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Patient-reported outcomes in the RELIGHT clinical trial of ranibizumab in diabetic macular oedema

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ABSTRACT

Background/aims The RELIGHT clinical trial used an individualised treatment regimen of ranibizumab to treat diabetic macular oedema (DMO). We report findings from two patient-reported outcome instruments.

Methods The National Eye Institute Visual Function Questionnaire (NEI-VFQ) was administered before starting treatment (M0) and at M6, 12 and 18. The Macular Disease Society Treatment Satisfaction Questionnaire (MacTSQ) was administered 1 month after treatment start (M1) and at M6, 12 and 18. Relationships between best-corrected visual acuity (BCVA) in the study eye (SE) and the status of the eye at baseline (as better or worse eye by BCVA) and the two instrument measures were investigated.

Results BCVA in the SE correlated strongly with the NEI-VFQ composite scores and the majority of the subscales but not with the MacTSQ subscales. Statistically significant improvements were observed in the majority of the subscales of the NEI-VFQ at M6, 12 and 18. For the MacTSQ, improvements between baseline M6, 12 and 18 were seen for subscale 1 but only reached statistical significance at M12. In subscale 2, the changes in mean scores were statistically significant at all timepoints.

Conclusions Although ranibizumab treatment in DMO over an 18-month period resulted in improvements in visual functioning and patient satisfaction, no correlation was found between the instruments used to measure these outcomes. Our finding of a lack of correlation between BCVA and the MacTSQ suggests the presence of psychophysical factors not measured by traditional means.

Key messages

What is already known about this subject?

► Anti-vascular endothelial growth factor (anti-VEGF) use has been established as an effective therapy in the treatment of diabetic macular oedema. However, there are only limited data published on the impact of this therapy on quantitative patient-related outcome tools.

What are the new findings?

► This study presents patient-related outcomes data using two validated tools, the National Eye Institute Visual Function Questionnaire and the Macular Disease Society Treatment Satisfaction Questionnaire. The data support the finding that improvements in vision are associated with favourable increases in visual functioning and patient satisfaction. However, Central Retinal Thickness (CRT) which is a morphological marker of the efficacy of treatment with anti-VEGF agents showed no relationship with the data recorded in the tools suggesting that these instruments may not be sensitive to improvements in retinal morphology with treatment. Patients recognise and report improvements in function when treated with an anti-VEGF regardless of whether treatment is applied to the better or worse of an individual's pair of eyes. Satisfaction with treatment and information provision was observed in our study.

How might these results change the focus of research or clinical practice?

► These data help build the body of patient-related outcomes data in diabetic eye disease and to stress the importance of data of this type in broadening the evidence base available for evaluation.

INTRODUCTION

Patient-reported outcome measures (PROMs) are increasingly recognised as necessary for determining the usefulness of interventions in all aspects of clinical care.[1] In retinal diseases that are usually bilateral and thus with vision loss in both eyes, studies have revealed an impact on quality of life and a disability that is equivalent to the severe health-impairing conditions.[2 3] Traditionally, the most frequently used outcome measure of ocular function has been distance visual acuity and when undertaken to standardised protocols after refraction; best-corrected visual acuity (BCVA) is easily measured in a robust and reproducible manner. Nevertheless, this metric merely indicates the level of reduced vision in a single eye and reflects only the function of the foveal retina.[4] Consequently, correlations between health-related quality of life (hrQOL) and BCVA are modest

at best even when the better-seeing eye is considered and there remain many aspects of vision-related function that are poorly explained.[5 6] Therefore, when designing clinical trials of new interventions, tools that assess the burden and acceptability of treatment are increasingly being included as outcome measures and are recognised as important components of the assessment of effectiveness of the therapy by payers and policy-makers.[7–9]

Diabetic macular oedema (DMO) is frequently bilateral and is associated with significant levels of visual morbidity.[10] The emergence of anti-vascular endothelial growth factor (anti-VEGF) as an effective treatment in DMO has been an important milestone in the therapeutics of this condition.[11] To achieve optimum benefit from treatment, most patients require repeated administration of drug and intensive monitoring thus resulting in a huge burden of illness for patients and carers and resource implications for service providers. The RELIGHT clinical trial was undertaken as a prospective, open-label, multicentre, single-arm, 18-month study to evaluate the use of ranibizumab 0.5 mg using an individualised treatment approach in the management of DMO.[12] In this trial, a number of PROMs were used and included the National Eye Institute Visual Function Questionnaire (NEI-VFQ)[13] and the Macular Disease Society Treatment Satisfaction Questionnaire (MacTSQ)[14] to better understand the impact of treatment on vision-related quality of life and the acceptability of treatment.

