EXTENDED REPORT

Quality of life and relative importance: a comparison of time trade-off and conjoint analysis methods in patients with age-related macular degeneration

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Aim: To investigate the relative priorities in quality of life (QoL) in patients with age-related macular degeneration (AMD).

Methods: Measures of visual function, QoL and utility associated with visual loss were obtained from 122 patients with AMD classified according to macular morphology. The two methods of utility assessment were time trade-off (TTO) and conjoint analysis (CA), which have been recommended by the UK's National Institute of Clinical Excellence as techniques for the assessment of healthcare priorities.

Results: Results show that the two methods for assessing utility are poorly related: TTO relates moderately to visual function and disease severity but CA does not. CA identified two different subgroups of patients: one with outdoor mobility and the other with reading as their main priority.

Conclusion: Further work is needed and caution required in interpreting data obtained using these methodologies for determining their relative importance in vision-related QoL studies.

Functional vision-related quality of life (QoL) questionnaires^{1–5} enquire about the degree of difficulty a patient experiences in carrying out daily tasks, but do not pursue the relative priority of these tasks; yet, the practical consequences of vision loss to a person's QoL are influenced by the priority given to different tasks which the person finds difficult to carry out. This is a key issue, both in the allocation of limited resources and also in rehabilitation strategies for patients.⁶ The UK National Institute for Clinical Excellence has suggested that studies about the value or utility of healthcare interventions should use only three different methodologies: standard gamble, time trade-off (TTO) or discrete choice methods.⁷ All these methods are characterised by patients making a choice between alternative situations from which relative importance or value can be derived. This study compares the latter two methods; the standard gamble approach was not selected because there is considerable evidence that most people do not use probabilities rationally,⁸ although there is evidence that it can be used successfully in aiding clinical decisions about alternative choices for individual patient management.⁹

The measurement of utility in the healthcare domain allows an "objective measurement of the desirability of a health (disease) state".¹⁰ Utilities are usually measured on a scale from 0 to 1, where 0 is equivalent to death and 1 is equivalent to perfect health, with intermediate values representing particular states of health that patients experience. For example, studies involving two different methods to assess utilities in patients with age-related macular degeneration (AMD)¹⁰ and also patients with diabetic retinopathy¹¹ found that the greater the degree of visual disability in the eye with better vision, the lower the mean utility, and that utilities of preoperative vision in cataract¹² were more closely related to subjective ratings of QoL than to objective measures of visual acuity (VA).

METHODS

In all, 122 patients, with mean (SD) age 77.8 (6.7) years, were recruited from the Low Vision and Macular Clinics of the Princess Alexandra Eye Pavilion in Edinburgh, UK. An

ophthalmologist and research assistant familiar with the examination techniques collected the data following regional ethics committee approval of the study. Data included the following:

- Clinical information:* monocular AMD severity was categorised into four grades using the International Classification System¹³: mild dry, moderate dry, late dry (geographic atrophy affecting the inner macular) and wet (including disciform scar). Three binocular categories of AMD severity were derived from the monocular grades as follows: "mild" binocular AMD = mild dry in both eyes or mild dry in one eye and moderate dry in the other eye; "moderate" binocular AMD = moderate dry in both eyes or mild dry in one eye and late dry in the other eye; and "severe" binocular AMD = late dry or wet AMD in both eyes. (Although there may not be unanimous acceptance of these grading categories, small changes in definition would not significantly affect the conclusions.)
- Visual function:* logarithm of the minimum angle of resolution (logMAR) distance VA (mean (SD) 0.49 (0.43)), logMAR near VA (mean (SD) 0.72 (0.46)) and Pelli-Robson contrast sensitivity (mean (SD) 1.10 (0.43)).
- Functional QoL questionnaires:* data were collected using a conventional QoL index, the National Eye Institute Visual Function Questionnaire 25,⁴ for comparison with the two utility methods. Patients were screened for dementia using the short version of the Mini-Mental State Examination test.^{14 15}
- Relative importance measures:* utilities were obtained using TTO and choice-based conjoint analysis (CA) methodologies. The TTO method has been used successfully to assess health-related QoL utilities.^{10 11 16–19} Further details, and a

Abbreviations: AMD, age-related macular degeneration; ANOVA, analysis of variance; CA, conjoint analysis; logMAR, logarithm of the minimum angle of resolution; QoL, quality of life; TTO, time trade-off; VA, visual acuity

description of the TTO task used in this study, are given in the appendix. CA methodology has been applied in diverse healthcare fields^{20–24}; a description of the development of the CA questionnaire used in the present study, and the power calculation of required sample size, is given in the appendix.

