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Creating a Health Utility Value for Birdshot Chorioretinopathy

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ABSTRACT

Purpose: To create a health utility value for birdshot chorioretinopathy (BCR) using Time Trade-Off (TTO) and Standard Gamble (SG) utilities.

Method: Adult BCR patients completed TTO, SG, EQ-5D-5L, and NEI VFQ-25 questionnaires and underwent a detailed history and clinical examination.

Results: A total of 28 BCR patients (9 M, 19 F; mean age 62 years, range 47–83) were included. There were 22 patients with a logMAR vision of 0.3 or better in both eyes. Mean TTO was 0.90 ± SD 0.18 (range 0.33–1.0) and mean SG was 0.94 ± SD 0.14 (range 0.5–1.0). TTO correlated with EQ-5D-5L index value (p = .024) and NEI VFQ-25 composite score (p = .015).

Conclusions: Of 28 patients with BCR, 11 would trade remaining life (mean 5.4 years), and 6 would take a risk of immediate death (mean 28% risk), in return for perfect vision in both eyes for the rest of their life.

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Birdshot chorioretinopathy; quality of life; time trade-off; standard gamble; EQ-5D-5L; NEI VFQ-25

Birdshot chorioretinopathy (BCR) is a chronic sight-threatening posterior uveitis with a distinct phenotype that affects less than 1 in 100,000 of the general population, typically arising in middle-age and more common in females.[1] Diagnostic criteria for research purposes state that it must be bilateral, with three or more "birdshot" lesions inferior or nasal to the optic disc in at least one eye, low-grade anterior segment intraocular inflammation (defined as no more than 1+ cells in the anterior chamber) and low-grade vitreous inflammation (no more than a grade 2 vitreous haze).[2] The birdshot lesion characteristic of this disease is defined as cream-colored, irregular, or elongated choroidal lesions with indistinct borders. It can be considered an "MHC-I (major histocompatibility complex class I)-opathy"[3] as the condition occurs almost exclusively in HLA-A29-positive individuals.[4] Patients may report a range of visual symptoms, including blurred vision, floaters, nyctalopia, and dyschromatopsia despite many having 20/20 vision or better in both eyes.[5–7] The leading cause of vision loss in BCR is cystoid macular edema and other causes include cataract, glaucoma, and choroidal/retinal neovascularization.[6,7] Apart from affecting visual function BCR has also been shown to have an important impact on vision-related quality of life (VRQOL).[8,9]

There are numerous methods of health-related quality of life (HRQOL) utility valuation that can be broadly classified into direct or indirect methods and are either disease specific or concerned with general health utility. Indirect questionnaires estimate an individual's health utility state based on standardized questions, the answers to which have previously been mapped to health utilities using direct methods to determine their weighting. Examples of indirect health utility questionnaires include the EuroQol Five-Dimension Five-Level (EQ-5D-5L) questionnaire[10] and the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25).[11] It is direct methods of health utility valuation that are the most sensitive and account for all dimensions that contribute to health utility in an individual. These principally include time trade-off (TTO) and standard gamble (SG), both of which allow direct comparison, without the need for mapping, of health utilities across different health conditions.[12] By convention, health utilities run on a scale between zero and 1.0, with zero representing a quality of life score equivalent to death and 1.0 equivalent to perfect health. The closer the health utility to a score of 1.0, the better the associated quality of life state. In ophthalmic studies, the health utilities are often adapted so that zero represents a quality of life score equivalent to blindness and 1.0 equivalent to perfect vision. There have been two recent publications reporting TTO in uveitis patients and both have shown a reduction in HRQOL, but only a small number of patients with BCR were included.[13,14]

We wished to create a direct health utility for BCR using TTO and SG. This may provide additional information on how the disease globally affects their HRQOL and as a consequence could lead to a change in the way these patients are assessed and the care they receive.

Patients and Methods

Consecutive adult patients (aged 18 years and older) who fulfilled the diagnostic criteria for BCR[2] and were HLA-A29 +ve were recruited from the dedicated BCR clinics at the Centre for Rare Diseases, University Hospitals Birmingham NHS Foundation Trust, UK, and the Uveitis clinics,

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Birmingham, and Midland Eye Centre, Sandwell, and West Birmingham Hospitals NHS Trust, UK. The study was registered as a service evaluation on the Clinical Effectiveness Department Safeguard Audit System with Sandwell and West Birmingham Hospitals NHS Trust (audit #1008).

