireland	19	2%	3%
Education			
Left after minimum leaving age	236	24%	
Continued; no degree	308	31%	
Continued; obtained at least one degree	456	46%	
Are your day-to-day activities limited?			
Yes, limited a lot	98	10%	
Yes, limited a little	227	23%	
No	675	68%	

Sources of general population statistics: Office for National Statistics, 2017; National Readership Survey, 2015

4.2. Discrete choice experiment

The regression results from the mixed logit model can be found in Table 3. The results suggest that the worse a group of patients' outlook is with current care, the less likely it was that respondents would choose to treat that group. This is the case for both quality of life with current care and life expectancy with current care (indicated by the negative coefficients on these variables). Respondents preferred larger health gains in terms of both quality of life and length of life. However, the magnitude of the coefficients suggest that quality of life improvements are valued more than length of life extensions. Respondents also preferred to treat greater numbers of patients, though there is some evidence of diminishing marginal utility in this attribute. Finally, whether a treatment was a cure or not did not appear to influence respondents' choices in the DCE task, as this coefficient was not statistically significant. These results are reflected in Figure 2, which illustrates the relative importance of each of the different factors. It is clear from Figure 2 that the health gain attributes are dominant, with a combined relative importance of 66%. The other attributes have a similar relative importance of around 11% each, and whether the treatment is a cure is not important *per se* (<1%) – respondents' choices appear to be driven by the size of the gains but not whether the gains happen to offer a cure (as defined in this study).

Table 3: Regression results

|	**Coefficient**	**Std. Dev.**
<u>**Current Care**</u> **Life Expectancy[1]**		
Die 10 years early	-0.804***	0.998***
	(0.184)	(0.318)
Die 20 years early	-0.461***	0.642***
	(0.175)	(0.301)
Die 40 years early	-1.449***	1.886***
	(0.215)	(0.235)
Quality of Life[2]		
Moderate Problems (50%)	-0.363**	1.845***
	(0.175)	(0.253)
Severe Problems (25%)	-1.516***	2.576***
	(0.192)	(0.280)
<u>**New Treatment**</u> **Life Expectancy Gain[3]**		
5 years	0.496***	1.384***
	(0.146)	(0.250)
10 years	1.410***	1.365***
	(0.166)	(0.236)
20 years	2.347***	2.289***
	(0.227)	(0.268)
40 years	3.552***	2.840***
	(0.288)	(0.323)
Quality of Life Gain[4]		
25%	2.169***	2.010***
	(0.202)	(0.246)
50%	3.715***	2.798***
	(0.314)	(0.296)
75%	5.013***	5.127***
	(0.419)	(0.480)
Treatment is Curative[5]	-0.00764	2.196***
	(0.172)	(0.320)
Number of Patients Treated[6]		
200	0.517***	2.021***
	(0.161)	(0.290)
400	1.223***	2.235***
	(0.158)	(0.273)
800	1.414***	2.811***
	(0.173)	(0.285)

[1]Base level is 'normal life expectancy'; [2]base level is 'minor problems (75%)'; [3]base level is 'no life expectancy gain'; [4]base level is 'no quality of life gain'; [5]base level is 'treatment is not curative'; [6]base level is '100' patients treated. ***P-value<0.01; **p-value<0.05. Mixed logit model details: all parameters modelled as random and normally distributed using 1,000 Halton draws and a full covariance matrix estimated.

The vast majority of respondents passed the dominance test i.e. chose the dominant alternative (n=935; 94%). In addition, the majority of respondents chose the cure in the 'equal QALY' test (n=744; 74%). In response to the debrief questions following the DCE tasks, 10% of respondents strongly agreed or agreed that the DCE was difficult to understand (n=96), while 43% of respondents strongly agreed or agreed that it was difficult to decide between the alternatives in the DCE task (n=426).