METHODS

RELIGHT enrolled 109 participants with macular oedema due to diabetes mellitus who were commenced on treatment with 0.5 mg of ranibizumab. Intravitreal injection of ranibizumab was performed 4 weekly as part of a 3-month loading phase. From months 3 to 5, participants underwent monthly review and subsequently follow-up occurred bi-monthly until month 18. An individualised approach was used to determine if re-treatment was required.[10] Re-treatment criteria were the presence of residual central subfield retinal oedema (an Optical Coherence Tomography reading of ≥225 µm), increase in central subfield retinal oedema by >10% or 25 µm from the lowest in-study reading, no residual central subfield retinal oedema, but a total drop of 5 or more ETDRS letters from the best-recorded BCVA in the study.[10] The NEI-VFQ 25-item version was used and this instrument has been extensively validated and its scoring system for calculation of the composite score and the 12 individual subscales has been previously described.[13] The composite and the 12 subscale scores were calculated for study visits at 0, 12 and 18 months and the mean change computed. The MacTSQ is administered only after treatment has commenced as it asks questions about the experience.[14] Therefore, its first administration occurred at M1, and subsequently at 6, 12 and 18 months. The MacTSQ has been validated for use in those macular diseases that require invasive drug administration and has two subscales namely treatment satisfaction and information provision/convenience.[12]

Descriptive statistics were generated for participant baseline demographics (table 1). The imbalance in the sexes was statistically significant and the variables of age, BCVA in the study eye (SE) and NEI-VFQ 25 and MacTSQ subscales scores were analysed by gender. As relationships with PROMS are mainly driven by the better eye, the baseline BCVA of the SE of the entire group of participants and after grouping by whether the SE was the better or worse compared with the fellow eye (FE) was computed along with changes in BCVA in SE from baseline to months 12 and 18. In the entire group of participants, the change from baseline to M6, 12 and 18 in the NEI-VFQ 25 subscales was calculated and analysed using paired-sample t-tests. For the MacTSQ where data were available for M1, 6, 12 and 18, change from the first time point to each subsequent time point of administration was calculated and subjected to analysis using paired-sample t-tests. The tests for this instrument were repeated after grouping participants into those whose SE was better than the FE or worse than the FE.

To assess the relationships between BCVA in the SE and the two instruments, Pearson's correlation coefficients were tested for the composite NEI-VFQ 25 (0, 12 and 18 M) and the two subscales of the MacTSQ (1, 12 and 18 M). Correlation coefficients were also generated to examine the relationship between percentage change in central retinal thickness from baseline to M12 and M18 and change from baseline in NEI-VFQ 25 subscales and composite scores to M12 and M18. Similarly, percentage change in central retinal thickness from baseline to M12 and 18 was correlated with the change in scores from month 1 to M12 and M18 for the MacTSQ subscales. Models with change at M12 and M18 in the NEI-VFQ 25 composite score and the two MacTSQ subscale scores as the dependent variables, models were constructed with the following explanatory variables (age, gender, baseline BCVA and baseline PROM score).

Patient and public involvement

This study did not have patient or public involvement in its design, participant recruitment or conduct. The results were not publicised on study completion to participants. While the burden of the intervention in the wider study was not assessed directly by patient participants, we included an outcomes measurement tool (MacTSQ) which evaluates levels of satisfaction with treatment.