As part of their normal clinical care patients self-completed two quality-of-life surveys, EQ-5D-5L and NEI VFQ-25. The EQ-5D-5L questionnaire is a health-related quality of life questionnaire that includes five domains related to mobility, self-care, usual activities (e.g. work, study, housework, family, or leisure activities), pain/discomfort, and anxiety/depression. It includes the EuroQol Visual Analogue Scale (EQ-VAS) where patients rate their health on the day as a score between zero and 100.[10] The NEI VFQ-25 is a vision-targeted survey that assesses the influence of visual impairment on HRQOL. It includes subscales to rate general health, general vision, ocular pain, difficulty with near vision, difficulty with distance vision, limitations in social functioning due to vision, mental health, and well-being due to vision, role limitations due to vision, dependency on others due to vision, future expectations for vision, driving difficulties, peripheral vision, and color vision. Each subscale is scored so that zero represents the lowest and 100 the best possible score.[11] The TTO and SG questionnaires were then administered by face-to-face interview. A standardized script was followed to ensure homogeneity. Our TTO and SG models, both summarized below, measured HRQOL at the precise time of questioning. Our TTO model first asked patients how many more years they expect to live. They were then asked to consider a hypothetical scenario where a new treatment was developed that was to give them perfect vision in both eyes for the rest of their life, but its side effect was to reduce the number of years of life remaining. They were then asked how many, if any, of those remaining years they would be willing to trade-off in return for guaranteed permanent perfect vision. For example, a patient expecting to live 40 more years but willing to trade-off 5 years in return for permanent perfect vision would infer a TTO utility of (40 − 5)/40 = 0.875. Our SG model was similar in that patients were again asked to consider a hypothetical scenario where a new treatment was developed that could give them perfect vision in both eyes for the rest of their life, but in this case, there was an immediate risk of death if the treatment was unsuccessful. They were then asked what the maximum percentage risk of death, if any, they would be willing to accept. For example, a patient willing to accept a 5% risk of death could infer an SG utility of 1 − 0.05 = 0.950.

As part of their routine clinical assessment patients underwent a standard profile of examinations and tests including best-corrected logMAR visual acuity, Ishihara color vision testing, 30 Hz photopic flicker electroretinogram (ERG) using the RET*eval*® (LKC Technologies, Gaithersburg, MD, USA), assessment of anterior chamber activity, intraocular pressure measurement, dilated fundal examination, and vitreous haze assessment,[15] and where appropriate ocular imaging (OCT). Any ocular complication, such as CME, cataract, glaucoma was documented. Basic demographic data were also recorded and included age, gender, ethnicity, education, employment, any medical co-morbidities, and current therapy. Visual acuity was further stratified by acuity in the better-seeing eye as this measure has been consistently found to correlate better with quality of life.[12]

Clinical data capture was facilitated using REDCap v9.6.3 (© 2020 Vanderbilt University, Nashville, TN, USA) and statistical analysis was undertaken using SPSS v26.0 (IBM Corporation, New York, USA). As the distribution of the TTO and SG scores was not normally distributed (one-sample Kolmogorov–Smirnov test statistic was 0.328 and 0.458, respectively, p = .000 for both), the Kruskal–Wallis test was used to evaluate the relationships between HRQOL scores and categorical measurements and Spearman correlation coefficients (r_s) were calculated for the relationship between HRQOL scores and continuous measurements. A p value of 0.05 or less was accepted as indicating statistical significance. Multivariable analysis was used (multiple linear regression) to predict HRQOL scores as the dependent variable based on other variables collected as independent variables. A Bonferroni correction for multiple comparisons was made; a p value of 0.00625 or less was accepted as indicating statistical significance, based on the number of comparisons.

