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ORIGINAL RESEARCH ARTICLE

Estimating Australian Population Utilities for Inherited Retinal Disease Using Time Trade-Off

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Abstract

Purpose Inherited retinal disease (IRD) causes progressive loss of visual function, degenerating towards complete blindness. Economic evaluation of gene therapies for rare forms of genetic IRDs have had to rely on health-related quality of life (HR-QoL) estimates from other diseases because there is limited data available for such a rare condition. This study aimed to estimate Australian societal-based utility values for IRD health states that can be used in cost-utility analyses (CUA) using a time trade-off (TTO) protocol adapted from a UK study.

Methods The EuroQol Valuation Technology (EQVT) protocol composite TTO (cTTO) framework was followed, which includes worse-than-death (WTD) states and quality control (QC) measures. Preferences were collected from a general population sample of 110 Australian adult participants. Five health state vignettes from the UK study which had been validated with patients and clinicians were presented randomly to participants during videoconferencing (VC) interviews with one of four interviewers. Technical and protocol feasibility were assessed in a pilot of 10 interviews. QC measures were used to monitor interviewers' performance during the study.

Results One participant withdrew consent. The final analysis was conducted on 109 respondents (including 4 non-traders). The average time to complete the interview was 44.2 minutes (SD 8.7). Participants reported mean visual analogue scale (VAS) scores between 63.15 for 'moderate impairment' and 17.98 for 'hand motion' to 'no light perception'. Mean health state utilities (HSU) varied between 0.76 (SD 0.26) in 'moderate impairment', and 0.20 (SD 0.58) in 'hand motion' to 'no light perception'. Of all HSU evaluations, 14% were considered WTD which most commonly occurred in the most severe visually impaired health state.

Conclusion This study provides valuable information on HSUs across a range of IRD health states from the Australian general population perspective. The utilities obtained in this study can be used as inputs into CUA of IRD therapies.

1 Introduction

Health technology assessment (HTA) agencies accept health-related quality of life (HR-QoL) data collected in clinical studies or HR-QoL valuation by the general public, with some HTA agencies favouring country-specific preferences [1]. However, for many conditions, such as rare diseases, capturing HR-QoL directly from patients may not be feasible for a number of reasons. Disease-specific measures

Key Points

Inherited retinal disease (IRD) is a rare disease so there is limited data on the impact on health-related quality of life (HR-QoL).

This study estimated Australian societal-based utility values for IRD health states which can be used in economic evaluations of IRD therapies.

A composite time trade-off protocol that included methods for valuing worse-than-death (WTD) health states was employed and 14% of the evaluations were considered WTD, mainly for the health state representing 'no light perception' blindness.

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often do not exist, generic multi-attribute utility instruments (MAUIs) may be too broad and insensitive to detect the change in symptoms that impact a patients' QoL, and statistical validation is limited due to small sample sizes [2].

This has led to alternative methods of estimating HR-QoL or health state utilities (HSUs), such as the use of proxy-reported MAUIs (i.e., an assessment of the health state experienced by someone else) or direct elicitation from unaffected populations asked to make hypothetical judgements using vignettes to value health state descriptions [3, 8, 14]. Another method is using HSUs from a separate sample of patients with characteristics similar to those enrolled in the clinical trials [15].

Inherited retinal diseases (IRDs) are rare heterogenous conditions that result in either progressive or stationary retinal dysfunction causing loss of visual function, including loss of visual acuity and peripheral vision, and night blindness [4–6]. There are over 250 disease-causing variants identified, with mutations in the retinal pigment epithelium-specific 65 kDa protein (*RPE65*) gene leading to an assortment of clinical diagnoses that present from early childhood and infancy to adolescence, degenerating towards complete blindness, thus having a detrimental impact on patients' QoL [7].

Gene replacement therapy, voretigene neparvovec-rzyl (VN), is now available in many countries for *RPE65*-mediated IRD, and other genetic therapies for other IRDs, including chloridaemia and x-linked retinitis pigmentosa, are being evaluated in clinical trials [8]. The advent of gene therapies for rare forms of genetic blindness is positive for patients, however prohibitively high treatment costs means that public subsidisation is required to ensure that these treatments are available as part of usual care.

Economic evaluation of interventions which affect HR-QoL commonly employs cost-utility analysis (CUA), which typically expresses the cost effectiveness of interventions as the cost per quality-adjusted life-year (QALY). The reliability of such analyses is partially dependent on accurately capturing the QoL impacts associated with the treatments. However, there is limited data on QoL and utility values in patients with IRD, with no trials providing primary data for patient-reported health utilities [4, 9]. Thus, in an HTA evaluation of VN by the National Institute for Health and Care Excellence (NICE), the HR-QoL estimates were based on two sources [9]. The first source was generic preference MAUI values (EQ5D and Health Utility Index [HUI]) collected from people with visual impairment due to diabetic retinopathy. The second source was from six retinal specialists based on proxy vignettes of IRD health states [10]. The use of retinal specialists was criticised because it was suggested that they would focus on issues related to vision rather than the impact on all areas of the patients' life, and the lower HSUs were thought to lack face validity [9]. The use of assumptions and reliance on data related to other diseases meant the reported cost-effectiveness values for the treatment of *RPE65* IRD using VN are contradictory [11, 12]. This highlights the importance of using HSUs from IRD because conditions such as diabetic retinopathy visual impairment commence at different stages of life, deteriorate at a different rate compared with IRDs and importantly may result in limited vision rather than no vision whatsoever, which can have vastly different impacts on HR-QoL [13].