RESULTS

Amongst 109 participants who were recruited, 100 (91.7%) and 99 (90.8%) completed 12 and 18 months in the study, respectively. DMO was bilateral in 76, and in the remaining 33 participants, only one eye met the criteria for DMO. Patient demographics and baseline BCVA in the SE for the entire group and by gender is shown in table 1. As gender was statistically significantly imbalanced with 78 (71.6%) being male, demographics,

Table 1 Baseline BCVA, NEI-VFQ 25 and MacTSQ subscale scores by gender

	All N=110	Male N=78	Female N=32	Mean difference	P value	95% CI
Age (years)	63.8	63.4	64.7	−1.3	0.51	−5.4 to 2.7
BCVA of study eye (letters)	62.8	63.8	60.5	3.5	0.18	1.5 to 8.0
NEI-VFQ 25 GH	49.3	49.7	48.4	1.24	0.81	−8.9 to 11.4
NEI-VFQ 25 GV	42.4	43.1	40.6	2.49	0.53	−5.3 to 10.3
NEI-VFQ 25 OP	79.4	80.4	77.0	3.50	0.48	−6.3 to 13.3
NEI-VFQ 25 NA	56.4	59.5	49.0	10.55	0.06	−0.23 to 21.3
NEI-VFQ 25 DA	67.0	70.8	57.8	13.02	0.02	2.0 to 24.0
NEI-VFQ 25 CV	88.3	89.6	85.2	4.45	0.32	−4.5 to 13.4
NEI-VFQ 25 PV	76.8	78.8	71.8	7.07	0.20	−3.7 to 17.8
NEI-VFQ 25 SF	79.7	79.3	80.5	−1.14	0.83	−11.8 to 9.5
NEI-VFQ 25 MH	54.1	54.7	52.5	2.19	0.72	−9.9 to 14.2
NEI-VFQ 25 RD	59.7	60.7	57.4	3.27	0.62	−9.7 to 16.2
NEI-VFQ 25 D	74.7	75.9	71.9	3.99	0.54	−9.0 to 17.0
NEI-VFQ 25 DR	60.4	61.0	58.3	2.69	0.80	−19.6 to 23.9
NEI-VFQ 25 composite	67.5			4.91	0.28	−4.1 to 13.9
MacTSQ subscale 1*	33.3	33.0	33.9	−0.88	0.20	−2.2 to 0.5
MacTSQ subscale 2†	28.9	29.3	27.9	1.41	0.18	−0.6 to 3.5

*Information provision and convenience.
†Impact of treatment and satisfaction.
BCVA, best-corrected visual acuity; CV, colour vision; D, dependency; DA, distance activity; DR, driving; GH, general health; GV, general vision; MH, mental health; NA, near activity;NEI-VFQ, National Eye Institute Visual Function Questionnaire; OP, ocular pain; PV, peripheral vision; RD, role difficulty; SF, social functioning.

NEI-VFQ 25 and MacTSQ subscale scores by gender are shown in table 1. BCVA was marginally better in the study eyes of men compared with women but did not reach significance on univariate testing. The composite score and most NEI-VFQ 25 subscale scores were similar between men and women apart from distance activities, in which men scored higher than women (p=0.02). The differences in the MacTSQ subscale scores were not statistically significant when analysed by gender.

Online supplementary table E1 shows the BCVA at baseline in SE and FE grouped by whether at baseline the SE was the better or the worse in terms of visual acuity. Mean BCVA was not statistically significantly different in the SE when grouped with reference to the FE. In the FE, mean BCVA at baseline was 6 lines better when the SE was the worse eye than when the SE was the better eye.

