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Developing an Algorithm to Convert Routine Measures of Vision into Utility Values for Glaucoma

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ABSTRACT

Purpose: Measures of quality of life called utility values (UVs) are needed to deliver the most cost-effective health care for glaucoma patients. UVs are rarely measured in clinical research and practice whereas clinical outcomes such as visual field are routinely collected. The aim was to develop an algorithm that calculates UVs directly from combinations of routine measures of binocular visual field, visual acuity, and contrast sensitivity.

Methods: A total of 132 outpatients with primary open angle glaucoma were recruited. The Time Trade-off (TTO) question was administered during face-to-face interviews. Binocular ETDRS logMAR visual acuity (VA_B), binocular Pelli-Robson contrast sensitivity (CS_B), and Humphrey 24-2 monocular visual field tests were performed on the same day. Integrated (binocular) visual field (IVF) scores were derived. Tobit regression analyses were used to model utility values based on combinations of IVF, VA_B, CS_B and other controlling factors.

Results: UVs recorded for 123 cases correlated significantly with both clinical measures of binocular visual function (r = -0.47, IVF; r = -0.48, VA_B; r = 0.50, CS_B; *P* <0.0001) and measures of vision-specific quality of life (r = 0.54-0.6, *P* <0.0001). Two final models incorporate terms for IVF and VA_B, with or without living arrangements, and explain 24% and 31% of variation in utilities. CS_B was not included in either model due to co-linearity between CS_B and VA_B confounding the models.

Conclusion: The models provide preliminary algorithms for predicting the expected UVs for glaucoma populations directly from clinical outcomes collected routinely in clinical practice. The predictions have limitations and further work is needed to improve these models.

INTRODUCTION

Glaucoma is the second leading cause of blindness in the world, affecting 1- 5% of people aged 40 years and above in developed countries.[1] Prevalence is predicted to increase by 50% from 2000 to 2010 due to rapidly ageing populations.[2] There are increasing numbers of surgical and medical options to prevent disease progression, but once occurred, any visual loss is irreversible.

Glaucoma is in the same position as many other ophthalmic and non-ophthalmic diseases in that demand for services and choice in therapies is expanding while health care resources are becoming increasingly constrained.[3] There is therefore a continuous demand to evaluate and compare the value for money of new and old treatments both within and across health departments. Cost-utility analysis is a type of economic evaluation that allows such comparisons to be made by applying a common metric of health outcome - the Quality Adjusted Life Year (QALY) - across diverse interventions and diseases.

Utility values (UVs) are an integral component of QALYs. They are preference-based measures of the quality of life (QoL) associated with a particular health state, be it glaucomatous sight loss or hearing impairment. UVs are typically single values between 0 and 1 that encompass all aspects of health-related QoL (HRQoL). By convention a value of one represents perfect health while zero represents death.

However, utility values are complex and time-consuming to elicit. Outcome assessment in ophthalmic practice and research relies heavily on clinical measures of vision (visual acuity (VA), visual field (VF)). Moreover there is currently no universally agreed staging system describing glaucoma progression by which mean utility values can be stratified for the purpose of economic modelling. For these reasons, economic evaluation would benefit greatly from a simple model to calculate UVs from clinical measures of vision readily available from routine tests.

Algorithms that convert clinical measures of visual function into utility values have been used previously for ophthalmic cost-effectiveness studies. Sharma *et al.* (2000) presented a formula

deriving time trade-off (TTO) utility values from VA in the better seeing eye for a group of mixed ophthalmic patients.[4] The model explained 22% of variation in utilities and has been used in numerous cost-effectiveness analyses.[5-9] Bansback *et al.* (2007) described a multivariable linear regression analysis predicting 16% of variation in HUI3 (Health Utilities Mark III) utility values from measures of binocular contrast sensitivity (CS) and age.[10] They developed a Markov model describing the progression of ARMD by contrast sensitivity states and used the algorithm to assign utilities to these states in a study comparing the cost-effectiveness of alternative interventions.[11] Conversion algorithms facilitated these health economic analyses considerably because utilities could be quickly generated from clinical outcome data measured routinely in clinical practice and research.