RESULTS

Analyses of the Visual Function Questionnaire 25 data showed that, although there were few significant changes or impact on QoL between mild and moderate binocular grades of AMD severity, there were many significant differences in the patients' ability to perform a range of daily tasks between moderate and severe states of the disease. This paper, however, concentrates on the results from measures of relative importance.

TTO utilities

Trading behaviour

The TTO task required respondents to assume that they have either 30, 20 or 10 years to live. An indication of the validity of the respondent's choice for one of these life-expectancy estimates is provided by a comparison of their actual age across the three response categories. Those expecting to live for 30, 20 or 10 years had, respectively, mean ages of 68.5, 76.8 and 81.5 years. The proportion of males to females in the sample was 0.42 and this was independent of the remaining year categories.

Although there was no significant difference across the three life expectancy groups in terms of binocular best-corrected VA ($F = 1.7$, $df = 2$, $p = 0.17$), near VA ($F = 2.0$, $df = 2$, $p = 0.14$) or binocular AMD severity ($F = 1.9$, $df = 2$, $p = 0.14$), the group expecting to live the longest had a significantly better contrast

sensitivity (Pelli–Robson) compared with the other two groups ($F = 3.7$, $df = 2$, $p = 0.02$). Figure 1 gives the distribution of the percentage of remaining life that respondents were prepared to trade for a cure.

Slightly more than half the respondents were unprepared to trade any of their estimated remaining life for a hypothesised cure of their visual disability due to AMD. For these people, the chance of death is preferred to the gamble of gaining an improved state of vision. When the TTO values were classified into two equal groups, $<50\%$ and $\geq 50\%$ of the expected remaining years traded, a one-way analysis of variance (ANOVA) showed that increasing age increases the willingness to trade a greater proportion of expected remaining years for perfect vision. The mean age of respondents trading $<50\%$ of their expected remaining life was 76.7 years and the mean age of those prepared to trade $\geq 50\%$ was 80.4 years ($F = 8.4$, $df = 1$, $p = 0.004$).

Effect of AMD type (ie, wet vs dry) on TTO utility

A one-way ANOVA showed no significant effect of AMD type on respondents' remaining life expectancy, or on the percentage of years that respondents would trade for perfect vision ($F = 1.05$, $df = 1$, $p = 0.31$). People with AMD, therefore, either do not discriminate between the two states of the disease, or are unaware of the more volatile effects of wet AMD on visual function and its potential for further vision loss.

Effect of binocular AMD severity on TTO utility

A one-way ANOVA showed a significant effect of the binocular AMD severity on the percentage of traded years as disease severity increased ($F = 15.2$, $df = 2$, $p = 0.001$), although, as expected, there was no effect on the number of expected remaining life years. Post-hoc comparisons between the means for the three grades of binocular AMD severity showed significant differences between mild and severe ($t = 4.3$, $p = 0.001$) and moderate and severe ($t = 4.6$, $p = 0.001$), but not between mild and moderate states ($t = 1$, $p > 0.05$). Hence, the greatest change in utility occurs for the progression of the disease from moderate to severe states (fig 2).

Figure 1 Percentage of expected remaining life years that patients were prepared to trade for a hypothesised cure of their vision. A pilot study on the form of the time trade-off question indicated that respondents were no more willing to trade smaller amounts of time (ie, months rather than years) for better, but not perfect, vision. Trading was therefore based on expected remaining life years.

Figure 2 Mean utilities from a time trade-off task for three binocular grades of age-related macular degeneration (AMD) severity. For definition of binocular AMD severity, see Methods. Vertical error bars represent 95% CIs.