The change in BCVA in all SE from baseline to M2 and M18, and after grouping by the status of the SE

Table 2 Change in BCVA study eye (SE) entire cohort, and categorisation by whether SE is 'better' or 'worse' relative to fellow eye in terms of letters at baseline*

	N included	Mean 1	Mean 2	Mean difference	95% CI	P value
All study eyes						
Change baseline—M12	100	63.2	68.1	4.9	2.9 to 7.0	<0.001
Change baseline—M18	104	62.9	69.6	6.7	4.4 to 9.1	<0.001
Study eye is 'better' eye						
Change baseline—M12	30	64.8	68.5	3.7	1.4 to 6.0	0.002
Change baseline—M18	32	65.1	68.2	3.1	−0.8 to 7.1	0.118
Study eye is 'worse' eye						
Change baseline—M12	70	62.5	68.0	5.4	2.6 to 8.2	<0.001
Change baseline—M18	72	62.0	70.1	8.3	5.5 to 11.2	<0.001

*RELIGHT protocol stated that if both eyes are eligible, the one with the worse visual acuity, as assessed at visit 1, will be selected for study treatment unless, based on medical reasons, the investigator deems the other eye the more appropriate candidate for study treatment.
BCVA, best-corrected visual acuity.

Table 3A Change in NEI-VFQ 25 subscale scores baseline to M12 in all participants

Change in NEI-VFQ 25 subscales	N	Baseline	Month 12	Difference	95% CI	Significance
General health	99	51.0	49.2	1.8	−2.7 to 6.2	0.434
General vision	99	42.2	47.9	5.7	1.6 to 9.7	0.007
Ocular pain	100	79.1	84.3	5.1	0.9 to 9.3	0.017
Near activities	100	56.8	62.2	5.5	1.2 to 9.7	0.013
Distance activities	100	66.9	73.4	6.5	2.2 to 10.8	0.003
Colour vision	99	87.9	87.1	0.8	−3.1 to 4.7	0.693
Peripheral vision	71	78.0	80.8	−2.8	−7.7 to 2.1	0.261
Social functioning	97	80.0	84.0	4.0	0.0 to 8.0	0.050
Mental health	99	55.3	65.5	10.2	5.5 to 14.9	<0.001
Role difficulties	100	60.2	67.2	7.0	1.4 to 12.6	0.014
Dependency	100	75.4	80.8	5.4	0.9 to 9.8	0.018
Driving	88	64.0	67.2	3.2	−2.8 to 9.2	0.288
Composite score	100	67.8	72.6	4.8	1.9 to 7.7	0.001

Table 3B Change in NEI-VFQ 25 subscale scores baseline to M18 in all participants

Change in NEI-VFQ 25 subscales	N	Month 0	Month 18	Difference	95% CI	Significance
General health	98	50.3	47.7	−2.6	−2.0 to 7.1	0.272
General vision	98	42.7	47.8	5.1	1.2 to 9.0	0.011
Ocular pain	100	79.4	86.0	6.6	2.1 to 11.1	0.004
Near activities	100	56.8	62.9	6.0	1.4 to 1.07	0.012
Distance activities	100	67.3	71.0	3.8	0.3 to 7.8	0.071
Colour vision	99	88.4	88.1	−0.3	−4.3 to 3.7	0.900
Peripheral vision	72	77.0	78.3	1.3	−3.6 to 6.1	0.603
Social functioning	99	80.3	83.0	2.8	−1.4. 6.9	0.193
Mental health	98	54.8	64.4	9.6	5.1 to 14.2	<0.001
Role difficulties	100	60.5	68.4	7.9	2.7 to 13.1	0.003
Dependency	100	74.9	79.3	4.4	0.4 to 8.5	0.034
Driving	98	60.5	63.4	2.9	−3.8 to 9.6	0.394
Composite score	100	67.9	72.0	4.1	1.3 to 7.0	0.005

NEI-VFQ, National Eye Institute Visual Function Questionnaire.

relative to FE is shown in table 2. Statistically significant improvements were seen for all comparisons except for the change between baseline and M18 in participants (N=32) where the SE was the better eye at baseline. The greatest mean improvement was from baseline to M18 in the subgroup where the SE had worse baseline BCVA compared with the FE (8.3 letters, 95% CI 5.5 to 11.2).

For the complete study population, NEI-VFQ 25 subscales were significantly correlated with each other (data not shown). The mean composite score changed from 67.9 at baseline to 72.0 by M18 (p<0.005). On testing change from baseline to M12 and M18 (table 3A and B) for the subscales, improvements were observed in all at both timepoints except in general health, colour vision and peripheral vision. At M18, changes from baseline in distance activities and social functioning were no longer statistically significant.