Unfortunately, the above algorithms are suboptimal for use in glaucoma populations because they do not incorporate changes in the VF, the primary outcome of glaucoma progression. CS is also affected and reductions in VF and CS functionalities from even the early stages of disease show significant associations with increased disability and difficulties in everyday life.[12-16] Glaucoma is unusual among eye diseases in that VA remains relatively uncompromised until the advanced stages when central VF loss ensues.

A recent study has put forward a model calculating utility values for different stages of VF losses in glaucoma patients.[17] However this model is not based on empirical evidence of the relationship between UVs and VF. Rather, it couples empirical evidence on the association of UVs with VA in a mixture of ophthalmic diseases, with theoretical and assumed relationships between VA and VF losses in glaucoma patients.[17]

Several empirical studies have evaluated utility values and their relationship with clinical measures of vision specifically among glaucoma patients.[18-26] Jampel *at al.* (2002) applied TTO and Linear Rating scale utility methods but found only weak correlations between those and the Esterman binocular visual field scores (partial correlation coefficients ≤ 0.17, $P \leq 0.06$).[20] The authors highlighted that clustering of Esterman Efficiency scores above 80% may restrict analysis of the relationship between UV and binocular VF loss, and in a further study provided evidence for using alternative binocular VF measures that are calculated using the best location algorithm and give a more even distribution of

scores.[19-20]

The objective of this study is therefore to develop a generic algorithm that can calculate UVs for patients with primary open angle glaucoma (POAG) based on a combination of routine VF, VA and CS tests. As perceived vision is a product of both eyes functioning together, binocular visual measures have been used. The Integrated Visual Field score (IVF) is the chosen measure of the binocular visual field as it is derived from routinely performed monocular VF tests using the best location algorithm. It has been demonstrated to be significantly better than the Esterman test at predicting 3 out of 9 self-reported visual disabilities, and equally as good at predicting the remaining 6 disabilities.[27]

MATERIALS AND METHODS

This study was approved by Moorfields and Whittington Local Research Ethics Committee and the London School of Hygiene and Tropical Medicine Ethics Committee.

Study Sample

Outpatients diagnosed with POAG in one or both eyes were recruited from Moorfields Eye Hospital (MEH, London, UK). Patients were included if they were >18 years of age, English-speaking, and free from impairments preventing reliable visual testing and interviewing. Patients who had undergone eye surgery in the past 6 weeks and patients with ocular morbidities other than POAG significantly contributing to their loss of vision were excluded.

Clinical visual function measurements

Visual acuity was measured in standardized conditions using a back-illuminated ETDRS logMAR chart (Lighthouse International, New York, NY).[28-30] Monocular and binocular VA (VA_B) was measured using the participants' habitual (distance) glasses, when possessed. The chart was read letter-by-letter at 4 metres, or 2/1 metre if s/he could not easily read the letters on the top line at 4/2 metres, respectively. If no letters could be seen at 1 metre, a value of 1.85 logMAR was designated to vision

of ‘counting fingers’ (CF), and 2.3 logMAR to vision of ‘hand movements’ (HM) or less. These values were adopted from a study estimating vision of HM and CF quantitatively, on a logarithmic scale.[31] Methods for converting between Snellen and LogMAR visual acuities are described in the same article.

Binocular CS (CS_B) with habitual (distance) glasses was measured using the Pelli-Robson chart with front illumination under standardized conditions at 1 metre.[32] A score of zero was recorded when participants could not see >1 letter on the chart.