Another criticism in the evaluation of VN by NICE was that the method to elicit the HR-QoL estimates did not align with the methodology required by the HTA bodies [13–18]. A study in the UK was therefore conducted to generate utility values for health states of varying levels of functional vision related to IRD via direct elicitation from the general public using a time trade-off (TTO) method in accordance with UK NICE HTA guidelines [19].

Vignettes for five health states that represent the functional impairment to daily living associated with declining sight because of IRD, from the low range of vision present at birth to no vision at all, were developed for the recent utility study in the UK [19]. The five health states were considered to be adequate, as they were developed based on testimonials from patients with IRD and aligned with those accepted in the economic model by HTA agencies such as NICE in the UK, Medical Services Advisory Committee (MSAC) in Australia and Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada. Although the HSUs from the study may therefore be applicable to the Australian context, HTA guidelines require country-specific preference-based HR-QoL utility weights. Implementing the existing UK TTO protocol in Australia was a pragmatic way to estimate HSUs that meet the requirements of HTA agencies and allows comparison with the values obtained for the UK [22]. There was, however, a limitation from the UK TTO study which was that valuation of worse-than-death (WTD) states were excluded [19]. Existing data supports the considerable stress among individuals with one variant of IRD called retinitis pigmentosa (RP), with documented links to suicidality, which is an outcome that should be considered in the valuation of these health states [20, 21].

The purpose of the current study is to estimate Australian societal-based utility values that can be used in CUA using a TTO protocol adapted from the UK study. This will produce values that are in line with the requirements of key Australian HTA bodies, including the Australian MSAC and Pharmaceutical Benefits Advisory Committee (PBAC) [17, 22, 23].

2 Methods

The protocol for this study was based on the TTO study from the UK. Changes from the UK TTO study were made to follow the existing best practice protocol for a composite TTO (cTTO) framework which includes methods for valuing WTD health states and quality control (QC) measures [3, 19, 24, 25]. Five health states from the UK TTO study which had been validated with five patients with RP and two ophthalmologists in the UK were used. The health states were defined according to American Medical Association (AMA) guidelines on visual disability that encompassed visual acuity (VA) changes reflecting the clarity of vision (i.e. ability of the eye to distinguish details of objects at a given distance) and visual field (VF) changes, reflecting peripheral vision or the ability to see above, below, and to the side of something observed [9, 19]. The scales of visual disability defining each health state vignette align with the range of visual standards in international guidelines that are applicable to Australia [26].

Each of the five health states were a written description of the functional experience of patients living with progressively worse visual impairment. Impairment was described in terms of independence, social life, family life, tangible limitations, and employment, both during the day and at night time.

- Health State 1 vignette defined as VA better than 20/200 or VF radius of >10° described as 'moderate visual impairment' [27].
- Health State 2 vignette defined as VA from 20/200 to 20/500 or VF radius of 6° to 10° described as 'severe visual impairment' [27].
- Health State 3 vignette defined as VA from 20/500 to 20/1250 or VF radius of 2° to 6° described as 'profound visual impairment' [27].
- Health State 4 vignette defined as VA from 20/1250 to 20/20,000 or VF radius of <2° described as 'counting fingers' [27].
- Health State 5 vignette defined as VA worse than 20/20,000 described as 'hand motion' to 'no light perception' [27].

These health states were reviewed for logic and applicability to the Australian population. The description of the symptoms were grouped under thematic headings such as 'physical', 'social', 'independence', and 'work' to make the lengthy written descriptions easier to read and comprehend (Online Resource Figures 1–6, see electronic supplementary material [ESM]). Emotional statements associated with a symptom within each vignette such as "You may feel sad or frustrated that you have slightly reduced independence now" were altered to avoid directing the respondent on how they should feel about a particular symptom. Instead, the emotional state was presented as "You feel sad or frustrated about your condition and its impact."

The target sample was 110 participants, which aligns with other TTO studies eliciting values for vision disorders (Lloyd et al. 2008 [16]: $N = 122$, Brown et al. 2001 [13]: $N = 65$). Quotas were applied for age, sex, education, and geographical distribution to be consistent with the Australian adult population with respect to those characteristics [28–32]. The interview protocol was piloted on the first 10 participants recruited to assess comprehension.

Members of the Australian general population who were not employed in healthcare or market research and with access to web-based tools (MS Teams) were identified using a panel of individuals who had previously indicated a willingness to participate in research studies. The study excluded any participants diagnosed with a visual disability (e.g., RP) or pre-existing eye conditions (e.g., glaucoma). Participants who required reading glasses were not excluded. Recruitment and interviews were scheduled by a market research agency (IPSOS Australia, North Sydney). Upon providing informed consent an interview was scheduled between the participant and the interviewer and the participant was provided a copy of the health states to review prior to the interview.