The scores from the two MacTSQ subscales were significantly correlated with each other for all visits (data not shown). Improvements in mean score between baseline M6, 12 and 18 were seen in the information provision and convenience (subscale 1) but only reached statistical significance at M12 (table 4A). In subscale 2 which dealt with the impact of treatment, the improvements in mean score from baseline to M6, 12 and 18 were all statistically significant (table 4A). The change over time in mean scores for the two MacTSQ subscales was also examined after classifying participants by whether BCVA in the SE was better or worse than the FE at baseline. In those where the SE was the better eye, all of the comparisons reached significance for subscale 2, but none of comparisons in subscale 1 were statistically significant (table 4B). Where the the SE was the worse eye, the change in MacTSQ from its baseline to each of the time points (table 4C) were statistically significant for both subscales.

The two MacTSQ subscales and the NEI-VFQ 25 composite showed no statistically significant correlations when co-administered. Correlations between the two

Table 4A Change in MacTSQ subscales between M1 (MacTSQ baseline) to M6, M12 and M18 in all participants

Change in MacTSQ subscales	Mean 1	Mean 2	Difference	95% CI	Significance
Subscale 1: information provision and convenience					
Pair 1 (n=99) Months 1–6	33.09	33.64	0.55	−0.02 to 1.11	0.058
Pair 2 (n=98) Months 1–12	33.41	34.22	0.82	0.32 to 1.31	0.002
Pair 3 (n=97) Months 1–18	33.38	34.02	0.64	−0.04 to 1.31	0.06
Subscale 2: impact of treatment and treatment satisfaction					
Pair 4 (n=100) Months 1–6	28.98	31.42	2.44	1.6 to 3.26	<0.001
Pair 5 (n=98) Months 1–12	29.07	32.49	3.41	2.61 to 4.22	<0.001
Pair 6 (n=97) Months 1–18	28.96	32.60	3.64	2.72 to 4.56	<0.001

Table 4B Change in MacTSQ subscales between M1 (MacTSQ baseline) to M6, 12 and 18 in the subset of participants in whom at baseline the study eye was the 'better' eye compared with the fellow eye in terms of BCVA letters

Change in MacTSQ subscales	Mean 1	Mean 2	Difference	95% CI	Significance
Subscale 1: information provision and convenience					
Pair 1 (n=30) Months 1–6	33.63	33.43	−0.20	−1.16 to 0.76	0.67
Pair 2 (n=28) Months 1–12	33.64	34.29	0.64	−0.33 to 1.61	0.18
Pair 3 (n=30) Months 1–18	33.70	33.97	0.27	−1.25 to 1.79	0.72
Subscale 2: impact of treatment and treatment satisfaction					
Pair 4 (n=30) Months 1–6	29.83	31.93	2.10	0.71 to 3.49	<0.004
Pair 5 (n=28) Months 1–12	29.57	32.86	3.23	1.94 to 4.64	<0.001
Pair 6 (n=30) Months 1–18	29.47	32.43	2.97	1.33 to 4.60	<0.001

Table 4C Change in MacTSQ subscales between M1 (MacTSQ baseline) to M6, 12 and 18 in the subset of participants in whom at baseline the study eye was the 'worse' eye compared with the fellow eye in terms of BCVA letters

Change in MacTSQ subscales	Mean 1	Mean 2	Difference	95% CI	Significance
Subscale 1: information provision and convenience					
Pair 1 (n=69) Months 1–6	32.86	33.72	0.87	0.18 to 1.56	0.015
Pair 2 (n=70) Subscale 1 Months 1–12	33.31	34.20	0.89	0.29 to 1.48	0.004
Pair 3 (n=67) Months 1–18	33.24	34.04	0.81	0.08 to 1.54	0.031
Subscale 2: impact of treatment and treatment satisfaction					
Pair 4 (n=70) Months 1–6	28.87	31.20	2.59	1.56 to 3.62	<0.001
Pair 5 (n=70) Months 1–12	29.57	32.34	3.47	2.46 to 4.48	<0.001
Pair 6 (n=67) Months 1–18	28.73	32.67	3.94	2.81 to 5.10	<0.001

BCVA, best-corrected visual acuity; MacTSQ, Macular Disease Society Treatment Satisfaction Questionnaire.