Results

A total of 29 adult patients who fulfilled the diagnostic criteria for BCR and were HLA-A29 + ve were recruited. One patient was excluded because of poor comprehension related to Parkinson's disease leaving 28 patients. There were 9 males and 19 females with a mean age of 62 years (range 47–83 years). All patients were White British. The duration of their disease ranged from 0.5–22 years (mean 9 years). Current systemic therapy is shown in Table 1.

Of the 28 patients their other co-morbidities (some patients had more than one) included hypertension (n = 10), arthritis (n = 3), previous diagnosis of cancer (n = 2), osteoporosis (n = 2), diabetes mellitus (n = 1), previous cerebrovascular accident (n = 1), cardiomyopathy (1), liver disease (n = 1), chronic kidney disease (n = 1), anemia (n = 1), asthma (n = 1), and chronic back pain (n = 1). There were five patients who stated a diagnosis of depression or anxiety but none of these patients were currently on treatment for this. The majority of patients (74%) had some form of educational qualification either at school, or at the undergraduate or postgraduate level. A total of 56% of patients were in employment with 11% unemployed and 33% retired.

Visual acuities (logMAR) are shown in Table 2. There were 9/56 (16%) eyes with a vision of worse than 0.3, and only two patients had a visual acuity of worse than 0.3 in both eyes. The 0.3 cutoff was chosen as this was used in a previous article on TTO and SG in uveitis.[13] The causes for visual acuities worse than 0.3 in any eye were CME (n = 4), foveal atrophy (n = 2),

Table 1. Systemic therapy in 28 patients with birdshot chorioretinopathy.

Medication(s)	Number of patients
Methotrexate	2
Methotrexate and Prednisolone	2
Ciclosporin A and Prednisolone	2
Prednisolone	4
Mycophenolate mofetil	4
Mycophenolate mofetil and Prednisolone	4
Mycophenolate mofetil and Adalimumab	1
Azathioprine	1
None	8*

*One patient had a fluocinolone intravitreal implant in each eye

Table 2. LogMAR vision, time trade-off and standard gamble utility values of 28 patients with birdshot chorioretinopathy.

Patient	LogMAR OD vision	LogMAR OS vision	Time Trade-Off	Standard Gamble
1	0.6	−0.2	0.75	1.00
2	−0.2	−0.2	1.00	1.00
3	0.9	−0.3	1.00	1.00
4	0.2	0.1	1.00	1.00
5	0.0	0.1	1.00	1.00
6	0.0	0.0	0.80	0.80
7	0.0	0.1	0.75	1.00
8	−0.2	−0.2	1.00	1.00
9	0.0	−0.1	1.00	1.00
10	0.4	0.3	1.00	0.75
11	−0.1	0.1	1.00	1.00
12	0.1	0.0	1.00	1.00
13	−0.2	−0.2	1.00	1.00
14	−0.1	0.1	0.95	1.00
15	0.2	1.0	1.00	1.00
16	PL	HM*	0.58	0.70
17	−0.1	−0.1	0.95	1.00
18	0.0	0.0	1.00	1.00
19	CF	1.0	0.50	1.00
20	0.1	0.1	0.90	1.00
21	0.1	0.0	0.80	1.00
22	0.1	0.1	1.00	1.00
23	0.6	0.2	0.33	0.50
24	0.0	0.3	1.00	1.00
25	0.06	0.1	1.00	1.00
26	0.0	0.0	1.00	0.60
27	−0.1	−0.1	1.00	0.95
28	0.0	0.0	0.80	1.00

*allocated value of logMAR 2.3 in analyses

macular hole (n = 1), macular epiretinal membrane (n = 1), and macular scar (n = 1). Ishihara color plates seen in the right eye (n = 22) were 0–5 (n = 6), 6–10 (n = 4), 11–15 (n = 12); and in the left eye (n = 20) were 0 = 5 (n = 4), 6–10 (n = 1), 11–15 (n = 15). No anterior chamber cells were seen in any eye, all intraocular pressures were normal, a degree of cataract was documented in 11 eyes and 8 eyes were pseudophakic. Vitreous haze was scored in 36 eyes and was zero in 32 eyes and +0.5 (trace) in four eyes. There were three patients with ocular hypertension using topical intraocular pressure-lowering agents and no patients with glaucoma.