Table 1 Pearson's product moment correlations (*r*) and associated significance (*p*) of time trade-off utility with visual function and binocular grade of age-related macular degeneration severity grade

Variable	All patients (n = 115)		Only patients prepared to trade (n = 52)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Binocular distance VA (logMAR)	0.38	<0.001		NS
Binocular near VA (logMAR)	0.35	<0.001	0.29	<0.05
Binocular Pelli-Robson contrast sensitivity	0.27	<0.01		NS
AMD binocular severity grade*	0.49	<0.001		NS
AMD grade in the better eye*	0.40	<0.001		NS
AMD grade in the worse eye*	0.25	<0.01		NS
General health		NS		NS

AMD, age-related macular degeneration; logMAR, logarithm of the minimum angle of resolution; NS, not significant (correlations not significant are not presented); VA, visual acuity.

*For definitions of AMD grading, see Methods.

Correlations between TTO utility, visual function and AMD severity

The above results, summarised as correlations in table 1, are based on the full dataset in which those who refused to trade are included and interpreted as trading zero years. By contrast, on examining only those patients who actually traded (ie, about half the sample), most results show no relationship between expected remaining years traded and either visual function or AMD severity (table 1).

The mean utility for all patients, including those unprepared to trade, was 0.805 (95% CI 0.56 to 1.05), which compares closely with the value of 0.72 (95% CI 0.66 to 0.78) reported elsewhere¹⁰ for a similar patient group, whereas the mean utility for only those patients prepared to trade was 0.575 (95% CI 0.41 to 0.75). When the binocular distance VA data were classified into approximately five equal groups across all patients, there was a significant reduction in utility as VA decreased from logMAR 0 to 1.30 ($r = -0.39$, $p < 0.001$). This finding is similar to that reported elsewhere^{10, 25} for the relationship between utility and VA in the better eye (table 2). Although the poorest VA category (logMAR < 1.3) is not directly comparable between the two studies because of the different measurement systems used, the higher mean utility and wide 95% CI among patients with these poor acuities in the present study could reflect increasing adaptation over time to their visual loss, with a resultant higher utility for their present visual state, a feature which is also suggested by Brown *et al.*²⁶

Choice-based CA utilities

Analyses of the conjoint data were based on responses to paired comparison profiles of daily living difficulties for two hypothetical people derived from five attributes of daily living, each attribute being presented at one of three levels of difficulty.¹ Patients were asked which hypothetical person was, in their opinion, in the worse state of health.

Using multinomial logit analysis,²⁸ the share of preferences in the data was converted into utilities based on the preference differences between the extreme levels of difficulty for each attribute (ie, between the levels of "no difficulties" and "a lot of difficulties"). In order to compare utilities between each of the

¹The five attributes of daily living were identified from previous studies as being relatively independent (see appendix). These were: "difficulty reading or seeing fine detail", "difficulty pouring liquids and performing household chores", "difficulty with glare from bright lights", "difficulty getting about outside the house alone" and "difficulty recognising faces". The first two attributes in the preceding list were excluded from the three-attribute version for patients with poorer visual acuity who were unable to read 36-point print. Three levels of difficulty were used to describe each attribute (ie, "no difficulties", "a few difficulties" and "a lot of difficulties").

attributes, utility scores were normalised about the mean preference within each attribute. Figure 3 summarises these calculations, in which the five attributes have been placed in order of relative importance. The same rank order was maintained in the data for the common attributes used in the three-attribute task.

As a further aspect of analysis of the five-attribute data, individual utilities were generated for each patient in the group using hierarchical Bayesian analysis.²⁸ A factor analysis of these individual utilities showed two relatively independent patient clusters in the sample in terms of their relative priorities, one group having outdoor mobility as their highest preference and the other group having reading as their highest preference (fig 4).

In order to examine the interrelationship between the individual conjoint utilities and the clinical, visual functional and QoL questionnaire data, a series of correlations and factor analyses were carried out. No significant relationships were found in comparisons between the individual conjoint utilities for any of the five attributes and age, gender, distance binocular VA, near binocular VA, binocular contrast sensitivity, binocular AMD severity, AMD type, or the grade of AMD in the better eye or worse eye. This means that these aspects of visual loss and clinical state were not influencing patients' perceptions of relative importance.