The Integrated VF score (IVF) was the main binocular VF score used in this study.[27] The IVF is derived from routinely performed (Humphrey 24-2) monocular VF tests. Following the published method, monocular Humphrey 24-2 full threshold tests were performed in both eyes (Humphrey Field Analyzer II, model 730; Humphrey Instruments, Dublin, CA, USA). The maximum sensitivity (dB) recorded between each of the 52 overlapping points of the right and left monocular fields was used to represent a 52-point integrated (binocular) VF. The IVF score was then calculated by scoring each point in the integrated VF (<10 dB = 2; 10-19 dB = 1; ≥ 20 = 0), and summing these scores. Minimum (0) and maximum (104) scores represent the best (>20 dB in all 52 points) and worst (<10 dB in all 52 points) binocular VF, respectively. IVF scores were based on the monocular VF for participants with a) no perception of light (NPL) in one eye or b) severe visual loss (mean deviation ≤ -25 dB) in one eye in their most recent test, and whose eyesight had deteriorated to the extent that their VF was unobtainable in that eye. An IVF score of 104 was designated to those participants who had NPL/severe visual loss in both eyes, such that a reliable VF was unobtainable from either eye. Only scores that were based on reliable VF tests were included in the analysis. Published criteria were used as a basis for reliability of Humphrey 24-2.[33] Tests with ≥33% false positives were automatically excluded. Machine-tested measures of fixation and false negatives can be unreliable in themselves if the blind spot is plotted incorrectly, or if the patient has severe/end stage glaucoma and/or loss of central vision. Therefore, fixation and performance by all participants was monitored throughout testing by a single observer and fields with ≥ 33% false negatives and/or ≥ 20% fixation losses were presented to a clinical expert, Dr A. Viswanathan, at MEH and the Institute of Ophthalmology (London), to determine reliability. The mean deviation (MD) of the visual field in the better eye was

also recorded for testing association with IVF scores.

Interviews

Questionnaires and visual tests were administered by the same researcher (YA) at MEH. Information was collected on: age, diagnosis of high or normal tension glaucoma (HTG/NTG), gender, ethnicity, education, marital status, vocation, living arrangements, current topical medication, previous glaucoma surgical or laser interventions, and time since diagnosis. Socio-economic status was recorded using the five-class National Statistics Socio-Economic Classification system, a UK occupation based government classification developed by the Economic and Social Research Council.[34]

The TTO question was used to elicit utility values, as it has been widely used in ophthalmic research and has demonstrated validity and test-retest reliability.[35-42] It was based on a two part-question that has been published elsewhere.[39, 43-44] Participants were first asked how many more years they expected to live (*Y*). They were then given the choice of living the remainder of their life (*Y*) with their current vision, or trading some of those years to live with restored, perfect vision. Utility values were calculated from the maximum number of years that the person was willing to trade for perfect vision (*Z*) as follows: UV = (*Y* – *Z*)/*Y*.

Generic HRQoL questionnaires administered were the Medical Outcomes Study 36-Item Short Form (SF-36, version 2) and the EuroQoL EQ-5D.[45] Outputs from the former include the norm-based physical and mental component summary scores (PCS, MCS), while those of the latter are the 5D3L (5 Dimension, 3 Level) health state index and the Visual Analogue Scale score (VAS). The PCS and MCS scores were based on the 1998 general U.S. population norms because data for the 1999 general UK population is limited to people under the age of 65,[46] whereas 38% of the 1998 U.S. population were aged between 65 – 96.[47] Vision-specific QoL questionnaires consisted of the 25-item National Eye Institute Visual Function questionnaire (VFQ-25) and the Daily Living Tasks dependent on Vision (DLTV), both of which result in a single output score.[48-51] Depression was screened using a tool developed by RAND's Partners in Care study.[52]

Questions eliciting socio-demographics were administered first, followed by the SF-36, EQ-5D, VFQ-25 and DLTV in randomised order. Due to the sensitivity of questions involved, the depression screener and TTO question were administered at an appropriate point in the second half of the interview.

Data analysis

Data was double-entered by two people on an Access based database, compared/corrected using the EpiInfo™ Data Compare tool and uploaded onto STATA. Given that the utility values were right-censored at one (79 participants provided an answer equal to 1.0 but are not likely to have truly the same HRQoL), tobit regression analysis was used to derive the algorithm relating VF, VA and CS to UVs. TTO utility values were first log-transformed because of their skewed distribution. The likelihood-ratio test was used to determine statistically significant contributors to the model during stepwise multiple regression. Coefficients of determination (R^2) were calculated between predicted and observed UVs as recommended for use with tobit analysis.[53] Spearman's rank correlation coefficient (with a 95% confidence interval (CI)) was used to analyse association between variables. The Wilcoxon signed-rank test was used to perform paired comparisons between binocular VA and best-corrected monocular VA. The Mann-Whitney *U* test was used to compare TTO utilities between independent samples.