Interviews were conducted between October 2022 and November 2022. Videoconferencing (VC) interviews were conducted one-to-one with audio and video connection via MS Teams with one of four interviewers. The one-to-one setting allowed interviewers to provide detailed instruction and feedback to the participant where appropriate. Participants were able to withdraw consent and/or 'change their mind' on the answers provided at any point by informing the interviewer. Participants were paid $AUD60 by IPSOS for attending the interview.

This study was approved for conduct under the Centre for Health Economic Research and Evaluation program ethics approval from the University of Technology Sydney Ethics Committee on September 8, 2022 (UTS HREC REF NO. ETH21-6090).

2.1 Health State Utility Elicitation (Quantitative)

The interview was structured in four parts: (1) background information provided to participant about condition including revision on health states; (2) two visual analogue scale (VAS) 'warm-up' exercises; (3) five TTO exercises; and 4) respondent feedback about questions asked.

To avoid biasing participants' responses, health state descriptions were not labelled in any manner that suggested differences in severity or importance and were presented to respondents in a random order. The interviewer shared their computer screen containing visual aids (VAS feeling thermometer and TTO board) with participants to improve respondents' comprehension of the valuation tasks, as is standard in TTO protocols [25]. The participants responded verbally, and the HSU scores were recorded on a score sheet developed for the study that was based on the TTO valuation of MAUIs [25, 33].

Prior to cTTO valuation, a VAS scoring of the same health state descriptions was used as a 'warm-up' exercise. The cTTO method was then used to elicit HSUs by asking the participant first of all to select between 10 years in the health state (followed by death), and 10 years in full health (FH) (followed by death), and then a variable shorter period of life in FH if FH was selected. The process then followed a 'ping-pong' approach with the time in FH reduced by half (to 5 years) and then traded back and forth between higher and lower values that were iteratively narrowed until the participant was indifferent between the two life choices (Online Resource Fig. 7a, see ESM]) [25]. A lead-time TTO (LT-TTO) method was used to elicit preferences for health states considered WTD (Online Resource Fig. 7b, c, see ESM). In the LT-TTO, 10 years in FH is added to the two life options such that participants choose between (1) 10 years of FH (lead-time) followed by 10 years in the health state followed by death, or (2) to live 20 − x years in FH (10 years' lead-time followed by up to another 10 years of FH), followed by death, or (3) to indicate that the two options were equally desirable (indifferent between the two life choices). The possible utility value ranges from − 1 to 1, with a 0 value 'equivalent to being dead', 1 indicating 'perfect health', and negative values indicating a state worse than being dead.

The TTO included debriefing questions for respondents that were not willing to trade any lifetime in the iteration with the longest time with FH (i.e., 10 years in FH). The purpose was to elicit the reasons behind non-trading (e.g., fatigue, lack of understanding, lack of interest) and to offer respondents an opportunity to trade lifetime in terms of weeks instead of years.

To ensure consistency among the four interviewers, training was conducted which included an introduction to related HR-QoL concepts, explanation of the TTO protocol, interviewer instructions, and practice in groups. After five interviews, compliance was assessed using the three QC measures proposed by the EuroQol Group (time taken to complete all five TTO tasks, negative values, and non-traders); QC assessment continued in a staged approach after every 20 interviews [34, 35]. The first QC measure was based on interview time because explaining the cTTO task takes time (expected 25 minutes) and thus short task duration may indicate poor engagement. The second QC measure of the proportion of negative values reflects that the WTD task is more difficult to understand than 'better than death' so respondents may be reluctant to value a health state as WTD if the task is not adequately explained (resulting in a lower proportion moving to WTD and fewer negative values). Finally, non-trading, where a participant assigns a value of 1 to all five health states, could signal that the participant is trying to shorten the task by expressing their indifference in the first step to the iterative procedure, or it could signal that the task has been misunderstood, or not wanting to trade life could be for religious reasons. If there are many non-traders per interviewer, even when the time for the interview looks appropriate, it could indicate poor task explanation. Similar procedures have previously been employed for the collection of EQ5D data and have shown to improve data quality [36].

Following the pilot interviews (n = 10), there were slight changes to the TTO interview script. The changes included the interviewer confirming the amount of time the participant is willing to trade to avoid the health state after the point of indifference is reached, and also providing a summary of the health states for interviewers to read if that participant asked for a brief review of the health state after having read the complete health states previously. No changes were made to the health state descriptions following the pilot interviews; data from the pilot were thus included in the final calculation of HSUs (giving a total sample size of n = 110).

2.2 Data Analysis

All score sheet responses were transcribed into an Excel spreadsheet for analysis by the primary investigator with a 10% sample of transcriptions checked against the source score sheet by EM. Any incorrect transcription was corrected, leading to a further 10% review until no further transcription errors were identified.