Comparison of TTO with conjoint utilities

A comparison of TTO utilities, conjoint utilities, visual function and AMD severity was carried out using factor analysis (table 3). The four derived components accounted for 71% of the total variance. The data show that aspects of visual function and disease severity are highly associated with component 1 having moderate linkage to TTO utilities (factor loading = 0.51) and conjoint utilities occupying the other three components being independent of visual function or disease severity. Utilities derived by CA, therefore, are not influenced by a patient's level of visual impairment or severity of AMD.

DISCUSSION

Preference based measures may be used in health economic analysis, in addition to an evaluation based on functional QoL measures that are based on the ability to carry out specific tasks. Recent guidance for QoL evaluation of clinical trials favours the use of discrete choice methods such as standard gamble, TTO or choice-based CA, and is against the use of rating scales.⁷ It would seem implicit in this recommendation that the three main methods of discrete choice comparisons will give rise to similar results and outcomes. Although others have reported limited concordance between TTO utilities and

Table 2 Time trade-off utilities and 95% CIs as a function of distance visual acuity: a comparison of findings from Brown *et al*¹⁰ with the present study

VA group	Data from Brown <i>et al</i> ¹⁰			Data from present study	
	Snellen fraction	LogMAR equivalent	Mean 95% CI	logMAR	Mean 95% CI
1	20/20 to 20/25	0–0.10	0.89 (0.82 to 0.96)	≤0.1	0.93 (0.86 to 0.99)
2	20/30 to 20/50	0.18–0.40	0.81 (0.73 to 0.89)	0.12–0.40	0.86 (0.78 to 0.93)
3	20/60 to 20/100	0.49–0.70	0.57 (0.47 to 0.67)	0.42–0.70	0.74 (0.64 to 0.83)
4	20/200 to 20/400	1.00–1.30	0.52 (0.38 to 0.66)	0.72–1.30	0.68 (0.57 to 0.79)
5	CF to LP	>1.30	0.40 (0.29 to 0.50)	>1.30	0.76 (0.37 to 1.15)

CF, counting fingers; logMAR, logarithm of the minimum angle of resolution; LP, light perception; VA, visual acuity.

Data from Brown *et al*¹⁰ are for distance VA in the better eye, whereas those from the present study are for distance binocular VA. Since our utility estimates are based on binocular viewing, we prefer to relate these to binocular measures of visual function, although practically there is little difference between the two measures. Others have shown that binocular VA and VA in the better eye are comparable predictors of visual disability.²⁷ The VA groups quoted in Brown *et al*¹⁰ are in Snellen, which have been converted here to their logMAR equivalence for ease of comparison, and the nearest equivalent categories have been used for data from the present study.

those derived from the standard gamble method,^{10 25 26} the results of this study indicate that similar findings do not result from utilities generated from TTO and CA judgements.

Previous investigators using TTO have demonstrated a progressive decrease in utility with increasing vision loss as the disease severity progresses,^{10 25 26} and some argue that the strong association between utility and VA in the better eye is an indication of the construct validity of this methodology.²⁹ The TTO data from the present study show similar trends, with significant effects for binocular VA data. However, the correlations between TTO utility and visual function, and TTO

utility and binocular AMD severity, are only moderate for the whole group ($r < 0.5$) and become insignificant if the 50% of patients who refused to trade (mainly those in the mild AMD severity group) are excluded. A factor analysis shows that utilities generated from TTO and CA are unrelated. Although the construct validity of CA cannot be determined, the factor structure of the five conjoint attributes suggests a plausible internal logic in that outdoor mobility and glare are related, reading and household chores are related, and recognising faces is linked to general health. The internal validity of the CA model was high, with predicted actual responses to a paired comparison at an accuracy of 80%.

