

Evaluating the Relationship Between Visual Acuity and Utilities in Patients With Diabetic Macular Edema Enrolled in Intravitreal Aflibercept Studies

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PURPOSE. The purpose of this study was to explore the relationship between visual acuity and utility (health-related quality of life) in diabetic macular edema (DME) using intravitreal aflibercept data.

METHODS. The relationship between visual acuity in the best-seeing eye (BSE) and worse-seeing eye (WSE) and utility was explored using ordinary least squares (OLS) and random-effects models adjusted for different covariates (age, age², sex, body mass index, smoking status, glycated hemoglobin, diabetes severity, comorbidities, and geographic region). Utility was measured using the EuroQoL-five dimensions questionnaire (EQ-5D) and Visual Functioning Questionnaire-Utility Index (VFQ-UI). For each model, coefficients (R^2) were reported, and WSE/BSE was expressed as the ratio of coefficients (OLS models). Models were independent of treatment effects, and outcomes from all time points (up to week 100) were included where available.

RESULTS. Data from 1320 patients with DME were analyzed. In all models, the association between visual acuity (BSE > WSE) was stronger with VFQ-UI- than EQ-5D-derived utilities. The estimated relationship between VFQ-UI and visual acuity in the BSE and WSE was robust, even with an increasing number of covariates. WSE/BSE coefficient ratios were similar across VFQ-UI OLS models (32%) compared with EQ-5D models (41%–48%). Actual (unadjusted) versus predicted data plots also showed a better fit with VFQ-UI- than EQ-5D-derived utilities.

CONCLUSIONS. These analyses show that VFQ-UI was more sensitive than EQ-5D-derived utilities for measuring the impact of visual acuity in the BSE and WSE. Visual acuity in the BSE was a major contributor to utility, but WSE is also important though to a lesser degree as shown by the coefficient ratios. These new data will be useful for health technology assessments in DME, where utilities data are lacking.

Keywords: diabetic macular edema, intravitreal aflibercept, utility

In clinical decision-making, interventions are primarily assessed based on efficacy and safety. However, it is also important to monitor the impact that treatments have on utility (i.e., health-related quality of life) using validated instruments.^{1,2} This is particularly relevant in chronic eye conditions, such as diabetic macular edema (DME), for which treatments are invasive and long term, but usually sight saving. Utility is a measure of health preference anchored around a value of 1 for perfect health and 0 for dead that is used in calculations of quality-adjusted life years (QALY). Unfortunately, patient utility assessments are often inferred from studies based on vision outcomes in one treated eye, which is not a complete

assessment of visual functioning.^{3,4} In addition, the EuroQoL-five dimensions questionnaire (EQ-5D), a commonly used generic instrument for measuring utility in retinal studies, lacks a vision-related domain; this insensitivity has been observed across all retinal conditions.^{2,5–8}

Most health technology assessments of treatments, including those for use in retinal conditions, are based on utility data generated in studies for the product under assessment. For such evaluations, the National Institute for Health and Care Excellence (NICE) states that the EQ-5D is the preferred measure of health-related quality of life in adults.⁹ They also acknowledge that the EQ-5D may not be appropriate in some



cases, but that additional evidence must be provided to support alternatives, including validation of data.⁹ Most recently, a NICE appraisal committee recognized that EQ-5D values may underestimate the effect of retinal conditions on health-related quality of life, including the impact of improvements in best-corrected visual acuity (BCVA).¹⁰ There are several alternative methods that can be used, such as condition-specific, preference-based methods; although these are acceptable by the NICE methods guidance, further research on such approaches is recommended.^{11,12} The latest International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines also acknowledge the use of health-related quality of life instruments that can be mapped to health utility.¹³ The ISPOR guidelines emphasize the importance of capturing actual patient experience using patient-reported outcomes and ensuring that they are valued and converted into utility. Outside of the United States, valuation should be based on a representative sample from the general population using a choice-based method.¹³ The algorithm of Rentz et al. is one such method that is valued by a general population sample.¹⁴ It is used to convert data obtained via the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25), an ophthalmology-specific measure that has been validated in patients with DME and other retinal conditions,^{15–17} into a condition-specific, preference-based measure that defines visual function health states (the Visual Functioning Questionnaire-Utility Index [VFQ-UI]). It is therefore ideal for exploring the issues described in more detail.