RESULTS

A total of 132 glaucoma patients were recruited. The main socio-demographic characteristics and the range of binocular vision are summarised in Tables 1 and 2, respectively. A reduced number (n = 124) of IVF values were calculated as 8 patients did not produce reliable Humphrey 24-2 visual fields. All stages of glaucoma progression were sampled, and age ranged between 27 and 93 years (mean (SD) = 71.8 (11.0)).

Preliminary analyses assessed relationships between IVF, VA_B, and CS_B in glaucoma patients. Scatter plots between each pair of measures showed little evidence of curvilinear effects. IVF correlated slightly better with CS_B (r = -0.65) than with VA_B (r = 0.55, Table 3). CS_B and VA_B were strongly associated (r = -0.76, Table 3). VA_B correlated highly with the vision in the better eye (VA_{Best}, r = 0.94, Table 3) and there was no statistical difference between these values (*P* = 0.49).

Utility Values and Quality of Life Indices

Utility values and other QoL scores are summarised in Table 4. A total of 123 utility values were estimated using the TTO question. The most common reason for missing UVs was inability to consider the question independently from religious beliefs (4/9 cases). UVs ranged upwards from 0.25 but the distribution was highly skewed towards the maximum value of 1. A total of 79/123 (64.2%) patients preferred to keep their current eyesight rather than accept reduced longevity, highlighted by the median value being 1.0. The mean (CI) UV for the 123 patients was 0.90 (0.87 – 0.93).

Consistent with UVs measuring changes in QoL due specifically to visual loss, correlation analysis confirmed moderate associations between UVs and IVF, VA_B and CS_B (*P* < 0.0001, Table 5). This association is demonstrated in Figure 1 which shows the distribution of UVs in groups of patients stratified according to the level of deterioration of the visual field, visual acuity, and contrast sensitivity. Table 6 gives the mean IVF, mean deviation in visual field, VA_B and UVs associated with the different stages of visual field reduction stratified in Figure 1a. Despite significant overlap in UVs between subgroups, there was a clear trend for a decrease in UVs with deteriorating IVF, VA and CS.

Moreover, there were significant differences in utility values when two-way comparisons were performed using cut-offs representing moderate reductions in visual field (IVF = 30) visual acuity (VA_B = 0.6 logMAR) and contrast sensitivity (CS_B = 1.20 log; $P < 0.01$ in all tests).

Further assessments compared the extent to which UVs correlated with other scales measuring similar (VFQ-25, DLTV) as opposed to different (EQ-5D Index, EQ-5D VAS, SF-36 MCS/PCS) constructs (Table 5). Consistent with the TTO question targeting vision-related QoL, UVs correlated significantly better with the VFQ-25 (r = 0.60, P < 0.0001) and DLTV (r = 0.54, P <0.0001) than with measures of overall health (EQ-5D Index/VAS, r = 0.23/0.21, P <0.05) and physical health (PCS, r = 0.27, $P < 0.01$). There was no significant correlation between observed UVs or other measures of vision-specific QoL (VFQ-25/DLTV) and mental health (SF-36 MCS, $P > 0.05$).

Development of a conversion algorithm

We estimated our equations of interest using Tobit models, which allow for the censoring of UVs at 1.0. As explained above, we log-transformed the TTO data to obtain a more normally distributed dependent variable, so that our dependent variable was y = log(TTO+1). The censoring at 1 was therefore accordingly shifted to censoring at log(2).

All models are based on the 116 cases for which TTO, IVF, CS_B and VA_B measures were obtained, except those incorporating the time since diagnosis. In the latter analyses observations were fewer (n = 112) due to the absence of any information on the date of diagnosis. Since scatter plots of UVs with visual measures showed no evidence of curvilinear relationships, linear specifications were chosen. We hypothesized that the simplest model would predict utility values from the 3 explanatory variables: IVF, VA_B, and CS_B.