Time Trade-Off

The TTO was undertaken in all patients. The mean TTO was 0.90 ± SD 0.18, median 1.0, range 0.33–1.0. The mean TTO for the 26 patients with vision 0.3 or better in their best-seeing eye was 0.925. There were 17/28 (61%) patients who would not trade-off any years and scored 1.0. The remaining 11 (39%) patients would trade a mean of 5.4 years (range 1–20) of their remaining years of life in return for perfect vision in both eyes for the rest of their life. There was a statistically significant association of TTO with current systemic therapy (p = .014) but not with the presence of co-morbidities (p = .373) or gender (p = .057). TTO correlated with EQ-5D-5L index value (r_s 0.450, p = .024), NEI VFQ-25 composite score (r_s 0.463, p = .015), and 30 Hz ERG in the left eye (r_s −0.440, p = .019). There was no significant correlation with best-corrected visual acuity in the better eye, SG, EQ-VAS, 30 Hz ERG in the right eye, or disease duration.

Standard Gamble

The SG was undertaken in all patients. The mean SG was 0.94 ± SD 0.14, median 1.0, range 0.5–1. The mean SG for the 26 patients with vision 0.3 or better in their best-seeing eye was 0.95. There were 22/28 (79%) patients who would not take any risk and scored 1. Of the 6 (21%) patients willing to take a risk, their mean SG was 0.72, i.e. a 28% (range 5–50) risk of immediate death if the treatment was unsuccessful. There was no association with current systemic therapy (p = .325), co-morbidities (p = .845) or gender (p = .355). There was no correlation with any of the other HRQOL utilities (TTO, EQ-5D-5L, EQ-VAS, NEI VFQ-25), best-corrected visual acuity in the better eye, 30 Hz ERG in either eye or disease duration.

EQ-5D-5L

The EQ-5D-5L was completed by 25 patients with a mean index value of 0.89 ± SD 0.154 where the index value was calculated using the UK standard EQ-5D-5L value set that gives a score between −0.285 (worst possible health status) and 1 (perfect health).[10] The EQ-5D-5L frequencies and proportions were also reported by dimension and level with the majority of patients having no problems (Level 1) in any of the five domains (Table 3). The EQ-5D-5L index value was not associated with systemic therapy (p = .068), co-morbidities (p = .069) or gender (p = .099). There was a statistically significant correlation with TTO (r_s 0.450, p = .024), EQ-VAS (r_s 0.397, p = .049), NEI VFQ-25 (r_s 0.760, p = .00001), and the 30 Hz ERG in both eyes (right eye r_s −0.523, p = .011; left eye r_s −0.512, p = .009). There was no correlation with best-corrected visual acuity in the better eye, SG, or disease duration.

EQ-VAS

The EQ-VAS was completed by 27 patients. The mean EQ-VAS was 80.33 ± SD 13.46, range 50–95. There was a statistically significat association with co-morbidities (p = .018) but not with systemic therapy or gender (p = .697). There was a statistically significant correlation with EQ-5D-5L (r_s 0.397, p = .049), NEI VFQ-25 composite score (r_s 0.539, p = .004) but not with best-corrected visual acuity in the better eye, TTO, SG, 30 Hz ERG in either eye or disease duration.

NEI VFQ-25

The NEI VFQ-25 was completed by 27 patients and the mean composite score was 73.24 ± SD 25.87, median 84.34 (range 9.17–95.73). The median subscale scores ranged from 50 for general health to 100 for social functioning, dependency, and color vision (Table 4). The NEI VFQ-25 was significantly associated with systemic therapy (p = .041), female gender (p = .024) but not with co-morbidities (p = .071). There was a statistically significant correlation with TTO (r_s 0.463, p = .015), EQ-5D-5L (r_s 0.760, p = .00001), EQ VAS (r_s 0.539, p = .004), best corrected visual acuity in the better eye (r_s −0.606, p = .001), and the 30 Hz ERG in both eyes (right eye

Table 3. EQ-5D-5L frequencies and proportions reported by dimension and level in 25 patients with birdshot chorioretinopathy.