Table 5 Correlations between BCVA at baseline, month 12 and month 18 with the NEI-VFQ 25 composite score and scores of the two subscales of the MacTSQ at the corresponding times

	NEI-VFQ 25 composite baseline	MacTSQ subscale 1 Month 1	MacTSQ subscale 2 Month 1
Baseline BCVA all eyes (N=110)	0.387**	0.009	0.153
Baseline BCVA SE better eye (N=35)	0.499**	0.199	0.205
Baseline BCVA SE worse eye (N=73)	0.360**	0.041	0.144
	NEI-VFQ 25 composite Month 12	MacTSQ subscale 1 Month 12	MacTSQ subscale 2 Month 12
Month 12 BCVA all eyes (N=100)	0.329**	0.065	0.027
Month 12 BCVA SE better eye (N=30)	0.496**	0.200	0.173
Month 12 BCVA SE worse eye (N=70)	0.297*	0.030	0.074
	NEI-VFQ 25 composite Month 18	MacTSQ subscale 1 Month 18	MacTSQ subscale 2 Month 18
Month 18 BCVA all eyes (N=98)	0.405**	0.144	0.000
Month 18 BCVA SE better eye (N=31)	0.548**	0.058	0.104
Month 18 BCVA SE worse eye (N=68)	0.350**	0.185	0.060

*Denotes significance at 0.01. Information provision and convenience and **Denotes significance at 0.001. Impact of treatment and satisfaction.
BCVA, best-corrected visual acuity; MacTSQ, Macular Disease Society Treatment Satisfaction Questionnaire; NEI-VFQ, National Eye Institute Visual Function Questionnaire; SE, study eye.

MacTSQ subscales and BCVA in the SE when the whole cohort was included or when the SE was the better eye or worse eye are shown in table 5, and none reached significance. Several of the NEI-VFQ 25 subscales showed statistically significant correlations with BCVA and were strongest when the SE was better than the FE.

None of the baseline characteristics such as age, gender, BCVA in the SE at baseline or M12, or CRT at baseline or M12 were significant predictors of improvement in the NEI-VFQ 25 composite or MacTSQ subscales (data not shown). Regression models with change in NEI-VFQ 25 composite score, as the explanatory variable showed that only the change in BCVA was significantly associated, while age, gender and CRT were rejected from the model.

DISCUSSION

In the RESTORE trial which compared monthly ranibizumab with sham or active laser and sham injections plus laser, hrQOL was tested using the NEI-VFQ 25.[15 16] In the ranibizumab arms, there was a vision gain of approximately 6 letters, CRT reduction of 118.7 µm and a 5-point increase in the NEI-VFQ 25 12M composite score. In RELIGHT, BCVA gain in the SE at M12 was on average 4.9 letters, CRT reduction, 127.1 µm and a 4.8-point increase in the composite score at M12. Thus, despite differences in algorithms for re-treatment in the two studies, the results are similar suggesting that minor variations in frequency of treatment with ranibizumab have limited impact on functional, morphological and patient-reported outcomes. It is, however, possible that despite the similar levels of improvement in BCVA, other markers of function such as reading speed and low luminance acuity may have revealed differences between RELIGHT and RESTORE. However, the similarity of the improvements in almost all the subscales of the NEI-VFQ between these two trials gives some degress of reassurance. It is worth noting that the RESTORE trial also reported that maximum improvement of approximately 9 points was seen in the near activities subscale and by 5.3 for distance activities.[16] Interestingly, the best improvements in this study occurred in the mental health and role difficulties subscales. Of particular note were the changes observed in the mental health subscale with an improvement of 10 points at M12 and M18. Similar levels of improvement has been reported in Age-Related Macular Degeneration (AMD) clinical trials with anti-VEGF therapy.[17] Comparing the outcomes from our study with those of RESTORE, although the level of improvement in the subscale scores for distance and near activities at 12 and 18 months were not of the same magnitude, the changes were positive and in most cases statistically significant.[16] As patient-reported outcomes are influenced by age, gender, geographical location and other factors, it is not possible to speculate on what may have caused the differences that were observed in NEI-VFQ 25 subscale improvements in these two studies.