In line with other studies, the present study shows that there is a greater impact on aspects of vision-related QoL as the disease progresses from a moderate to severe form, rather than from a mild to moderate form, a fact often not appreciated by

Figure 3 Conjoint analysis: comparison of the utilities derived for five quality of life attributes among patients with age-related macular degeneration (AMD). To allow a comparison of the relative importance associated with each attribute, the utility score has been normalised about the mean for each attribute. The utility for each attribute is described by the difference in utility score between the extreme attribute levels of “no difficulties” and “a lot of difficulties”. A large difference in utility score means a high utility—for example, for people with AMD, getting about outside is about twice as important as recognising faces. A similar order of magnitude was obtained from the three-attribute data from patients with poorer visual acuity. Vertical error bars represent 95% CIs.

Figure 4 Multi-attribute preference analysis of individual utilities from a conjoint analysis of five attributes of daily activity ($n = 122$ patients with age-related macular degeneration). The figure shows the factor structure of the two principal components of the individual utilities for all patients ($n = 122$). Respondents are represented as vectors radiating out from the intersection of the two principal axes and are mapped as a contoured density plot. The contours represent different degrees of agreement between the respondents; the darker the shade, the greater the density and the higher the correlation of individual vectors. The plot reveals two principal cluster groups of patients with different relative priorities (A = priority for outdoor mobility, B = priority for reading). The principal components for the five attributes of daily living are superimposed to show their relationship to the density and clustering of the individual patient utilities.

Table 3 Summary of the factor analysis* of clinical and visual function data with utilities from time trade-off and conjoint analysis tasks

Variable	Component			
	1	2	3	4
Binocular distance VA (logMAR)	0.894			
ARM grade in the better eye	0.879			
AMD binocular severity grade	0.861			
Binocular near VA (logMAR)	0.848			
Binocular Pelli-Robson contrast sensitivity	-0.783			
ARM grade in the worse eye	0.646			
Time trade-off utility	-0.512			
Utility for difficulty reading or seeing fine detail		-0.908		
Utility for difficulty pouring liquids or household chores		0.902		
Utility for difficulty with glare from bright lights			0.872	
Utility for difficulty getting about outside the house alone			-0.773	
Utility for difficulty recognising faces across a room				-0.800
General health				0.719

AMD, age-related macular degeneration; ARM, age-related maculopathy; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity.

*Factor analysis using varimax rotation and an eigen inclusion criterion of 1.0. For clarity of factor structure, only factor loadings ≥ 0.5 are shown.

clinicians.¹⁹ Such evidence suggests that any new drug treatment for AMD would be most cost effective if it were to prevent the disease progressing from the moderate to severe state. It remains to be seen, however, whether the vision-related QoL utilities in AMD remain unchanged over time in the late stable stage of the disease, or following rehabilitative intervention at any stage of the disease.

Although there are relative advantages and disadvantages to the use of TTO and CA, studies involving these measures should aim to maximise the utilities gathered, be consistent with the methodology and ensure an adequate sample size to provide narrow CIs for each level. Only by adopting this approach will outcomes be comparable across different ophthalmic diagnoses and over all medical disciplines.

CONCLUSION

The discrete choice techniques of TTO and CA describe different priorities for individuals affected by AMD, although the high proportion of non-responders to the TTO task suggests this methodology to be of limited value. Others have also reported a high proportion of non-responders to a TTO task, despite claims of its high reliability.³⁰⁻³¹ It would seem, therefore, that CA offers the potential for a more relevant and discriminating measure of vision-related QoL utilities. Although two patient priority groups were identified, caution must be exercised in drawing conclusions within and between different patient populations. Further work is needed to define the role of these techniques in the health economics of AMD and the rehabilitation of affected individuals.

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APPENDIX

THE TIME TRADE-OFF (TTO) METHOD

Utility scores are a representation of the relative desirability of a particular state of health compared with the reference states of death (utility score = 0) and perfect health (utility score = 1). The following two-part question was used to generate the percentage of the remaining years of expected life that a respondent was prepared to trade-off for a hypothesised cure to normal vision:

1. How many additional years do you expect to live? Choose from one of three estimates: 30, 20 or 10 years.
2. How many of these years would you be prepared to give up if you could receive a new technology that would restore your sight to a normal level?

The time trade-off (TTO) variable is the percentage of remaining expected life years (P) that the respondent would trade for a cure. The relationship of this variable to utility is: $utility = (100 - P) / 100$. A high percentage of years that a person is willing to trade, therefore, represents a low utility associated with a respondent's current state of health.