Each visual function score explained 18.8% - 19.4% of the variation in utility values when used as unique explanatory variables ($P < 0.0001$). However, when all three variables were incorporated into one multiple variable regression model, VA_B and CS_B were statistically insignificant ($P \geq 0.40$; Table 7, column 1). Further statistical tests and visual examination of the relationship between VA_B and CS_B revealed that there was high co-linearity between the two variables (r = -0.76, Table 3) which

confounded the individual effects of each variable and resulted in larger standard errors and lower levels of significance. CS_B was therefore excluded from further analyses on the basis that it is not routinely measured in clinical settings.

The results of the simplified model including IVF and VA_B only are presented in column 2 of Table 7 and demonstrate that VA_B and IVF predict 24 % of variation in TTO utility scores. Based on column 2 of Table 7, the best-fit algorithm estimating TTO scores from IVF and VA_B is:

Model 1:

$logUV = 0.8912 - 0.0024(IVF) - 0.1304(VA_B)$

$UV = (e^{logUV}) - 1$

Where:

IVF = Integrated Visual Field Score

VA_B = Binocular ETDRS logMAR visual acuity score

The algorithm may result in UVs >1.0 but these are taken as 1.0. As an example of how this equation is used, glaucoma patients with moderate visual impairment (IVF = 70, VA_B = 0.4 logMAR) would be estimated a mean UV as follows:

$logUV = 0.8912 – (0.0024 \times 70) – (0.1304 \times 0.4)$

$logUV = 0.8912 – 0.168 – 0.05216 = 0.67104$

$UV = (e^{0.67104}) – 1 = 0.96$

Further univariate regressions were carried out with all other potential explanatory variables to identify those that should be tested for inclusion within a second model. The following factors did not significantly explain any variation in UVs ($P > 0.05$): gender, age, self-reported life expectancy (extracted from the TTO responses), years diagnosed, treatment history (drops/surgery), diagnosis, and all sub-classifications of education, race, socio-economic status, living arrangements, marital status, and vocation. The only significant predictor of UVs was whether or not patients lived in supervised accommodation ($P = 0.001$). There was some indication that failing the depression screener might explain some variation in utility values although this was not significant at the 95% level of certainty ($P = 0.075$). Exploring the role of mental health further, the SF-36 MCS and its subscales (mental health; role emotional; vitality; social functioning) significantly explained 4% - 15%

of variation when regressed separately with UVs ($P \leq 0.02$) and were significant predictors when combined with IVF and VA_B in multivariate models. However, for practical reasons, we finally opted for not including it in the multivariate model as the SF-36 is not administered routinely.

Column 3 of Table 7 shows the final best fitting specification in which participants living in supervised/sheltered accommodation (n = 5) had significantly lower UVs, and 31% of variation in UVs is accounted for. Based on these results, the second best fitting predictive model is:

Model 2:

$\log UV = 0.8876 - 0.0024(IVF) - 0.1136(VA_B) - 0.2664(LIVSUP)$

$UV = (e^{logUV}) - 1$

Where:

IVF = Integrated Visual Field Score

VA_B = Binocular ETDRS logMAR visual acuity

LIVSUP = Indicator variable equal to 1 if person lives in a supervised/sheltered home

Model 2 provides some added value with respect to Model 1 as it explains 7% more of the variation in utility values than Model 1. Therefore, when information on patients' living arrangements is available, Model 2 is preferable.