	Mobility n (%)	Self-Care n (%)	Usual Activities n (%)	Pain/Discomfort n (%)	Anxiety/Depression n (%)
Level 1 (No problem)	16 (64)	24 (96)	18 (72)	16 (64)	17 (68)
Level 2 (Slight problems)	6 (24)	0 (0)	4 (16)	5 (20)	3 (12)
Level 3 (Moderate problems)	2 (8)	1 (4)	1 (4)	4 (16)	5 (20)
Level 4 (Severe problems)	1 (4)	0 (0)	2 (8)	0 (0)	0 (0)
Level 5 (Extreme problems/unable to do)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	25 (100)	25 (100)	25 (100)	25 (100)	25 (100)

Table 4. NEI VFQ-25 composite and subscale scores in patients with birdshot chorioretinopathy compared with two previous studies.

Composite score (n = 27)	Present study	Levinson *et al.*[8] (n = 80)	Kuiper *et al.*[9] (n = 105)
Mean ± SD	73.24 ± 25.87	69.12 ± 21.6	71
Median (range)	84.34 (9.17–95.73)	76.8 (7.8–99.4)	75.8 (7–99.1)
Subscale scores			
***General health* (n = 26)**		**(n = 78)**	
Mean ± SD	52.88 ± 19.14	50.6 ± 19.7	61.6
Median (range)	50 (25–100)	50 (0–100)	60 (25–100)
***General vision* (n = 26)**		**(n = 79)**	
Mean ± SD	67.69 ± 25.97	62.0 ± 17.4	63.8
Median (range)	80.0 (20–100)	60 (20–100)	65 (10–100)
***Ocular pain* (n = 25)**			
Mean ± SD	81.0 ± 18.79	70.2 ± 24.1	75.1
Median (range)	87.5 (37.5–100)	75 (12.5–100)	75 (0–100)
***Near vision* (n = 27)**			
Mean ± SD	69.75 ± 32.72	65.5 ± 27.7	68.6
Median (range)	83.33 (0–100)	66.7 (0–100)	75 (0–100)
***Distance vision* (n = 27)**			
Mean ± SD	73.46 ± 30.93	68.0 ± 26.4	70.3
Median (range)	91.67 (0–100)	75 (0–100)	75 (0–100)
***Social functioning* (n = 27)**			
Mean ± SD	81.02 ± 30.49	84.7 ± 23.4	84.5
Median (range)	100 (0–100)	100 (0–100)	91.7 (16.7–100)
***Mental health and well-being* (n = 27)**			**(n = 104)**
Mean ± SD	72.07 ± 32.56	49.8 ± 26.6	71.2
Median (range)	87.5 (0–100)	50 (0–100)	75 (12.5–100)
***Role difficulties* (n = 25)**			
Mean ± SD	77.5 ± 27.24	62.5 ± 29.3	64.5
Median (range)	87.5 (0–100)	62.5 (0–100)	62.5 (0–100)
***Dependency* (n = 27)**			
Mean ± SD	83.64 ± 30.18	76.6 ± 29.1	84.2
Median (range)	100 (8.33–100)	91.7 (0–100)	91.7 (0–100)
***Driving* (n = 24)**			**(n = 65)**
Mean ± SD	65.63 ± 32.81	63.6 ± 30.2	66.8
Median (range)	75 (0–100)	75 (0–100)	66.7 (8.3–100)
***Color vision* (n = 27)**			
Mean ± SD	82.41 ± 32.39	82.2 ± 26.4	80.2
Median (range)	100 (0–100)	100 (0–100)	100 (0–100)
***Peripheral vision* (n = 25)**			
Mean ± SD	74.0 ± 28.39	77.5 ± 26.3	67.6
Median (range)	75 (25–100)	75 (0–100)	75 (0–100)

SD: standard deviation (not given for the study by Kuiper *et al.*[9])

r_s −0.414, p = .04; left eye r_s −0.392, p = .043). There was no correlation with SG or disease duration.