Quantitative results (including demographic characteristics, TTO HSUs, and VAS scores) were tabulated and analysed descriptively using Microsoft Excel and are presented as means, medians, standard deviations, and 95% confidence intervals (where appropriate). Demographic data were consistent with the characteristics of the 2021 Australian Census (ABS 2021/2022).

Utility values were calculated from TTO results using the EQ-VT protocol. Statistical analysis was conducted using RStudio 2022.02.3 [37]. The distribution of individual TTO HSUs was examined by Shapiro-Wilk test and differences between scenarios were tested using nonparametric Wilcoxon signed-rank test. A p-value <0.05 was considered statistically significant. To analyse the association between HSU, demographic characteristics (education, employment, age, gender, and marital status), and interviewers, an ordinary least squares (OLS) regression model was employed using the R package lme4. Analysis residuals were reviewed after each regression, and the following goodness-of-fit statistics were presented for each model: adjusted R-squared, F-statistic *p*-value, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

3 Results

The demographic characteristics of the sample are presented in Table 1. Compared with the population statistics for Australia (ABS 2021/2022), the sample had a slightly higher proportion of participants in their third decade (22% vs 15%), a higher proportion who were married (60% vs 47%), and a higher proportion of degree-level or higher education qualifications (47% vs 31%).

Of the 110 planned interviews, one participant withdrew consent after completing the VAS; thus, the final analysis was conducted on 109 respondents (including four non-traders).

The average time to complete the interview was 44.2 minutes (SD 8.7). Twenty interviews were completed by interviewer 1, 25 by interviewer 2, 4 by interviewer 3, and 60 by interviewer 4. The quality assessment of the initial and ongoing interviews did not identify any issues of data quality.

Utility and VAS values by TTO for each health state are presented in Table 2, the frequency of HSU distributions can be found in Fig. 1, and boxplots are shown in Online Resource Fig. 8 (see ESM). Mean HSU and VAS values followed the logical and expected order, with increasing visual impairment leading to decreased utility in each case. Participants had a high mean VAS (77.39) indicating good overall health on average. Mean HSUs varied between 0.76 (SD 0.26) in ‘moderate impairment’, and 0.20 (SD 0.58) in ‘hand motion’ to ‘no light perception’.

Nonparametric testing results of the Shapiro-Wilk test indicated that the distribution of utility values for all health states was skewed (Online Resource Fig. 9, see ESM). The Kruskal-Wallis test showed a significant difference in HSUs ($p < 0.05$), and a pairwise Wilcoxon test was conducted to determine significant differences between individual states.

Table 1 Demographic characteristics

Study sample	*n*	%	Australian public demographics	%
Age, y			**Age, y**	
18–24	8	7	15–19	6
25–34	17	15	20–29	13
35–44	24	22	30–39	15
45–54	17	15	40–49	13
55–64	21	19	50–59	12
65 and over	23	21	60 and over	23
Sex			**Sex**	
Female	60	55	Female	51
Male	50	45	Male	49
Marital status			**Marital status**	
Married/de facto	66	60	Married or civil partnered	47
Separated/divorced/widowed	21	19	Divorced/widowed	14
Education level			**Education level**	
Degree-level education	52	47	Degree-level education	31
Employment status			**Employment status**	
Employed	74	67	Employed	78
Geographic distribution			**Geographic distribution**	
New South Wales	35	32	New South Wales	32
Victoria	30	27	Victoria	26
Queensland	23	21	Queensland	20
South Australia	8	7	South Australia	7
Western Australia	8	7	Western Australia	10
Tasmania	3	3	Tasmania	2
Australian Capital Territory	2	2	Australian Capital Territory	2
Northern Territory	1	1	Northern Territory	1

All pairs of health states showed significant differences in utility values ($p < 0.05$).

Of the total 545 (109*5) HSU evaluations across all respondents, there were 75 (14%) instances that were considered WTD which most commonly occurred in the most severe visually impaired health state (hand motion to no light perception, 41%, 31/75) (Table 3).

Regression analysis revealed that not being married was significantly associated with lower HSUs for the four worst visual impairment health state valuations (severe impairment to no light perception), and not being employed was significantly associated with a lower value for the least visually impaired health state (moderate visual impairment) (Table 4). One interviewer was also found to be associated with higher HSUs across all health state valuations. An alternative specification of the model tested age as a squared variable but it was not significant, and it did not improve the model fit so modelling age as a linear variable was retained. Random and normal distribution of residuals were evident in residual plots and the goodness-of-fit statistics support the robustness of each of the models.