Figure 2: Relative importance of different factors
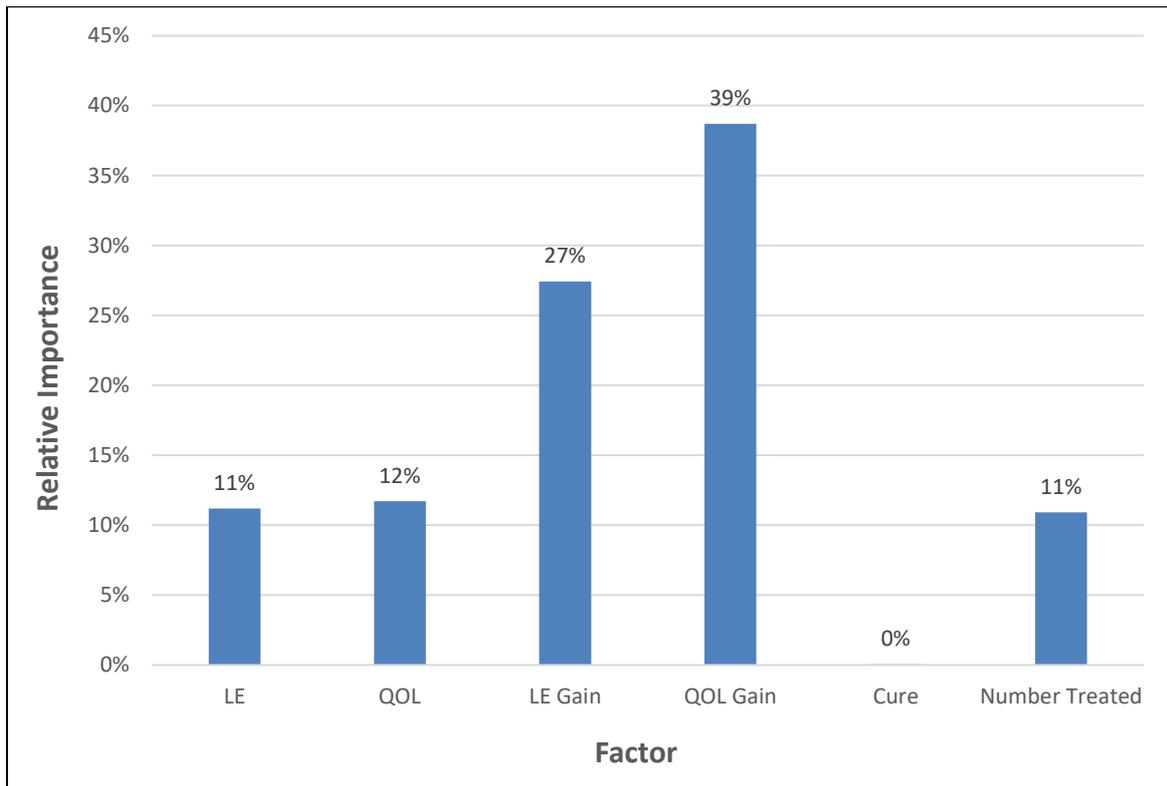
The analysis of relative probabilities is illustrated in Figure 3. The alternatives in the experimental design that were associated with higher probabilities typically described patient groups that would receive larger QALY gains (per person) as a result of the new treatment and had fewer QALYs (per person) with current care. However, the effect on the probabilities appears to be far greater with respect to QALY gains, as can be seen when comparing the slopes of the orange dotted line (QALY gain with new treatment) and the blue dotted line (QALYs with current care). It should be noted that these two effects are not unrelated because larger QALY gains are possible when fewer QALYs are received with current care and therefore these two effects cannot be disentangled.

Figure 3: Relative probabilities
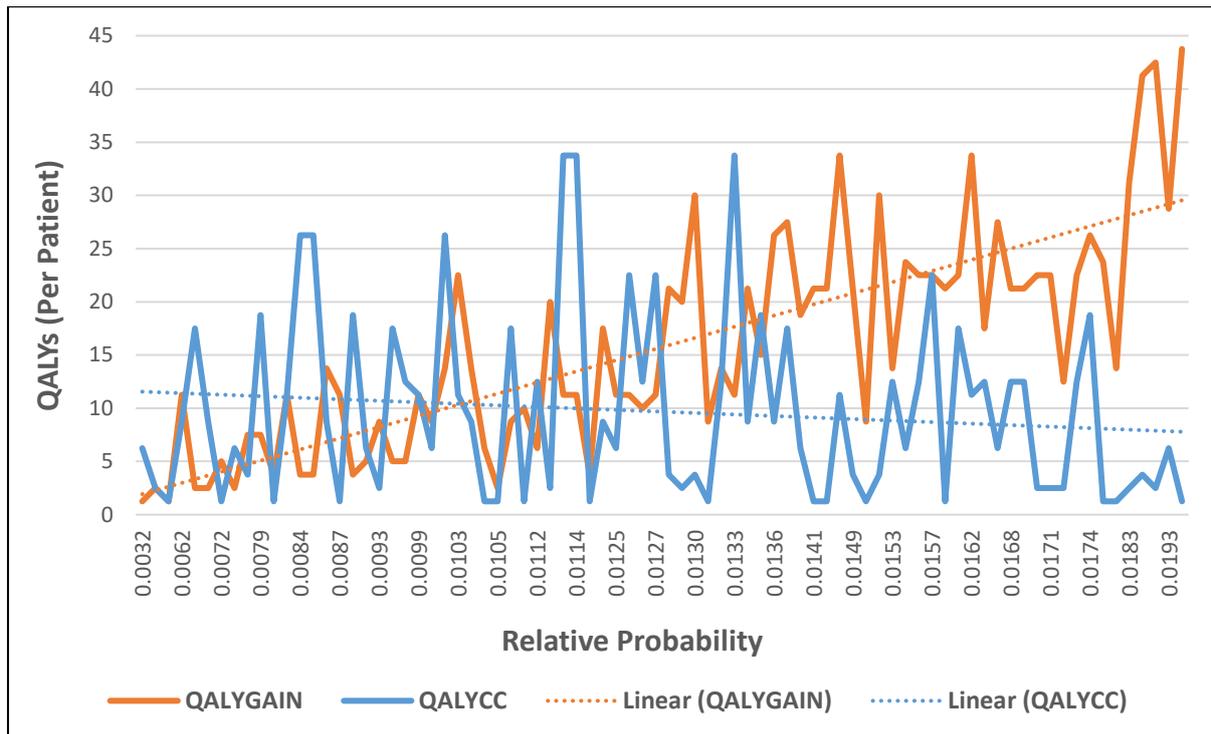
4.3. Attitudinal questions