DEVELOPING THE CONJOINT ANALYSIS (CA) QUESTIONNAIRE

The conjoint analysis (CA) questionnaire was developed in conjunction with consultants specialising in health state utilities questionnaires (Adelphi Research Group, Bollington, Cheshire, UK). The "choice-based conjoint" method³² allows the researcher to present different combinations of health states to a person and ask them which is considered to be the more or less desirable state. The health states (or levels of disability) are defined by a set of attributes associated with a disease and a set of levels or degrees of difficulty associated with each of these attributes. In the present study the attributes were aspects of central vision, outdoor mobility, recognising faces, household chores and problems with glare from bright lights. The set of three levels of difficulty associated with these attributes were "none", "a few" and "a lot". These reflect the type of descriptors used almost exclusively in vision-related QoL

or functional disability instruments (eg, the Visual Function 14² and the National Eye Institute Visual Function Questionnaire 25⁴). The attributes used in this study were selected from previously published factor structures of visual disability^{2–5} and our own previous work,³³ as they were relatively independent and representative of daily activity problems. In the present study the discrete choice method involved paired comparisons of daily activity profiles in which the subject considered each pair and decided which would be the least desirable scenario. A "pair" comprised a set of attributes and descriptors representing two profiled hypothetical people with different characteristics of visual impairment. For each paired comparison judgement, patients were asked to state which of the two hypothetical people could be considered to be in the worst state. Box 1 shows an example of a five-attribute conjoint analysis paired comparison task used in this study.

In the present study a comparison of each attribute at each impact level of difficulty involved 243 potential treatment combinations (ie, 3⁵: three levels of difficulty for each of the five attributes). To reduce this set to a manageable number, an orthogonal fraction of the full factorial design that preserved first-order interactions was derived,²⁸ resulting in 15 paired comparisons. The combinations of attributes and levels of difficulty were subsequently checked by two ophthalmologists specialising in retinal disease to avoid implausible combinations and at the same time ensure a balance between the natural progression of the disease and a spread of realistic options. Patients were all given "practice" using different comparisons before collecting data. The five-attribute paired comparisons were presented visually, with the profiles side by side in 36-point size print, and relied on simultaneous comparison. For those patients with poor visual acuity who were unable to read 36-point print, a reduced three-attribute design was used and the paired comparison profiles were presented verbally, thus relying on temporal comparisons.

Box 1: An example of a five-attribute conjoint analysis paired comparison task used in the present study

Question: If you were in the shoes of one of these people, which person, in your opinion, is the worse off?

Person 1

- A lot of difficulty reading and seeing fine detail.
- No difficulty seeing faces across a room.
- No difficulties getting about outside the house alone.
- A few difficulties with glare from bright lights.
- A lot of difficulties with pouring liquids and performing household chores.

Person 2

- A few difficulties reading and seeing fine detail.
- No difficulty seeing faces across a room.
- A lot of difficulties getting about outside the house alone.
- No difficulty with glare from bright lights.
- A few difficulties with pouring liquids and performing household chores.

Note: In the study format, the profiles of the two hypothetical people were presented side by side.

The CA data were recorded and analysed by multi-nominal logit analysis³⁴ to provide (1) the relative importance of each attribute for the aggregate total sample level and for each individual respondent, and (2) the utility scores for each attribute-by-level combination for the aggregate total sample and for each individual respondent.

SAMPLE SIZE AND INCLUSION CRITERIA

With conjoint methods nothing is known about the SEs of the statistics being estimated. There is no sampling theory to use, and the only information available would be from previous studies, if these existed. The Sawtooth “rule of thumb” for a

choice-based CA of the type used here is that the sample size (n) should be greater than $(500c)/(ta)$, where t is the number of tasks, a the number of choices per task and c the maximum number of levels for any one attribute for a main effects model or the largest product of the levels of any two attributes for all first-order interactions.³⁴ For a five-attribute, three-level, two-choice model, this means a sample size of 50 for a main effects model and of 150 for a model containing all first-order interactions. In the present study, we were only interested in a small number of first-order interactions and, therefore, the sample size of $n = 122$ seemed to be more than sufficient.

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