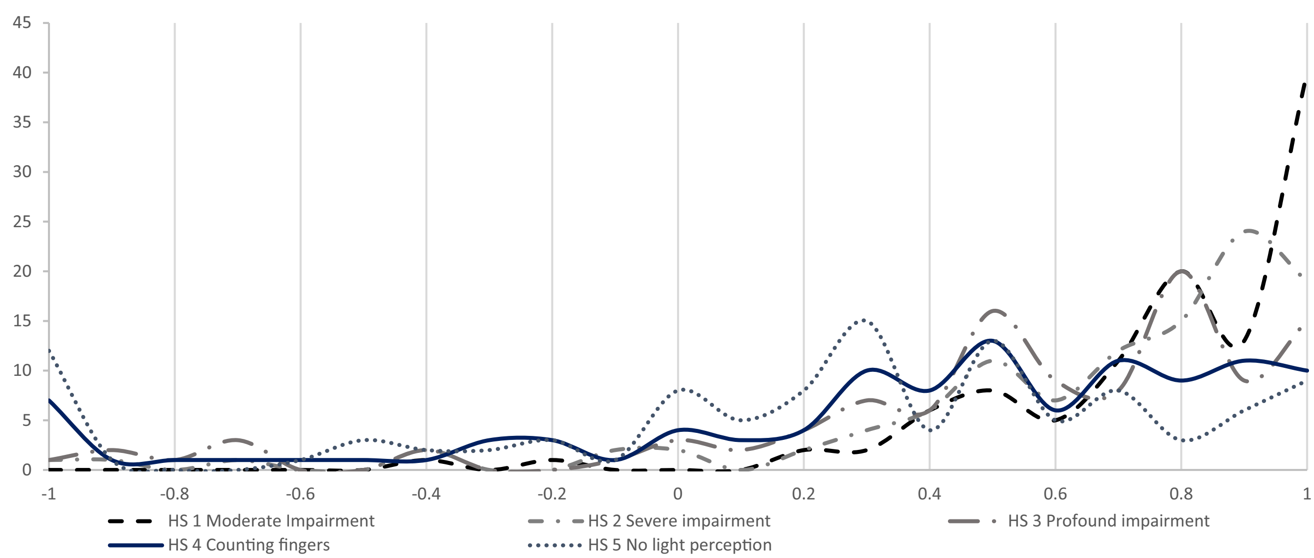
4 Discussion

This study elicited societal utility values for five health states for IRD using the TTO methodology with members of the Australian general public. The health states describe visual disability from 'moderate impairment' to the most visually disabled 'no light perception' and align with prior research in the disease area [9, 19]. The utility values, which varied between 0.76 for 'moderate impairment', and 0.20 for 'hand motion' to 'no light perception', were similar to the average health-related utility of 0.58 reported from 70 Australian

Table 2 Mean VAS score and health state utility values

Health state	*n*	VAS score				Utility			
		Mean	SD	Median	Range (min., max.)	Mean	SD	Median	Range (min., max.)
Own health	109	77.39	13.80	80	(30, 100)				
Moderate impairment	109	63.15	16.52	65	(15, 95)	0.76	0.26	0.80	(−0.4, 1.0)
Severe impairment	109	52.16	15.13	50	(15, 85)	0.63	0.39	0.75	(−1.0, 1.0)
Profound impairment	109	40.43	14.27	40	(15, 70)	0.50	0.46	0.60	(−1.0, 1.0)
Counting fingers	109	27.48	14.76	25	(5, 65)	0.35	0.55	0.48	(−1.0, 1.0)
Hand motion to no light perception	109	17.98	15.29	10	(0, 60)	0.20	0.58	0.30	(−1.0, 1.0)

SD standard deviation, *VAS* visual analogue scale



Abbreviations: HS, health state; IRD, inherited retinal disease

Fig. 1 Frequency of utility values across IRD health states

Table 3 Distribution of worse-than-death trades across health states

Health state	n	WTD
Moderate impairment	109	2 /75 (3%)
Severe impairment	109	9 /75 (12%)
Profound impairment	109	12 /75 (16%)
Counting fingers	109	21 /75 (28%)
Hand motion to No light perception	109	31 /75 (41%)

WTD worse than death

patients with various forms of IRD, but are substantially lower than the average utility value reported by the wider Australian population for their own health (for whom a normative utility value of 0.81 was measured by Assessment of Quality of Life–8 Dimension (AQoL-8D) rather than direct TTO) [4, 38].

This study was replicating prior research and thus utilised the TTO methods of eliciting societal utility values. Caution may therefore be warranted when comparing utilities derived through other methods such as discrete choice experiments (DCE), since different valuation methods may elicit different utility values. In the context of TTO-based research, notwithstanding the utility value associated with the most severe health state ('hand motion' to 'no light perception'), the values from the present study are within the range of other published utility values established using TTO methodology in patients with impaired vision which have been identified through a systematic literature review (0.78–0.26, Table 5) [13, 15, 19].

In this study, married participants reported higher HSU values for the most severe health states (severe visual impairment to no light perception). Marital status has been shown in other TTO studies to influence the number of years traded off [39]. This consistent finding across health states may infer that being married improves a persons' outlook on life when faced with a trading exercise. Alternatively, it may suggest that married participants, especially those with children, consider the broader impact of their choices and focus on longevity rather than quality of life due to their desire to live long enough with their spouse and for their children [40].