Following completion of the DCE and the related debrief questions, respondents provided responses to five attitudinal questions. The results are displayed in Table 4. By combining "agree" and "strongly agree" responses, the sample provided strongest support for statement 2 (prioritising those that will get the largest amount of benefit), with 71% agreeing with this statement. This was followed by statement 4 (prioritising those experiencing very poor quality of life) with 63% and statement 5 (same priority for all) with 58%. Statement 1 (prioritising curing patients as opposed to treating symptoms) had a slim majority with 51% agreement and statement 3 (prioritising those near the end of their lives) had only 43% agreement. For all statements, very few respondents disagreed and even fewer strongly disagreed, which could reflect acquiescence bias (Messick, 1967).

Table 4: Responses to the attitudinal questions

Statement	Strongly Disagree		Disagree		Neither Agree or Disagree		Agree		Strongly Agree	
	n	%	n	%	n	%	n	%	n	%
1. The health service should give priority to **curing patients of disease**, as opposed to treating patients' symptoms.	11	1%	103	10%	380	38%	398	40%	108	11%
2. The health service should give priority to treating patients who will get the **largest amount of benefit** from treatment.	11	1%	37	4%	246	25%	521	52%	185	19%
3. The health service should give priority to improving the health of patients who are **expected to die soon** as a result of a medical condition.	14	1%	122	12%	430	43%	334	33%	100	10%
4. The health service should give priority to improving the health of patients who have a **very poor quality of life**, even if they are not at risk of dying prematurely.	5	1%	62	6%	302	30%	488	49%	143	14%
5. The health service should give the **same priority to treating all patients**, regardless of how ill they are or when they will die.	25	3%	129	13%	265	27%	313	31%	268	27%

5. DISCUSSION

5.1. Our findings

The DCE tasks appear to have been well understood by respondents, with 94% of respondents passing the dominance test and only 10% agreeing that the task was difficult to understand. Nonetheless, as identified during piloting, the tasks did provide difficult choices for respondents to consider, with 43% of respondents agreeing that it was difficult to decide between the alternatives.

The results of the DCE indicate that respondents prefer larger health gains over smaller health gains; and prefer to treat more patients. This is in line with our *a priori* expectations. It is also notable that the two health gain attributes had a combined relative importance of 66%, suggesting that the levels of these attributes dominated respondents' decision-making throughout the task. In addition, there is some evidence in our results of diminishing marginal utility for health gains with respect to both quality of life and length of life (TU_2 in Section 2). This is at odds with the "a QALY is a QALY" assumption but is consistent with other empirical evidence (Gu et al., 2015).

The finding that respondents prefer to treat those in a better condition with current care was not expected, but our *a priori* expectations were not strong for these attributes given that the existing evidence is mixed regarding the impact of severity of illness and remaining life years (Lancsar et al., 2011; Skedgel et al., 2013; Shah et al., 2018). It should be noted that there is a clear link in our experimental design between the potential size of health gains and the initial health status with current care, as the hypothetical patient groups in the DCE task were of the same age. The analysis of

predicted probabilities suggests that the negative coefficients on the current care attribute levels may be better explained by the experimental design rather than a legitimate preference to treat those that are in better health initially (i.e. with current care). Further, it should be noted that these coefficients were relatively small – it does not appear as though patients' health with current care was a major driver of respondents' choices.