30 HZ Photopic Flicker ERG (RET*eval*)

The 30 Hz flicker ERG implicit times could be measured in 26 right eyes (mean 33.24 ms ± SD 3.92, range 24.8–39.7) and in 28 left eyes (mean 33.51 ms ± SD 4.03, range 25.2–42.4). A previous pilot study using the RET*eval* on 21 eyes with BCR showed mean implicit times of 29.1 ms ± SD 3.7, range 24.4–35.2. The authors used an upper cutoff value of 28.6 ms (mean + 2SD) after testing over 300 normal subjects and reported a high correlation with conventional ERG testing.[16]

Vision in the better eye and disease duration were both significantly associated with female gender (p = .018 and p = .028, respectively). Spearman correlation coefficients (r_s) and statistically significant values are shown in Table 5.

Multivariable Analysis

A multiple linear regression was run to predict each of the HRQOL utilities (TTO, SG, EQ-5D-5L, EQ-VAS, NEI VFQ-

Table 5. Spearman correlation coefficients in patients with birdshot chorioretinopathy. *p* values are shown in parentheses for those correlations that were statistically significant.

	SG	EQ-5D-5L	EQ-VAS	NEI VFQ-25	Vision better-seeing eye	30 Hz ERG OD	30 Hz ERG OS	Disease duration
TTO	0.226	0.450 (0.024)	0.268	0.463 (0.015)	−0.292	−0.093	−0.440 (0.019)	0.078
SG		0.189	0.111	0.188	−0.355	−0.078	−0.195	−0.079
EQ-5D-5L			0.397 (0.049)	0.760 (0.000)	−0.396	−0.523 (0.011)	−0.512 (0.009)	0.150
EQ-VAS				0.539 (0.004)	−0.087	0.065	0.055	−0.056
NEI VFQ-25					−0.606 (0.001)	−0.414 (0.040)	−0.392 (0.043)	−0.034
Vision better-seeing eye						0.436 (0.026)	0.319	0.026
30 Hz ERG OD							0.737 (0.000018)	−0.030
30 Hz ERG OS								−0.075

TTO: Time Trade-Off; SG: Standard Gamble; EQ-5D-5L: EuroQol Five-Dimension Five-Level questionnaire; EQ-VAS: EuroQol Visual Analogue Scale; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; 30 Hz ERG: 30 Hz photopic flicker RET*eval* electroretinogram.

25) from gender, age, duration of disease, co-morbidities, systemic therapy, logMAR vision in better-seeing eye, and 30 Hz photopic flicker ERG in each eye. None of the eight variables were statistically significant predictors for any of the HRQOL utilities.

Discussion

We have demonstrated that TTO and SG methods of direct health utility analysis can successfully be applied to BCR patients to measure HRQOL. Of the 28 patients, 11 (39%) would trade between 1 and 20 of their remaining years of life (mean 5.4 years) in return for perfect vision in both eyes for the rest of their life. When the whole BCR cohort of 28 patients was considered (including the 17 patients who would trade no years), the mean TTO value was 0.9, a small but important reduction. It is interesting to consider the reasons for the variation in response noted between patients. It is a possibility that younger patients may have higher TTO valuations than older patients as they will perceive their life expectancy and quality differently, but we did not find any correlation between TTO and age (r_s −0.014, p = .942). Of the 11 patients who were willing to trade years of life, 7 had logMAR vision 0.1 or better in each eye (Table 2). It is possible their reason for trading may have been due to experiencing other BCR symptoms, such as floaters, nyctalopia, and poor color vision. Floaters may be a possibility despite the majority of these eyes having a vitreous haze score of zero or +0.5 (trace) as a few large floaters could have a subjective impact on vision but these 7 patients did have reduced color vision as the Ishihara color plates correctly identified by them were right eye mean 6.4 ± SD 5.89, median 9 (range 1–13) and left eye mean 7.7 ± SD 6.02, median 3 (range 1–13). Also, their NEI VFQ-25 subscale color vision showed a mean score of 82.41 ± SD 32.39, median 100 (range 0–100). Nyctalopia may have contributed as the NEI VFQ-25 subscale questions on (a) going down steps, stairs, or curbs in dim light or at night were answered by 25 patients with a mean score of 66.0 and (b) difficulties driving at night was answered by 22/28 patients with a mean score of 64.7. A previous study on BCR reported that symptoms of nyctalopia were statistically significantly associated with lower NEI VFQ-25 composite scores.[8] It is also feasible that patients with good vision at the time of undertaking the study may be concerned that they could experience loss of vision in the future and would be willing to trade-off some their remaining years of life to guarantee they would always have perfect vision. Although there was a significant association with systemic therapy, multiple linear regression showed that it was not a predictor of TTO. TTO correlated well with the EQ-5D-5L index value and the NEI VFQ-25 composite score.