Prior research has focused on the range of utility values in the most severe states of visual impairment because vision loss-related disability is not linearly proportional to deteriorating visual acuity or field. Indeed 'legal blindness' (defined as VA ≤20/200) captures a wide range of impairment from 'severe vision loss' to 'near-blindness' (which encompasses the ability to count fingers [CF] or detect light [LP]) and finally complete blindness (no light

Table 4 Results of regression analyses (n = 109, standard error in parentheses)

Subgroup	Moderate impairment (N = 109)	Severe impairment (N = 109)	Profound impairment (N = 109)	Counting fingers (N = 109)	No light perception (N = 109)
Intercept	0.609 (0.102)	0.361 (0.152)	0.388(0.177)	0.147 (0.220)	−0.064 (0.226)
Age	0.003 (0.002)	0.004 (0.003)	0.000 (0.003)	0.004 (0.004)	0.002 (0.004)
Gender[a]	0.000 (0.051)	−0.020(0.076)	−0.015 (0.088)	−0.00 (0.111)	0.111 (0.113)
Marital status[b]	−0.042 (0.050)	−0.161 (0.074)*	−0.209 (0.086)*	−0.247 (0.108)*	−0.333 (0.110)**
Education[c]	−0.017 (0.056)	0.015 (0.083)	0.079 (0.097)	0.044 (0.121)	0.142 (0.124)
Employment[d]	−0.176 (0.065)**	−0.164 (0.097)	−0.179 (0.113)	−0.192 (0.141)	−0.179 (0.144)
Interviewer 2[e]	−0.004 (0.077)	0.043 (0.002)	−0.013 (0.133)	−0.076 (0.166)	0.083 (0.170)
Interviewer 3[e]	−0.043 (0.135)	−0.106 (0.202)	−0.171 (0.236)	−0.045 (0.294)	0.099 (0.301)
Interviewer 4[e]	0.160 (0.064)*	0.299 (0.095)**	0.336 (0.111)**	0.282 (0.138)*	0.386 (0.141)**
Adjusted R^2	0.1069*	0.1335**	0.1511**	0.07792*	0.1256**
F-statistic	2.62*	3.08**	3.40**	2.14*	2.94**
AIC	14.16	100.84	134.05	182.01	187.48
BIC	41.07	127.75	160.96	208.92	214.40

All variables other than age were entered as categorical variables

[a]Reference category: Female

[b]Reference category: Married

[c]Reference category: Degree educated (bachelor or post graduate degree)

[d]Reference category: Employed (full time or part time)

[e]Reference category: Interviewer 1

[*] Significant at $p < 0.05$, ** significant at $p < 0.01$, *** significant at $p < 0.001$

AIC Akaike information criterion, *BIC* Bayesian information criterion perception [NLP]) [26]. A TTO conducted in patients that were 'legally blind' by Brown et al. (2001) [13] aimed to discriminate utility values across a range of vision for these patients. The study showed a mean utility of 0.26 for patients with NLP and 0.47 for those with CF-LP, which demonstrates that utility value decreases dramatically with the total loss of light perception in each eye. This granularity of QoL impairment has had a substantial impact on the economic modelling of IRD and highlights the importance of elucidating utility values across the full spectrum of visual impairment [11]. The HSU reported in this study for the most severe health state 'hand motion' to 'no light perception' (0.20) aligns with the HSUs elicited by Brown et al. (2001) [13] but is lower than the HSU for the same health state from the UK TTO study (0.33). This is likely a consequence of allowing health states to be rated as WTD in the current study which meant that respondents used it, while in the UK study they were unaware of WTD and thus bounded at 0. A WTD state was selected in 14% of scenarios, most commonly for the most severe visually impaired health state ('Hand motion' to 'no light perception'), reducing the HSU value. This finding aligns with the increased suicide rates associated with severe vision impairment reported in the literature, thus highlighting the importance of including methods for valuing WTD health states [21].

HSU values are used to inform the estimation of QALYs in CUA required for HTA. HTA bodies prefer estimates of quality of life or utility from the within-trial evidence of patients (using generic or disease-specific utility instruments); however, in the absence of such data or where there are particular health state impacts for a condition that are not well captured by existing generic instruments, direct elicitation of utility weights by the general public, via TTO methods for example, are acceptable [23]. Direct elicitation based on the general population in their own country is requested because resources allocated for health technology in countries such as Australia and the United Kingdom come from the public such that preferences should reflect their own society [22, 41]. However, there is a resource burden, in terms of time and money, associated with conducting TTO studies and notwithstanding the differences in the HSU for the most severe visually impaired health state ('Hand motion' to 'no light perception'), a similar study using the same health state vignettes conducted in the UK produced HSUs similar to those in the present study. This study therefore supports the consideration of the HSUs from this study in CUA conducted in other countries with similar cultures and HTA processes as in Australia.