PROMs are particularly useful for ascertaining the acceptability of a treatment.[18 19] It is recognised that patients with diabetes have higher rates of non-attendance and reduced compliance compared with persons without diabetes.[20] Furthermore, treatment for DMO with anti-VEGF agents necessitates invasive intraocular administration of drug on a repeated basis. In the analysis that included the entire cohort, there was evidence of increasing satisfaction with treatment with numeric improvement in MacTSQ scores observed between M1 to 12 and 18. Additionally, consistent improvements across all time points were observed for the subscale dealing with impact of treatment. On subdividing the cohort into groups on the basis of whether the SE had better or worse baseline BCVA compared with the FE, improvements in subscale 2 were evident for all comparisons when the SE was the worse eye. Surprisingly, the change from M1 to 6, 12 and 18 was not significant in subscale 1 when the SE was the better eye. One possible explanation is the small sample of participants where the SE was the better eye resulting in an inability to detect a significant change. Alternatively, we also observed that the largest improvements in BCVA over time was seen in the group where the SE was the worse eye. Therefore, it is possible that an improvement of around 8 letters is more noticeable and thus influenced the participants' response indicating satisfaction with treatment. However, the absence of correlation between the MacTSQ subscales and BCVA and between the change in subscale scores and change in BCVA is not in accord with this latter conclusion.

Unlike the MacTSQ subscales which showed no correlation with BCVA, the NEI-VFQ 25 composite score correlated strongly with BCVA regardless of whether the SE was the better or worse seeing eye and positive relationships were observed at all time points. Our findings are consistent with high internal validity for this instrument with respect to the key functional measure of vision and reflect the positive relationship between the NEI-VFQ 25 and vision in the better eye.[18]

The change in CRT which is a morphological marker of the efficacy of treatment with anti-VEGF agents showed no relationship with the composite NEI-VFQ 25 or with the two MacTSQ subscales at M12 or M18 (online supplementary table E2). We hypothesised that the change in CRT while not correlating with the NEI-VFQ 25 composite score may do so with one of the subscales. However, no correlations of significance were observed between any of the NEI-VFQ 25 subscales and the CRT suggesting that this instrument is not sensitive to improvements in retinal morphology with treatment.

The current study has some limitations, and these include the small sample size limiting the power of our observations and the unequal proportions of better and worse eyes within the SE group. The MacTSQ is a treatment satisfaction questionnaire and has not been used widely in trials nor has its use been reported extensively in the literature. Because it does not correlate with VA, it is difficult to the estimate criterion validity of this instrument. Many factors are involved in treatment satisfaction and the degree of attention and care given to clinical trial participants may have influenced their responses. However, the administration of an invasive treatment at repeated intervals did not result in poor scores, and we contend that intraocular drug administration does not appear to be associated with high levels of anxiety in the patient population with DMO.

Nonetheless, our study has several strengths, and these include the collection of data at specified time points, the use of validated hrQOL instruments within the context of a randomised controlled trial and the low chance of bias under these circumstances.

In summary, the study has shown that patients recognise and report improvements in function when treated with ranibizumab for DMO regardless of whether treatment is applied to the better or worse of an individual's pair of eyes. In addition, there was evidence of awareness within the patient population of subjective improvement that was consistent with the changes from objective measures that are recorded in clinical trials and high levels of satisfaction with treatment and information provision were observed in our study.

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Contributors UC, IP, SB, BJLB, LD, RG, JP, SP and SS were involved in patient enrolment, history taking, clinical examination, data collection and interpretation. UC, MS and SL developed and performed additional statistical analysis of the core data. UC developed the initial manuscript outline which was further developed and reviewed by IP, SB, BJLB, LD, RG, JP, SP, SS and SL. SL provided medical writing and project management services.

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