The interaction term used in our study to explore whether respondents preferred curative treatments over and above non-curative treatments was not statistically significant. This suggests that curative treatments, by our definition (restoring patients to full quality of life and normal life expectancy), were not preferred over and above non-curative treatments, controlling for other variables. 74% of the sample did choose the cure in the 'equal QALY' test. However, there were other differences between the two alternatives in the 'equal QALY' test, which might explain why the cure alternative was chosen more often. For example, the health gains were larger per individual in the cure alternative and the number of patients treated was lower. The DCE results suggest that increases in health gains were valued more than increases in the number of patients treated, meaning that the health gain in the cure alternative could also be a driver of this result.

Whilst the responses to the attitudinal questions cannot be directly compared to the DCE results, as no trade-offs are made in the former, overall the results are relatively consistent. For example, the statement with the greatest support related to prioritising those with greater health gains and the DCE results are very much aligned with this viewpoint. In addition, the statement about prioritising curative treatments had one of the lowest rates of agreement, and the DCE results indicated that a treatment being curative had little impact on the choices that were made.

5.2. Strengths and limitations

The major strength of our study is that the DCE task forced individuals to trade-off between different characteristics of health treatments. This is important because, as shown by our attitudinal statement results, it is typical for individuals to agree with a range of different (potentially conflicting) statements about health service priorities. Another strength is that we attempted to avoid biases and framing when designing our DCE. For example, by choosing an age for the hypothetical patient groups, we minimised the potential for biases regarding the age of patients. Additionally, whilst we were interested in determining whether cures were valued to a greater extent than non-cures, we attempted to minimise potential framing effects. This was done by minimising the number of mentions of cures prior to and within the tasks as well as avoiding discussion of the potential implications (e.g. reduced future medical use). We also avoided the use of the phrase 'one-off treatment' in order to make sure that our results were applicable to the broad range of curative treatments. By implication, we were relying on the respondents' understanding of the wider benefits of a cure.

However, the precise definition of a cure that we used in the study and the lack of detail about the implications of a curative treatment are also significant limitations of our study. As described earlier, there are many different definitions for curative treatments. Our definition is only one of these and is arguably a stricter definition than many others that could have been chosen for this study, given the need for the treatment to restore *both* life expectancy and quality of life to that of a 'normal' individual. The lack of additional information on the potential benefits of a cure means that we are unable to

determine the extent to which respondents might have considered the implications of cures throughout the DCE task. It may be possible that respondents did not consider these at all, and therefore may have underestimated the potential value of curative treatments.

We opted to use an internet survey to administer the DCE, as this offered a cost-effective means of obtaining a large sample in a short amount of time. However, the self-compete nature of internet surveys is a limitation in that it is difficult to observe whether respondents have paid attention to and/or have understood the instructions and tasks sufficiently. On the other hand, this mode of administration avoids other problems such as interviewer bias.

5.3. Further research

This report details the first study (that we are aware of) that attempts to elicit society's preferences over curative therapies and health gains. It is preliminary research, and we hope further studies will emerge in this area. Further research would be useful to explore preferences over different definitions of cures (i.e. ones that are less 'strict' than ours), and in different populations, for example in children. It may also be interesting to explore the inclusion of additional information about cures (such as indicating that they would be 'one off' or reduce future heath care usage).

6. CONCLUSIONS

Our study adds to the priority setting literature that suggests that there is limited public support for the "QALY is a QALY" assumption, due to evidence of diminishing marginal utility in both length and quality of life. In the face of difficult policy decisions, our evidence suggests that decision-makers may be justified in considering factors beyond simply the size of the incremental QALY gain provided by a new treatment. However, it should be noted that when respondents were not faced with trade-offs, 58% agreed that the same priority should be given to treating *all* patients. A relaxation of this assumption may not be easy to implement politically.

With respect to cures, our study does not provide evidence to suggest that society prefers curative treatments over non-curative treatments, after controlling for the size of the health improvement. However, we used a very specific definition of a cure and therefore suggest that our results are taken with caution. We did not specify that a curative treatment would be a 'one-off', nor did we highlight that it may reduce potential future health care use. Curative treatments that offer sizeable health gains, but do not necessarily restore health to that of a 'healthy' individual, would no doubt be of significant social value given the preferences of our respondents for larger health gains. This reflects the benefits offered by some advanced therapy medicinal products, which have the potential to result in substantial health benefits but may not entirely restore patients to the health of a disease-free individual.