In addition, economic models in a bilateral disease, such as DME, should ideally track outcomes in each eye. NICE has criticized prior economic model submissions of anti-VEGF agents in which this has not been done appropriately.¹⁸ Although the best-seeing eye (BSE) is regarded as the most important parameter for determining daily visual functioning, the independent contribution of the worse-seeing eye (WSE) is based on expert opinion and estimates rather than new research.^{3,19–21} It would therefore be important to determine the contribution of the WSE in more detail using actual data rather than estimates.

Based on these considerations, including the need for further research to assess the appropriateness of the EQ-5D and the validation of condition-specific, preference-based measures, we used actual patient-generated EQ-5D and NEI-VFQ-25 data from four intravitreal aflibercept injection (IAI) studies²² (NCT01512966 and NCT01783886) to develop new utility data in DME. Specifically, the aims of this analysis were to apply the algorithm of Rentz et al. using actual NEI-VFQ-25 data from the IAI studies; identify the most suitable statistical model to explain variation in patient utility in DME, enabling comparison of EQ-5D and VFQ-UI; estimate the contribution of visual acuity in the BSE and WSE and other factors to utility; and calculate WSE/BSE coefficient ratios; similar ratios have previously been estimated at ~30% using ranibizumab data.^{23,24} Herein we report the findings from these analyses.

METHODS

Study Data

Patient-level data from four studies evaluating IAI in DME (VISTA-DME, VIVID-DME,^{22,25} VIVID-Japan [NCT01512966], and VIVID-EAST [NCT01783886]) were available at the time of analysis. The designs are summarized in Supplementary Table S1. Only the visual acuity, NEI-VFQ-25, and EQ-5D (VISTA-DME/VIVID-DME and VIVID-Japan only) data at baseline, week 24, week 52, and week 100 (VISTA-DME/VIVID-DME only) from these studies were included.

Derivation of Utility Data

Utility was measured using the generic EQ-5D and the vision-specific VFQ-UI. The EQ-5D is a generic preference-based measure with five single-item dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three levels.²⁶ This study used a value set estimated by preference elicited from the UK general population using time trade-off.²⁷ The VFQ-UI was calculated from the NEI-VFQ-25 questionnaire through application of the algorithm of Rentz et al.¹⁴ One item from each of six NEI-VFQ-25 subscales (near vision activities, distance vision activities, vision-specific social functioning, role difficulties, dependency, and mental health) was selected to develop a simplified eight vision-related health state classification (from best to worst function) using clinical input and Rasch analysis. These states were valued by 607 adults from the general population from four countries (UK, Canada, Australia, and the United States) using a variant of time tradeoff; these values represent direct valuation of VFQ states rather than a mapping. Item response theory was used to derive the severity score (theta) for each state, and regression was used to map the severity score to a utility weight. In this previous analysis the VFQ-UI was found to discriminate significantly between BCVA levels. The algorithm of Rentz et al.¹⁴ was applied to the NEI-VFQ-25 data in the four IAI studies to derive VFQ-UI utilities. Only observed data were included in the analyses, and missing data were not imputed.

Identification of Statistical Models

We used ordinary least squares (OLS) and random-effects panel models. These models were chosen because they have been applied in ophthalmology studies and described previously.^{5,6,19} A key assumption of OLS is that the error term is independently distributed and not correlated across observations. However, one may expect that observations at different time points from the same patient may be more correlated than observations at different time points between different patients. Therefore, a random-effects model, which relaxes the assumption of independence between repeated observations from the same individuals, was also performed.

Generation of New Utility Data and Comparison of Different Models

The relationship between vision and EQ-5D versus VFQ-UI utility was enabled in the models using both the BSE (defined independently at each time point as the eye with the highest mean BCVA value of the two eyes) and the WSE (defined as that with the lowest mean BCVA value of the two eyes) at any given time point, and other factors, including patient characteristics. The models were independent of treatment effects as data from all treatment arms and time points were included.