One of the criticisms of the vignette approach is that it may not accurately reflect the extent to which patients

Table 5 Comparison of health state utility values from the current study and existing literature

Vision health state	Current TTO study	Brown et al. 1999 [15] TTO ($N = 325$)[a]	Brown et al. 2001 [13] TTO ($N = 75$)[b]	O'Brien et al. 2023 [19] TTO UK study ($N = 110$)
Moderate vision impairment	0.76 (0.26)	0.67 (0.21)	0.65 (0.21)[e]	0.78 (0.20)
Severe vision impairment	0.63 (0.39)	0.63 (0.16)		0.65 (0.25)
Profound vision impairment	0.50 (0.46)	0.54 (0.17)		0.50 (0.27)
Counting fingers	0.35 (0.55)	0.52 (0.29)	0.47 (0.29)[f]	0.43 (0.28)
Hand motion to No Light perception	0.20 (0.58)[c]	0.35 (0.29)[d]		0.33 (0.26)[g]
No light perception			0.26 (0.08)	

SD values are in parentheses

[a]Patients included in the study primarily had age-related macular degeneration or diabetic retinopathy

[b]Patients included in the study had age-related macular degeneration, diabetic retinopathy, retinal detachment, cataract, glaucoma, endophthalmitis, and central retinal vein obstruction

[c]The utility value 0.20 (SD 0.58) is for the combined 'hand motion-light perception' and 'no light perception' health states

[d]The utility value 0.35 (SD 0.29) is for the combined 'hand motion-light perception' and 'no light perception' health states

[e]The utility value 0.65 (SD 0.21) is for the combined 'moderate vision impairment', 'severe vision impairment' and 'profound vision impairment' health states

[f]The utility value 0.47 (SD 0.29) is for the combined 'counting fingers' and 'hand motion to light perception' health states

[g]The utility value 0.33 (SD 0.26) is for the combined 'hand motion to light perception' and 'no light perception' health states

SD standard deviation, *TTO* time trade-off learn to cope with and adjust to their disease [42]. For instance, elements of adaptation might be expected among individuals with IRD considering that they live their whole lives with the deteriorating condition and do not know of anything else. Vignettes may also lead people to focus specifically on certain aspects of the description and could place undue weight on a specific descriptor [17]. There are, however, criticisms that can be made with other quality-of-life instruments such as generic instruments, which lack sensitivity to vision loss (EQ5D), and the use of vision-specific instruments (National Eye Institute Visual Function Questionnaire, NEI VFQ), which focus on physical rather than social or personal aspects of QoL [43–45]. There is also the problem of collecting QoL data from other diseases, which may not accurately reflect that circumstances of patients with IRD and may have a different impact upon HR-QoL. For example, generic instruments showed a greater impact of glaucoma (a disease the impacts peripheral vision) on mental rather than physical aspects of QoL, and vice-versa for age-related macular degeneration (a disease diagnosed later in life that affects central vision and thus the ability to conduct tasks day to day). This was attributed to patients with early stages of glaucoma (in whom there is minimal functional impairment) worrying about blindness that affects their mental QoL, while physical aspects of QoL remain relatively unaffected [44, 45]. Patients with *RPE65*-mediated IRD are impacted from birth and suffer loss of central vision and peripheral vision as well as night blindness, therefore vignettes that adequately represent changes in this rare disease that has limited HR-QoL and utility data was important. The health state development for this study was based on patient and carer testimonials, supported by qualitative findings from previous research to comprehensively represent the spectrum of disease and its daily impact on patients with IRD [19, 20]. For example, the health states in the current study provide the context to living with impaired vision due to IRD that includes limitations to everyday activities such as commuting and socialising during the day and at night time and the increasing worry experienced from impending loss of vision due to the degenerative nature of the condition.

The adaptations made to the health state vignettes have some strengths and limitations that should be considered when interpreting the study results. Best practice guidance on the development of health state vignettes suggests that uncertain statement such as “you may feel” should be avoided because respondent interpretation of such statements may vary [3]. However, by rewording such statements and presenting such emotional impacts as certainties, as occurred in this study, the vignettes may no longer be a reasonable representation of the typical experience of an IRD patient, It is important to note that although the updated health state descriptors were not revalidated with patients or clinicians, the similarity of the resulting HSUs with those from the UK study indicates that the changes to the health states didn’t impact on the respondent interpretation.

Despite the development of vignettes that reflect real-life experience of patients, the utility values from this study do not represent all IRDs. IRDs are a large group of clinically heterogeneous conditions such that visual acuity, visual field, and night vision may not deteriorate in parallel as they are presented in the vignettes, but rather at different trajectories than is reflected in the health states. Furthermore some IRDs do not affect visual acuity, visual field, and night vision. For example, cone dystrophies typically present with progressive loss of visual acuity, photophobia and colour vision disturbance [46]. The potential difference in utilities between different IRDs could be explored in future research.

IRD is detected in early childhood with vision deteriorating over the patient's life [7]. The average age of patients receiving VN for *RPE65*-mediated IRD in clinical trials was 15 years and the product is available to children over the age of 3 years [47]. The current study was, however, restricted to adults and this can be an issue for the comparability of these values and their use in economic evaluations, and it raises the question of whose values should be sought when valuing children’s health [1]. While there is the argument that the adult general public as taxpayers and potential beneficiaries from publicly funded healthcare should be the source of valuations, it can be argued that children are also beneficiaries of healthcare services and older children may contribute financially through the tax system. However research indicates that TTO tasks are unreliable in young adolescent populations because they have difficulty in understanding and interpreting the TTO tasks [48]. In addition, adolescents have been found to underestimate the effects of mild, moderate, and severe vision loss upon HR-QoL compared with patients with actual vision loss, and thus are not good patient surrogates for utilities used in cost-utility analysis [49].