DISCUSSION

In this paper we present two models for predicting mean utility values for with primary open angle glaucoma from clinical measures of visual field and visual acuity functioning (with/without living conditions) that are readily available in clinical settings. Binocular VA (VA_B) and monocular VA in the better eye (VA_{Best}) did not differ significantly in this study and we confirm that VA_{Best} can be used in place of VA_B if binocular measurements are not available. There is also a linear relationship between binocular (IVF) and monocular (MD in the better eye) visual field scores, and algorithms for converting between them are given in Table 6. The amount of variation explained by these models is 24-31%, at least as good as those developed by Sharma (22%)[4] and Bansback (16%)[10] and used in the cost-effectiveness studies described in the Introduction. The models are currently the best available

resource for the calculation of mean preferences for different stages of glaucoma progression in economic modelling. The models are unsuitable (and not intended) for the prediction of a particular individual's quality of life.

Contrary to our original hypothesis, neither model includes contrast sensitivity as a predictor of UVs due to co-linearity between CS_B and VA_B confounding the models. Similarly high correlation coefficients between VA and CS have been described in eyes with intermediate uveitis (r = -0.69) and age-related macular degeneration (r = -0.74).[10, 54]

People living in various types of supervised accommodation may have been willing to trade greater proportions of their remaining life as a result of any number of factors associated with their circumstances. We speculate these might include people feeling lonely, unsupported and/or vulnerable; having reduced mental/physical health; not having close dependents to reinforce a 'will to live' for as long as possible. We note however that this finding was based on small sample size (n = 5) and requires further validation.

The large proportion of variation remaining unexplained by the models (76 - 66%) can be attributed to several factors including:

- Real differences in the way that a given visual state is experienced as a disability. As a study into the impact of sight loss from POAG concluded, "The meaning of sight loss for any individual clearly depends on a combination of environmental, social and psychological factors, including physical environment, family circumstances, work roles and adaptive responses to symptoms, rather than medically defined measures of disability" [55]. In this study VA and IVF explain 60% of variation in VFQ-25 composite scores (data not shown), illustrating that up to 40% of variation in the disability experienced by glaucoma patients is due to unique interactions of personal circumstances. These personal circumstances may also include non-vision systemic co-morbidities including mental health as indicated by several subscale dimensions of the SF-36 being significant predictors of UVs in uni- and multi-variate models.[26, 56-57]
- Real differences in the way a given level of disability is valued in relation to an external metric (longevity, in this study). Revicki and Kaplan (1993) have demonstrated that preference-based

measures of quality of life correlate, at best, only moderately with psychometric-based measures of health status and quality of life. This has been iterated in more recent work aiming to map between the two types of measure and has been confirmed in this study (Table 5).[58-61]

- Sample Size: Similarly to Brown's investigations of 325-500 patients with diverse ocular morbidities, this study found no effect of variables such as age, race, gender, type of primary open angle glaucoma, marital status, vocation (retired/employed), socio-economic status, education and time since diagnosis on utilities.[4, 43-44, 62] However differences in TTO valuations with age and gender have been reported elsewhere and it is possible that the number of cases in this analysis (n = 116) may have lacked the power to detect such associations.[63-64]
- Elicitation method: The large percentage of zero traders is well documented across chronic disease including ophthalmology.[63] Similar glaucoma studies using the TTO report percentages of 38 - 83%.[20-21, 25, 43] Preference elicitation methods such as the TTO have been shown to be influenced by non-health dimensions such as attitudes towards death, impact of death on significant others, time preferences, numeracy skills, and emotional responses to the question.[65-66] It is well recognised that preference elicitation methods such as the TTO are insensitive to small but important changes in QoL when applied to 'mild' health states (such as the early stages of glaucoma) because it is 'unreasonable to compare them to death'.[67] More work to develop more sensitive and standardised methods that are less prone to non-health dimensions is needed.

A previous study developed similar conversion algorithms based on theoretical/assumed relationship between the visual field (MD) and visual acuity losses.[17] For example, mean deviations of -23dB and -30dB were predicted to be analogous to visual acuities of 1.0 and 1.7 logMAR, and associated with UVs of 0.66 and 0.26, respectively. The empirical values of MD and VA_B shown in Table 6 indicate that the these are significant overestimates of the level of VA and UV losses at the advanced stages of disease, as the mean (SD) VA_B associated with similar MDs of -23 and -29 dBs in this study were 0.25(0.39) and 0.65(0.52), respectively. The mean (95% CI) UVs observed (Table 6) for the same groups were 0.85 (0.74 – 0.95) and 0.72 (0.59 – 0.85). The algorithms published by Rein *et al.* (2007) may therefore significantly overestimate UVs reductions associated with visual field loss.[17]