The models are described algebraically as follows:

$$U_{it} = \beta_0 + \beta_1 \ln VA_{it}^{BSE} + \beta_2 \ln VA_{it}^{WSE} + \beta_3 (\ln VA_{it}^{BSE} \times \ln VA_{it}^{WSE}) + \beta_4 X_{it} + \epsilon_{it}$$

where U_{it} is utility (measured as VFQ-UI or EQ-5D utilities) for patient i in time period t ; $VA_{it}^{BSE(WSE)}$ is vision health states for the BSE (WSE); and X is a vector of covariates, including patient characteristics (age, age squared [age²], sex [dummy variable taking the value of 1 if the patient is male], and body mass index [BMI]), medical history, and geographical region. For the regression, concurrent clinical covariates were adjusted using a reference category as follows: glycated hemoglobin (HbA1c) (reference category: $\leq 8\%$), duration of diabetes in years/quartiles (reference: second quartile), smok-

TABLE 1. Baseline Characteristics of DME Patients Enrolled in the IAI Studies

	VISTA-DME	VIVID-DME	VIVID-EAST	VIVID-Japan	Total
 <i>N</i>	466	404	377	73	1320
Age, years, mean (SD)	62.3 (9.8)	63.5 (8.3)	58.6 (10.2)	63.5 (9.5)	61.7 (9.7)
Male, %	54.3	61.9	50.4	64.4	56.1
BMI, kg/m ² , mean (SD)	32.2 (7.3)	28.6 (5.2)	25.1 (3.7)	25.6 (5.5)	28.7 (6.4)
Pseudophakia, %	29.8	14.4	17.2	16.4	20.8
Diabetic neuropathy, %	12.4	13.9	7.4	11.0	11.4
Diabetic nephropathy, %	1.5	10.1	8.0	19.2	7.0
Peripheral vascular disorder, %	4.3	0.7	0.0	0.0	1.7
Proteinuria, %	7.1	1.2	1.9	0.0	3.4
Hypertension, %	84.3	73.5	52.3	67.1	70.9
Cardiovascular disease, %	31.8	23.5	13.8	28.8	23.9
Smoking status, %					
Current	10.1	8.2	12.5	17.8	10.6
Former	32.6	36.2	13.0	34.3	28.2
Never	57.3	55.6	74.5	48.0	61.2
HbA1c, %					
≤8%	64.2	64.4	70.8	82.2	67.1
>8%	34.8	34.9	28.9	16.4	32.1
Unknown	1.1	0.7	0.3	1.4	0.8
Diabetes duration, years, median	17	15	12	6	14
Diabetes severity score, n					
0	259	278	262	45	844
1	164	96	100	23	383
2	36	23	15	4	78
3	7	7	0	1	15
4	0	0	0	0	0
5	0	0	0	0	0

ing status (reference: never smoked), hypertension (reference: none), cardiovascular disease (reference: none), and diabetes severity score from 0 to 5, which was based on the presence of one or more of pseudophakia, diabetic neuropathy, diabetic nephropathy, peripheral vascular disorder, and proteinuria. The presence of none of these conditions was scored 0 and presence of all five conditions was scored 5 (reference: score 0), and geographical region, with North America as the reference category based on sample size.

For each regression model, a table of coefficients, standard errors, *P* values, observation numbers, and goodness-of-fit statistics are reported. These models enabled a comparison of VFQ-UI with EQ-5D, and an estimation of the relative contribution of visual acuity in the BSE and WSE to utility was adjusted for the factors listed. There were three OLS models that included a different set of covariates: model 1 (BSE and WSE visual acuities); model 2 (BSE and WSE visual acuities, age, age², sex, and BMI); and model 3 (BSE and WSE visual acuities, age, age², sex, BMI, and concurrent clinical covariates as described). Two random-effects models were reported: the first included all covariates listed for OLS model 3 (best-fit model), and the second was expanded to include an interaction term for BSE and WSE. The WSE/BSE coefficient ratios were calculated by dividing the WSE coefficient by the BSE coefficient (OLS models). We calculated the expected VFQ-UI or EQ-5D at different BSE and WSE visual acuity levels or health states, using eight levels (>85, 85–76, 75–66, 65–56, 55–46, 45–36, 35–26, and <26 letters), thus generating a wide range of new utility data.