The mean value for SG was higher (0.94) than for TTO (0.9). A previous study also reported SG values higher than TTO values in patients with uveitis[13] and this has been attributed to inherent biases that differ in SG and TTO.[17,18] Yet it may also reflect that despite being worried about their condition patients would prefer to continue with their present level of visual function rather than risk any chance of immediate death. There were only 6/28 patients willing to gamble a mean risk of 28% of immediate death in return for perfect vision in both eyes for the rest of their life. This is not surprising as there were 26/28 patients with a vision of logMAR 0.3 or better in their better-seeing eye (and 22 patients with a vision of 0.3 or better in both eyes, Table 2). Of the 11 patients with a TTO value less than 1.0, only 3 had an SG value of also less than 1.0. This leaves the other three patients who would take a risk on immediate death yet not trade in any of their remaining life to achieve the perfect vision in each eye. This is difficult to explain as patient A is a healthy 52-year-old male with no co-morbidities, patient B a healthy 70-year-old male with no co-morbidities, and patient C a healthy 58-year-old male on medication for hypertension.

There have been two previous studies looking at direct health utilities in patients with uveitis[13,14] and they both found a reduction of TTO in their patient cohorts. The methodology of these studies differed as one used a 10-year horizon, i.e. patients were asked to choose between *x* years with healthy eyes and 10 years in their current state of eye health,[14] and the other used the same methodology as this study.[13] There is debate as to the most appropriate TTO methodology to use.[19] In their series of 200 uveitis patients Shamdas *et al.* reported a mean TTO value of 0.831 (lower than this study) and showed that the worse the visual acuity in the better-seeing eye the lower the TTO value.[13] The study of Niemeyer *et al.* of 102 uveitis patients showed a median TTO value of 0.975 (higher than this study) and they identified that patients taking oral corticosteroids for more than 6 months were 10.5 times more likely to trade 20% or more years of their remaining life.[14] In both studies, patients with BCR were included. Shamdas *et al.* reported on 14 BCR

patients and found a mean TTO of 0.968 higher than in this study and interestingly a lower mean SG of 0.925.[13] Niemeyer *et al.* included 7 BCR patients but the authors did not report TTO values in their uveitis sub-groups and we were unable to replicate their findings regarding oral corticosteroid and TTO values in our cohort of patients.[14] Both these studies had larger cohorts of patients with different types of uveitis and a wider range of visual acuities, and this may be a possible explanation.

Direct health utility measurement (TTO) has also been undertaken in other ophthalmic conditions including age-related macular degeneration (AMD),[12,20] diabetic retinopathy (DR),[21,22] primary open-angle glaucoma (POAG),[23–25] and dry eye disease (DED).[26,27] Mean TTO values for AMD were 0.83 mild, 0.68 moderate, 0.47 severe in one study[12], and overall 0.81 in another.[20] In DR mean values can range from 0.77 to the group as a whole[21] to background 0.78, proliferative 0.78, macular edema 0.82.[22] In POAG they range from 0.64 to 0.90.[23–25] In DED mean TTO values were 0.78 for moderate and 0.72 for severe dry eye in one study[26] but 0.72 for self-reported mild-to-moderate and 0.61 for self-reported severe dry eye in another.[27] Our mean TTO value of 0.90 is higher than the other ocular conditions studied and this may reflect the better visual acuity and the small number of ocular complications in our cohort that mainly affected one eye.

It was not too surprising that the patients scored high EQ-5D-5L index values and dimensions and EQ-VAS scores as BCR is an inflammation purely limited to the eyes, although a number of patients were on oral prednisolone and systemic immunosuppression with some co-morbidities. Shamdas *et al.* identified that patients whose uveitis was a manifestation of an underlying systemic disease had lower mean EQ-5D-5L index values.[13] In our study, the EQ-5D-5L significantly correlated with the other QOL utilities, but there was no association with systemic therapy or co-morbidities.