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APPENDIX 1: EXAMPLE CHOICE TASK

Imagine that you are a **health care decision maker** that is responsible for making funding decisions. You must choose between funding two treatments as only one can be funded. When making your decision, remember that:

- All treatments are for patients that are **35 years old** and do not have any other conditions. Currently, a typical life expectancy is around **80 years**.
- All patients already receive health care for their condition, and their current care will not change if they are **not selected** to receive the new treatment.

Condition A	Condition B
With the **current care**, patients with condition A: - Die **40 years earlier** than if they did not have the condition - Live for the rest of their lives with **mild health problems** (75% quality of life).	With the **current care**, patients with condition B: - Die **40 years earlier** than if they did not have the condition - Live for the rest of their lives with **severe health problems** (25% quality of life).
The **new treatment** would **cure** patients of condition A. It would: - Extend patients' lives by **40 years**. - Offer a **small improvement** in patient's quality of life (25% gain).	The **new treatment** would **not cure** patients of condition B. It would: - Extend patients' lives by **10 years**. - Offer a **very large improvement** in patient's quality of life (75% gain).
If this option is chosen, **400 patients** would be treated in total	If this option is chosen, **800 patients** would be treated in total

I would choose to fund the new treatment for:

○ Condition A	○ Condition B

APPENDIX 2: DOMINANCE TEST

Imagine that you are a **health care decision maker** that is responsible for making funding decisions. You must choose between funding two treatments as only one can be funded. When making your decision, remember that:

- All treatments are for patients that are **35 years old** and do not have any other conditions. Currently, a typical life expectancy is around **80 years**.
- All patients already receive health care for their condition, and their current care will not change if they are **not selected** to receive the new treatment.

Condition A	Condition B
With the **current care**, patients with condition A: - Die **20 years earlier** than if they did not have the condition - Live for the rest of their lives with **severe health problems** (25% quality of life).	With the **current care**, patients with condition B: - Die **20 years earlier** than if they did not have the condition - Live for the rest of their lives with **severe health problems** (25% quality of life).
The **new treatment** would **not cure** patients of condition A. It would: - Have **no change in life expectancy.** - Offer a **small improvement** in patient's quality of life (25% gain).	The **new treatment** would **not cure** patients of condition B. It would: - Extend patients' lives by **5 years**. - Offer a **very large improvement** in patient's quality of life (75% gain).
If this option is chosen, **100 patients** would be treated in total	If this option is chosen, **800 patients** would be treated in total

I would choose to fund the new treatment for:

○ Condition A	○ Condition B

APPENDIX 3: 'EQUAL QALY' TEST

Imagine that you are a **health care decision maker** that is responsible for making funding decisions. You must choose between funding two treatments as only one can be funded. When making your decision, remember that:

- All treatments are for patients that are **35 years old** and do not have any other conditions. Currently, a typical life expectancy is around **80 years**.
- All patients already receive health care for their condition, and their current care will not change if they are **not selected** to receive the new treatment.

Condition A	Condition B
With the **current care**, patients with condition A: - Die **40 years earlier** than if they did not have the condition - Live for the rest of their lives with **mild health problems** (75% quality of life).	With the **current care**, patients with condition B: - Die **40 years earlier** than if they did not have the condition - Live for the rest of their lives with **moderate health problems** (50% quality of life).
The **new treatment** would **not cure** patients of condition A. It would: - Extend patients' lives by **20 years**. - Offer a **small improvement** in patient's quality of life (25% gain).	The new treatment would **cure** patients of condition B. It would: - Extend patients' lives by **40 years**. - Offer a **large improvement** in patient's quality of life (50% gain).
If this option is chosen, **800 patients** would be treated in total	If this option is chosen, **400 patients** would be treated in total

I would choose to fund the new treatment for:

○ Condition A	○ Condition B

APPENDIX 4: EXAMPLE CHOICE SUMMARY FOLLOWING PRACTICE TASK

When you make your choices, please remember that you are choosing **which patient group the health service should treat**, rather than which patient group you would rather be in the position of.

In the practice question:

- Without the new treatment, patients with condition A **die 10 years earlier** than they would have without the condition and spend the remainder of their life (approximately 35 years) with **mild health problems (75% quality of life)**.
- Without the new treatment, patients with condition B **die 40 years earlier** than they would have without the condition and spend the remainder of their life (approximately 5 years) with **severe health problems (25% quality of life)**.
- Both new treatments provide the **same amount** of life extension (an additional 5 years) and the **same improvement** in quality of life (25% gain).
- Both patient groups have the **same number** of patients (800).

By choosing to treat patients with condition A, you are prioritising the group of patients that is **less severely ill** over the group that is more severely ill.

Do you wish to stick with your current choice?

Select only one answer

◯ Yes
◯ No