Sensitivity analyses based on OLS model 3 were also included. In these models, geographic region was replaced by country (Australia, Austria, China, Czech Republic, Germany, Denmark, Spain, France, Hong Kong, Hungary, Italy, Japan, Korea, Poland, and Russia).

RESULTS

Study Data

Data from a total of 1320 patients with DME who were enrolled in VISTA-DME, VIVID-DME, VIVID-EAST, and VIVID-Japan were included. Most patients were enrolled from the United States (35.3%), China (22.7%), and Japan (11.4%) (Supplementary Table S1). Overall, the mean age was 61.7 years, 56.1% were male, and the mean BMI was 28.7 kg/m²; the most common comorbidities were hypertension (70.9%) and cardiovascular disease (23.9%) (Table 1). The mean baseline visual acuity was 72.2 letters and 57.4 letters for the BSE and WSE, respectively (Table 2). The mean baseline VFQ-UI and EQ-5D scores were 0.78 and 0.81, respectively. The distribution of VFQ-UI and EQ-5D utilities are shown in Supplementary Figure S1; there was clustering around 1 for EQ-5D, but VFQ-UI was more widely distributed.

Generation of New Utility Data and Comparison of Different Models

There were 4991 VFQ-UI and 3736 EQ-5D observations available for regression analysis (Table 3). In the OLS models, the association between visual acuity (BSE and WSE) and VFQ-UI was stronger than the association between visual acuity (BSE and WSE) and EQ-5D-derived utilities, as shown by the greater coefficients. These analyses also showed that the regression coefficient for BSE visual acuity was consistently greater than that observed with WSE visual acuity in all OLS models (Table 4). In OLS model 3, for example, the regression coefficients (SE) for BSE and WSE visual acuities and VFQ-UI were 0.232 (0.014) and 0.075 (0.008) (both *P* < 0.001), respectively. The regression coefficients for BSE and WSE visual

TABLE 2. Visual Acuities and Utility Scores for DME Patients Enrolled in the IAI Studies

	VISTA-DME	VIVID-DME	VIVID-EAST	VIVID-Japan	Total
					
N	466	404	377	73	1320
BSE, mean visual acuity (n)					
Baseline	71.8 (466)	72.7 (403)	67.5 (377)	71.5 (73)	72.2 (942)
Week 24	76.0 (431)	76.2 (380)	71.2 (363)	73.3 (71)	75.9 (882)
Week 52	77.8 (360)	77.7 (311)	72.9 (355)	74.5 (66)	77.5 (737)
Week 76	78.5 (329)	78.2 (285)	-	-	78.3 (614)
Week 100	76.7 (298)	78.9 (263)	-	-	79.3 (561)
WSE, mean visual acuity (n)					
Baseline	56.9 (466)	58.5 (403)	54.3 (377)	54.3 (73)	57.4 (942)
Week 24	63.3 (431)	63.2 (380)	58.6 (363)	60.3 (71)	63.0 (882)
Week 52	66.0 (360)	66.0 (311)	62.8 (355)	61.2 (66)	65.5 (737)
Week 76	66.9 (329)	66.8 (285)	-	-	66.9 (614)
Week 100	68.8 (298)	66.8 (263)	-	-	67.8 (561)
VFQ-UI score, mean (n)					
Baseline	0.78 (465)	0.81 (404)	0.76 (376)	0.79 (73)	0.78 (1318)
Week 24	0.81 (431)	0.82 (381)	0.78 (360)	0.83 (71)	0.81 (1243)
Week 52	0.83 (360)	0.84 (357)	0.79 (353)	0.82 (66)	0.82 (1136)
Week 76	0.84 (329)	0.84 (342)	-	-	0.84 (671)
Week 100	0.85 (297)	0.85 (326)	-	-	0.85 (623)
EQ-5D, mean (n)					
Baseline	0.78 (466)	0.83 (403)	-	0.89 (73)	0.81 (942)
Week 24	0.78 (431)	0.83 (380)	-	0.88 (71)	0.81 (882)
Week 52	0.79 (360)	0.85 (311)	-	0.92 (66)	0.83 (737)
Week 76	0.81 (329)	0.85 (285)	-	-	0.83 (614)
Week 100	0.81 (298)	0.86 (263)	-	-	0.83 (561)