The TTO scores observed and predicted from Model 1 are comparable with TTO-based UVs in other

empirical ophthalmic studies based in industrialised countries. Table 8 presents predicted UVs from feasible combinations of VA and IVF scores (based on stratifications in Table 6 and Figure 1) using the algorithm in Model 1 and compares them with observed and predicted values from three other studies of mixed ophthalmic patients based on VA. Predicted UVs of patients with severe/end stage glaucoma (e.g. UV = 0.51 when IVF = 99, VA_B = CF) are similar to estimates of UVs associated with VA of counting fingers in other studies.

By contrast, patients whose central vision is preserved (VA_B = 6/6 Snellen or 0.0 logMAR) until relatively late in disease despite severe visual field loss (IVF = 99) are predicted utilities of 0.92 using Model 1. These high values may be explained by several factors. Firstly, the patients' abilities to adjust their life styles and expectations to cope with progressively reduced fields of view over time, and to assign increasing value and importance to activities performed using central rather than peripheral vision.[22, 25] Secondly, patients (60% of whom were >70 years old) attributing some problems caused partially or wholly by glaucoma (e.g. falls and accidents) to the general deterioration of health associated with 'old age'.[68] Thirdly, TTO utilities aim to value the utility of the present state, not a future state that may or may not follow.[69] Therefore, they may not capture reductions in HRQoL associated with having to live with the uncertainty and fear of eyesight deteriorating or going blind in the future.[70]

However, the model does not predict the small but significant losses in utilities estimated in the earlier stages of disease (compare UVs for IVF ≤50 in Tables 5 and 8). Thus whereas Rein *et al*.'s (2007) model overestimates losses in quality of life[17], the models presented here underestimate UV reductions in the early stages of disease. This lack of precision may partly be due to limitations in the linear tobit model in describing this data set, and errors introduced into the predicted values when re-transforming the logged UVs in tobit back to natural units. Methods to more accurately retransform logged dependent variables in ordinary least squares regressions have not been reported for tobit models.[71] Thus, neither model perfectly predicts the empirical UVs elicited in this paper. Future studies using a greater sample size and more sensitive utility elicitation methods (that does not produce large ceiling effects) may develop more accurate predictive algorithms using alternative modelling techniques such as two part models.[72]

This study has other limitations. Since the implementation of this study, a debate has arisen as to whether utilities anchored as in this study with perfect vision/death, rather than perfect health/death, can automatically be translated into Quality Adjusted Life Years.[73] It has been suggested that respondents do not necessarily conceptualise vision as part of their 'health' and so utilities anchored at perfect vision are not measuring the same construct as those based on perfect health/death anchors.[73-74] It is the latter which are used in for making policy decisions based on costs per QALY. As TTO question in this study used a perfect vision/death anchor, that the UVs in this study may not be appropriate for estimating QALYs and making policy decisions across health departments.

In addition, there is also ongoing discussion as to whether preferences should be elicited from patients or the general population. The National Institute for Clinical Excellence in the UK recommends general population over patient preferences because of the influence of adaptation to poor health on patient's valuations.[75-76] However critics may argue that members of the general population tend to imagine a quality of life that is worse than actually experienced.[77]

Lastly, the generalisability of the model(s) may be a limitation given that the participants were selected from a single, London-based hospital.

Considering all of the above limitations, we conclude that the models presented in this paper are not perfect, fully validated models. They are preliminary models based on the data and methods available, but need improvement and validation.

The elicitation of preferences in health care is a relatively new field of research and methodologies are under ongoing discussion for advancement. New approaches in preference measurement that are more sensitive to QOL reductions associated with mild disease states (such as the chaining of questions), and solutions to issues such as the use of different anchor points (vision/health) and viewpoints (societal/patient),[76] are needed for further advancing and validating the models presented in this paper.

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