The feasibility of conducting valuation studies online via VC interviews has been challenged for two reasons [50]. Firstly, the iterative procedure in the TTO task is complex, which is why face-to-face interviews have traditionally been used, and thus VC interviews may result in poor quality data. Second, despite the advantage of greater geographical reach and more rapid data collection, a requirement for VC interviews can pose a barrier preventing older people, less educated people, diseased populations, and less technically skilled people from being sampled. Indeed, the sample enrolled in this study shared demographic characteristics consistent with the Australian population generally but there was a higher proportion of participants with degree-level or higher education qualifications compared with the general population (47% vs 31%, Table 1) in the study. However, no significant differences in HSU by education were observed in the regression analyses (Table 4). Moreover, recent research demonstrates that VC-administered interviews provide equivalent data quality to face-to-face interviews and that VC as a mode of administration does not impact on TTO interview task duration, number of moves, or proportion of specific responses [35, 50].

There are some limitations to discuss. The study had a sample size of 109, which is in line with the UK TTO study but may be considered a limitation due to it being smaller than other TTO utility studies [15, 50]. This study intended to replicate a prior TTO study conducted in the UK as closely as possible. Consequently, images representing visual impairment in each health state were not presented to participants; only text descriptions of each health state were provided, which could be a further limitation of this study. In addition, because the health states describe impairment associated with either visual acuity or visual field changes, the HSUs will need to be applied to specific IRDs with caution because the health states cannot necessarily be attributed to various levels of visual acuity and visual field impairment. Finally, despite developing an interviewer script and training the interviewers, interviewer effects were detected in regression analyses with a single interviewer, who had conducted over half of the interviews, positively impacting the HSUs across the health states (Table 4).This reinforces the need for continuous data monitoring and checks during data collection as recommended in TTO protocols [24]. Protocol compliance by interviewers is also a possible limitation that can lead to poor comprehension of the valuation task by the respondent. The HSU order in a small proportion of the sample (10%, 11/109) was not logical, that is, at least two of the five health states were not clearly ordered in terms of severity and the difference in HSU was >0.05, which may signal poor comprehension and task misunderstanding. However, the average interview duration (44.2 minutes) is greater than what is expected for five health states; according to standard QC measures, respondents generally take 5 minutes to complete each TTO task. This indicates that interviewers spent sufficient time explaining the task to participants and participants had time to ask questions [34, 36]. Furthermore, only four respondents (4%) were classic 'non-traders', which was a QC measure of task comprehension used in the study. Otherwise, non-trading occurred in 28 (26%) interviews, similar to other TTO studies, most commonly for one health state only (12%) and generally in the mildest health state, moderate vision impairment, on the basis that it did not impact much on HR-QoL (Online Resource Tables 1 and 2, see ESM) [51, 52]. The percentage of non-trading, as a measure of possible interviewer effects, indicates respondents had a reasonable understanding of the task.

5 Conclusion

This study provides valuable information on HSUs across a range of IRD health states from the Australian general population perspective. Overall, our findings provide important insight into the perception of vision loss with health state utility values. These utility values were elicited using a method and sample that may allow the resulting values to be incorporated into economic evaluations for HTA purposes in Australia and other countries with similar cultures and HTA processes, in assessing the value to society of new technologies for IRD.

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Declarations

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Competing interests Financial interests: MF was employed by Novartis at the time the study was conducted. No other authors have financial interests to declare. Non-financial interests: None to declare. Maria Farris received a salary from Novartis during the study conduct. This research was part of an Industry Doctorate Program in collaboration with Novartis Pharmaceuticals Australia and the Centre for Health Economics Research and Evaluation, University of Technology Sydney. Maria Farris is now an employee of AstraZeneca Pharmaceuticals Australia.

Ethics approval This study was approved for conduct under the Centre for Health Economic Research and Evaluation program ethics approval from the University of Technology Sydney Ethics Committee on September 8, 2022 (UTS HREC REF NO. ETH21-6090).

Consent to participate and publish Informed consent was obtained from all individual participants included in the study.

Data availability The data that support the findings of this study are not openly available due to reasons of sensitivity but are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Centre for Health Economic Research and Evaluation, University of Technology Sydney, Australia.

Code availability The code for the current study are available from the corresponding author upon reasonable request.

Authors' contribution statements Conception and methodology: Maria Farris, Stephen Goodall, Richard De Abreu Lourenco, Brendan Mulhern. Data acquisition: Maria Farris, Kathleen Manipis, Elena Meshcheriakova, Milena Lewandowska. Data analysis: Maria Farris. Interpretation of data: Maria Farris, Stephen Goodall, Richard De Abreu Lourenco, Brendan Mulhern. The first draft of the manuscript was written by Maria Farris and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript and confirm the manuscript.

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