acuities and EQ-5D were 0.100 (0.027) ($P < 0.001$) and 0.042 (0.014) ($P < 0.01$), respectively. The regression coefficients for BSE and WSE visual acuities were robust across all three VFQ-UI models, even with an increasing number of covariates. The coefficient of determination (R^2) estimates were greater in the three VFQ-UI models (range, 0.16–0.20) compared with the three EQ-5D models (range, 0.01–0.13) even after including comorbidities. The WSE/BSE coefficient ratios were more similar across the VFQ-UI OLS models (32%) compared with the EQ-5D models (41%–48%).

In the random-effects model (Table 5), there were also stronger associations between BSE and WSE visual acuities and VFQ-UI compared with the EQ-5D model. In the VFQ-UI model, the regression coefficients (SE) were 0.213 (0.014) for BSE visual acuity and 0.052 (0.007) for WSE visual acuity (both $P < 0.001$). For EQ-5D, the regression coefficients (SE) were 0.104 (0.029) ($P < 0.001$) for BSE visual acuity and 0.025 (0.014) for WSE visual acuity. Addition of the interaction term for BSE and WSE was positive and statistically significant but did not improve the model (Table 5). The R^2 s suggest an approximate 20% association between visual acuity and utility in the VFQ-UI models, compared with 13% in the EQ-5D models, and a 62% correlation between actual and predicted values. The correlation between the actual and predicted values (ρ) was stronger with VFQ-UI than EQ-5D (0.618 vs. 0.541). The actual (unadjusted) versus predicted data plots also showed a better fit with VFQ-UI than EQ-5D-derived utilities (Supplementary Figs. S2, S3). The actual and predicted utilities in the eight-level visual acuity health states for all analyses are shown in Supplementary Tables S2–S4. The results for both sets of utility instruments did not differ in the sensitivity analyses, which replaced region by country for either the OLS or random-effects models (Supplementary Table S5).

DISCUSSION

This paper explores the relationship between visual acuity and health-related quality of life in DME using data from four IAI studies²² (NCT01512966 and NCT01783886). The algorithm of Rentz et al.¹⁴ was successfully applied, resulting in the generation of usable VFQ-UI utilities from actual study data valued by general population samples. Utility was modeled as a function of BSE and WSE vision health states, and clinical covariates (age, age², sex, BMI, smoking status, HbA1c, diabetes severity, comorbidities, and geographic region) were included in OLS and random-effects regression analysis of the best-fit model. The study was also feasible, in part, due to the volume of data available and the wide range of visual acuities. This is not the case for other conditions in which IAI has been studied, such as neovascular AMD, edema secondary to central or branch retinal vein occlusion, or myopic choroidal neovascularization. This is also the first study to compare VFQ-UI with EQ-5D in DME; it has previously been compared with EQ-5D in 224 patients with uveitis treated with dexamethasone implants (0.35 or 0.7 mg) or sham for 26 weeks.²⁸ In this study, patients completed the NEI VFQ-25 at screening and at weeks 8, 16, and 26/exit, and the EQ-5D and SF-36 Health Survey (SF-36) at screening only. The VFQ-UI demonstrated good internal consistency with the NEI VFQ-25, independent of treatment effects. The VFQ-UI and EQ-5D were moderately correlated at screening; however, only 21%–24% of variance was shared between the vision-related and generic preference measures. These authors also concluded that generic measures may not be sensitive for assessing impairments in vision-related functioning.