Our NEI VFQ-25 composite scores were slightly higher than previous studies reporting BCR patients: mean 73.24, median 84.34 for our study vs mean 69.12, median 76.8 for Levinson *et al.*[8], and mean 71, median 75.8 for Kuiper *et al.*[8] (Table 4). Our mean and median subscale scores were broadly in line with these studies. The mental health and well-being subscale score in our cohort of mean 72.07, median 87.5 was almost comparable with Kuiper *et al.* values of mean 71.2, median 75,[9] yet the study from Levinson *et al.* reported a mean of 49.8 and median of 50.[8] It is difficult to explain why the latter study differs. The authors highlighted the importance of recognizing that living with chronic disease can take its toll on the mental health of the patients. It was interesting that the NEI VFQ-25 general health subscale scored quite low in all three studies with means 52.88, 50.66, 61.6 and medians 50, 50, 60 for our cohort and the other two BCR studies, respectively (Table 4) when our EQ-5D-5L mean index value was 0.89 and mean EQ-VAS was 80.33, the latter being a quantitative measure of the patient's perception of their overall health. This may reflect there being only one general health question in the NEI VFQ-25, hence the importance of including a general HRQOL as well as a VRQOL when assessing patients.

The strengths of this study are that, to the best of our knowledge, this is the first to examine direct health utilities in BCR using TTO and SG, in combination with the use of a VRQOL instrument (NEI VFQ-25) and HRQOL instruments (EQ-5D-5L, EQ-VAS), as well as patients being deeply phenotyped when attending specific BCR clinics that included measuring the 30 Hz photopic flicker ERG that has been accepted as an indicator of disease activity.[28–30] We also looked at co-morbidities that were not mentioned in some previous studies.[8,9] We were only constrained by the number of BCR patients registered at our clinics.

Although none of the variables measured were a predictor for any of the QOL instruments, TTO correlated well with the EQ-5D-5L index value and the NEI VFQ-25 composite score. Despite very good vision and good EQ-5D-5L and EQ-VAS scores some of our patients were still prepared to give up years of their life or risk immediate death because of the effect BCR has on their quality of life. Our reduced composite NEI VFQ-25 score may in part reflect the low general health subscale score. When comparing our mean TTO value of 0.90 with values found in general health states it is equivalent to patients with a mild stroke (able to perform usual activities) and slightly worse than patients with osteoporosis, post-myocardial infarction with no symptoms, and asymptomatic HIV infection.[12]

There is increasing acceptance that the "patient voice" must be heard at an individual and collective level.[31] Patients are key decision-makers in their care and patient experience of their disease and the impact of the treatment is an important aspect of this. The UK BCR patient group, the Birdshot Uveitis Society (www.birdshot.org.uk), has been involved in the construction and validation of a specific BCR QOL instrument comprising three questionnaires.[32] It is important to recognize the need for appreciating and evaluating holistic aspects of health in the clinic. The highly variable nature of a patient's experience, despite an apparently similar disease/severity of the disease, may lead to very different treatment choices. Unlike the Centres of Excellence for Behcet's Syndrome in England where a Clinical Psychologist is an integral part of the multi-disciplinary team,[33] BCR patients do not have a similar arrangement. Nevertheless, the BCR-specific instrument[32] in conjunction with more general HRQOL instruments, such as the EQ-5D-5L and TTO could form part of a standardized BCR QOL assessment. This direct measure of the health utility of BCR in an unselected cohort provides an early indication of the range of impact that the condition may have and complements earlier studies that used indirect QOL measures such as the NEI VFQ-25. There would be value in undertaking the TTO on a larger BCR cohort, but this is something that cannot be undertaken by post or e-mail. It does require face-to-face delivery in a sensitive manner as obligatory questions related to life expectancy and risk of death can be emotive, and patients' cultural and religious beliefs may influence responses.[14]

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Declaration of Interest

The authors report no conflicts of interest.

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