Our study showed that both OLS and random-effects models were suitable for examining patient utility in DME, even when an increasing number of covariates were included. However, the consistency of the R^2 value and WSE/BSE

TABLE 3. Number of VFQ-UI and EQ-5D Observations by Eight-Level Visual Acuity Health States

VFQ-UI									
WSE visual acuity (letters)	BSE visual acuity (letters)								Total
	>85	85–76	75–66	65–56	55–46	45–36	35–26	<26	
5	100								100
85–76	289	511							800
75–66	186	817	538						1541
65–56	64	429	493	237					1223
55–46	20	167	220	200	94				701
45–36	10	48	90	92	58	34			332
35–26	2	21	46	39	32	26	19		185
<26	2	13	26	18	23	13	9	5	109
Total	673	2006	1413	586	207	73	28	5	4991
EQ-5D									
>85	79								79
85–76	262	389							651
75–66	171	667	352						1190
65–56	60	333	369	145					907
55–46	17	134	167	142	42				502
45–36	9	34	63	60	36	12			214
35–26	2	15	30	24	24	9	10		114
<26	2	11	22	13	18	8	4	1	79
Total	602	1583	1003	384	120	29	14	1	3736

TABLE 4. Association Between VFQ-UI- and EQ-5D-Derived Utilities and Visual Acuity Using OLS Models Adjusted for Different Baseline Characteristics

	VFQ-UI						EQ-5D					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	RC	SE	RC	SE	RC	SE	RC	SE	RC	SE	RC	SE
Observations	4967		4955		4571		3716		3705		3654	
Intercept	-0.465‡	0.045	-0.407‡	0.059	-0.397‡	0.064	0.265†	0.101	0.471‡	0.131	0.410†	0.127
Log (BSE visual acuity)	0.228‡	0.013	0.227‡	0.013	0.232‡	0.014	0.093†	0.029	0.088†	0.028	0.100‡	0.027
Log (WSE visual acuity)	0.073‡	0.008	0.072‡	0.007	0.075‡	0.008	0.038*	0.015	0.042†	0.014	0.042†	0.014
Age			-0.003*	0.001	-0.004†	0.001			0.000	0.003	-0.003	0.003
Age ²			0.000†	0.000	0.000‡	0.000			0.000	0.000	0.000	0.000
Male			0.019‡	0.004	0.017‡	0.004			0.035‡	0.007	0.055‡	0.007
BMI			0.000	0.000	0.000	0.000			-0.006‡	0.001	-0.004‡	0.001
HbA1c >8%					-0.008*	0.004					-0.005	0.007
Diabetes duration (quartile 1)					0.006	0.005					0.025*	0.010
Diabetes duration (quartile 3)					-0.018†	0.005					-0.007	0.010
Diabetes duration (quartile 4)					-0.013*	0.005					-0.036‡	0.010
Diabetes severity 1					-0.028‡	0.004					-0.062‡	0.008
Diabetes severity 2					-0.029‡	0.008					-0.041†	0.014
Diabetes severity 3					-0.046†	0.016					-0.054*	0.026
Hypertension					-0.011*	0.005					-0.029†	0.009
Cardiovascular disease					-0.027‡	0.005					-0.074‡	0.008
Current smoker					-0.002	0.007					-0.054‡	0.012
Former smoker					0.000	0.004					-0.016*	0.008
Europe and Australia					0.003	0.004					-0.007	0.008
Japan					-0.006	0.007					0.068‡	0.011
Other Asia-Pacific region					-0.037‡	0.006						
Adjusted R ²	0.16		0.17		0.20		0.01		0.06		0.13	
WSE/BSE ratio	32%		32%		32%		41%		48%		42%	

WSE/BSE ratio refers to the ratio of coefficients. Log, logarithm; RC, regression coefficient.

* $P < 0.05$.† $P < 0.01$.‡ $P < 0.001$. (P value > t -statistic).

TABLE 5. Association Between VFQ-UI- or EQ-5D-Derived Utilities and Visual Acuity Using a Random-Effects Model Adjusted for Different Baseline Characteristics and With Interactive Term for BSE and WSE Visual Acuities

	Model Without Interaction				Model With Interaction			
	VFQ-UI		EQ-5D		VFQ-UI		EQ-5D	
	RC	SE	RC	SE	RC	SE	RC	SE
Observations	4571		3654		4571		3654	
Intercept	-0.344‡	0.064	0.416†	0.129	0.936*	0.387	1.105	0.761
Log (BSE visual acuity)	0.213‡	0.014	0.104‡	0.029	-0.088	0.091	-0.057	0.178
Log (WSE visual acuity)	0.052‡	0.007	0.025	0.014	-0.289†	0.102	-0.159	0.200
Log (BSE visual acuity) * Log (WSE visual acuity)	-	-	-	-	0.080†	0.024	0.043	0.046
Age	0.001*	0.000	0.001	0.001	0.001†	0.000	0.001	0.001
Male	-0.016*	0.007	-0.050‡	0.012	-0.015*	0.007	-0.050‡	0.012
BMI	0.001	0.001	-0.004‡	0.001	0.001	0.001	-0.004‡	0.001
HbA1c >8%	-0.008	0.007	0.002	0.012	-0.009	0.007	0.002	0.012
Diabetes duration (quartile 1)	0.003	0.009	0.020	0.017	0.004	0.009	0.020	0.017
Diabetes duration (quartile 3)	-0.014	0.009	-0.004	0.016	-0.013	0.009	-0.004	0.016
Diabetes duration (quartile 4)	-0.012	0.009	-0.042†	0.016	-0.013	0.009	-0.042†	0.016
Diabetes severity 1	-0.029‡	0.007	-0.062‡	0.013	-0.028‡	0.007	-0.061‡	0.013
Diabetes severity 2	-0.020	0.014	-0.036	0.023	-0.019	0.014	-0.035	0.023
Diabetes severity 3	-0.055*	0.028	-0.048	0.044	-0.054	0.028	-0.048	0.044
Hypertension	-0.011	0.008	-0.034*	0.014	-0.010	0.008	-0.033*	0.014
Cardiovascular disease	-0.025†	0.008	-0.074‡	0.013	-0.025†	0.008	-0.074‡	0.013
Current smoker	0.002	0.011	-0.042*	0.020	0.003	0.011	-0.042*	0.020
Former smoker	0.002	0.008	-0.014	0.013	0.002	0.008	-0.014	0.013
Europe and Australia	0.007	0.008	-0.005	0.013	0.007	0.008	-0.005	0.013
Japan	-0.003	0.011	0.063†	0.018	-0.001	0.011	0.064‡	0.018
Other Asia-Pacific region	-0.037‡	0.010			-0.035†	0.010		
Adjusted overall R ²	0.20		0.14		0.20		0.14	
WSE/BSE ratio	24%		24%		NA		NA	
Correlation between actual and predicted	0.618		0.541		0.617		0.541	

WSE/BSE ratio refers to the ratio of coefficients. NA, not applicable due to interactive term.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$ (P value $>$ z-statistic).

coefficient ratios across the OLS models suggests that this may be a more robust approach. Across all models, the association between visual acuity (BSE and WSE) and VFQ-UI was stronger in terms of coefficient size and statistical significance than the association between visual acuity (BSE and WSE) and EQ-5D-derived utilities. These findings indicate that VFQ-UI-derived utilities are a suitable alternative to EQ-5D in DME evaluations.

The stronger association between visual functioning and utilities derived from an ophthalmologic-specific measure, such as the NEI-VFQ-25, is consistent with studies in other retinal conditions.^{3,29} In their analysis, Kay et al.²⁹ mapped NEI-VFQ-25 to EQ-5D using data from DME patients enrolled in the RESTORE study; this approach resulted in low predictive power, possibly due to the insensitivity of the EQ-5D to discriminate vision-related activities. In the current analyses, we applied the algorithm of Rentz et al. to develop the VFQ-UI, which represents direct valuation of VFQ states rather than mapping to avoid this limitation.

The current VFQ-UI calculations also provide new utilities data for DME and will be beneficial in future health technology assessments of DME treatments. In a previous assessment of IAI in DME that was submitted to NICE (NICE TA346), the bilateral BCVA utilities, which were based on the work of Czoski-Murray et al.,³⁰ were estimated for the WSE by assuming that the change in utility in the WSE was 30% lower than that observed in the BSE based on the difference in visual acuity between them. Although NICE considered such estimates acceptable for decision-making, they added that it was not an

ideal approach. The utility estimates were based on AMD-simulated vision states and subsequent EQ-5D assessments in a limited sample of healthy volunteers from a UK population and were not based on treatment outcomes in DME patients. Although the current WSE/BSE coefficient ratios were also approximately 30% in the VFQ-UI OLS models, this estimate was based on actual, albeit log-transformed, data in DME patients. There was, however, slightly wider variation with the EQ-5D models.

Previous coefficients for ranibizumab have also been estimated at 30%; these are largely based on RESTORE, in which vision changes following treatment in the WSE had ~30% of the health-related quality of life impact for the same vision changes following treatment in the BSE.^{23,24} It must be noted that these are estimates and relate to health-related quality of life rather than health utility. We have developed accurate models to determine the coefficients for IAI using actual data and we cannot exclude the possibility that this similarity is coincidental.

The outcomes from the statistical models also showed that the regression coefficient for BSE visual acuity was consistently greater than that observed for WSE visual acuity in all models, which confirms that the WSE is important, although less so compared with the BSE. A number of other studies have also reported a correlation between baseline visual acuity and NEI-VFQ-25.³¹⁻³³ This indicates that the distinction between BSE and WSE is beneficial for assessing treatment outcomes, particularly when considering the definition and also the impact of only including one study eye in long-term treatment

24

assessments in clinical studies. In a systematic review, Hirneiss²¹ also found that visual functioning in the WSE had a greater effect on quality of life than previously assumed, although research was hampered by lack of a consistent definition of BSE and WSE. In contrast to previously used definitions,^{23,24} the current findings are based on simplified definitions of WSE and BSE for use with either measure (EQ-5D and VFQ-UI) that produce easy to use coefficients across several models. The ongoing AQUE and VIOLET studies (clinicaltrials.gov), which are further evaluating IAI regimens in DME patients, will include NEI-VFQ-25 assessments in addition to visual acuity outcomes in the BSE and WSE to enable further estimates of the relationship between them. These studies are expected to be completed in 2017 and 2019, respectively. A systematic review and meta-analysis of the available utility data in patients with diabetic retinopathy is also under way.³⁴ It is hoped that this will provide a protocol for use in selecting data for decision analytic models and health technology assessments.

Although the analyses did adjust for baseline characteristics, such as age and sex, there are a number of limitations inherent with cross-sectional regression models. The use of pooled data from four different studies and diverse populations may introduce heterogeneity. It must also be noted that in the VISTA-DME and VIVID-DME studies, improvements in the NEI-VFQ-25 from baseline were observed over time, but differences between the treatments (IAI 2 mg every 4 weeks [2q4] and every 8 weeks [2q8] versus laser) were limited; however, the difference between treatments (IAI 2q8 versus laser) in the VIVID-EAST study was significant. All studies prespecified that the WSE was the study eye and anti-VEGF treatment was allowed in the non-study eye, but the impact of these inclusion criteria on NEI-VFQ-25 is not fully understood.

Caution should be applied when directly comparing VFQ-UI and EQ-5D measures of vision-specific and generic health utility. Nevertheless, the lack of association between the two health utility measures appears fairly marked (Supplementary Fig. S4). This may be anticipated from these instruments given that the EQ-5D is a generic measure that has been applied to a DME population that also has a range of comorbid illnesses, which would contribute to utility outcomes, or it could be from sampling variation. However, this lack of association also suggests that EQ-5D underestimates the impact of visual acuity on utility.

In summary, this paper explores the relationship between BSE and WSE visual acuities and both generic and condition-specific, preference-based health measures (EQ-5D and VFQ-UI) using regression analyses of data from four IAI studies in DME. The analyses show that VFQ-UI was more sensitive than EQ-5D for measuring the impact of visual acuity in the BSE and WSE on utilities, and models were more robust to the addition of other explanatory factors. Not surprisingly, visual acuity in the BSE was shown to be a major contributor to health-related quality of life, but the findings confirm that the WSE contribution was ~30%, which is similar to the estimate used in previous publications. From a practical perspective, these analyses provide new and specific utilities data, which may prove valuable in future health technology assessments in DME. These results highlight the importance of both the BSE and WSE on quality of life and the importance and usability of NEI-VFQ-25 data. Use of the utility data generated in these analyses for health technology assessments in other retinal conditions or treatments is limited because the analyses were based on health-related quality of life responses in DME patients treated with IAI and/or laser, but these data may be useful where alternatives are sparse.

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