Vision-Related Quality of Life Outcomes in the BEVORDEX Study: A Clinical Trial Comparing Ozurdex Sustained Release Dexamethasone Intravitreal Implant and Bevacizumab Treatment for Diabetic Macular Edema

Christine Aroney,[1] Samantha Fraser-Bell,[1] Ecosse L. Lamoureux,[2–4] Mark C. Gillies,[1] Lyndell L. Lim,[2] and Eva K. Fenwick[2,3]

[1]The Save Sight and Eye Health Institute, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
[2]The Centre for Eye Research, University of Melbourne, Royal Victoria Eye and Ear Hospital, Melbourne, Australia
[3]Singapore Eye Research Institute, National University of Singapore, Singapore
[4]Duke-NUS Medical School, Singapore

Correspondence: Samantha Fraser-Bell, Macula Research Group, Save Sight and Eye Health Institute, University of Sydney, 8 Macquarie Street, Sydney, NSW 2000, Australia; sfraserbell@gmail.com.

Submitted: April 12, 2016
Accepted: September 4, 2016

Citation: Aroney C, Fraser-Bell S, Lamoureux EL, Gillies MC, Lim LL, Fenwick EK. Vision-related quality of life outcomes in the BEVORDEX study: a clinical trial comparing Ozurdex sustained release dexamethasone intravitreal implant and bevacizumab treatment for diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2016;57:5541–5546. DOI:10.1167/iovs.16-19729

Purpose. To determine the patient-centered effectiveness of treatment with the slow-release dexamethasone intravitreal implant (DEX implant) and intravitreal bevacizumab using the Impact of Vision Impairment Questionnaire (IVI), a vision-related quality of life (VRQoL) measure, in patients with visual impairment secondary to center-involving diabetic macular edema (DME).

Methods. Patients with DME were enrolled in a phase 2, prospective, multicenter, randomized, single-masked clinical trial and received either DEX implant 4 monthly or bevacizumab monthly, both pro re nata. Vision-related quality of life was measured at baseline and 24 months, using the IVI's three component scales, namely reading, mobility, and emotional well-being. Rasch analysis was used to generate interval-level estimates of VRQoL, which were then analyzed using *t*-tests to assess changes over time.

Results. Forty-eight patients completed the main study; 43 (90%) answered the IVI at the baseline and 24-month (final efficacy) visits. Vision-related quality of life improved significantly, with average increases of 1.44, 0.99, and 1.49 logits, for the reading, mobility, and emotional well-being scales respectively, from baseline to 24 months, ($P < 0.001$). There was no significant between-group difference in improvement in VRQoL in the DEX implant only compared with the bevacizumab-only group, in any of the three scales listed above (with 1.41, 1.08, and 2.11 logits improvement, in reading, mobility, and emotional well-being, respectively, for DEX implant group, compared with 1.48, 1.06, and 2.11 for bevacizumab; *P* values > 0.1.)

Conclusions. We found that both DEX implant and bevacizumab treatment result in significant and similar improvements in VRQoL in patients with DME over a 24-month period. (Clinicaltrials.gov identifier NCT01298076)

Keywords: diabetic macular edema, therapeutics, quality of life

Diabetic macular edema (DME) is the major cause of visual loss in patients with diabetes. A breakdown of the retinal–blood barrier results in the leakage of plasma and lipids into interstitial layers of the macula, causing the thickening of the fovea and severely compromising central vision.[1,2] The impact of DME on patients' quality of life is considerable,[3,4] and comparable to that of AMD.[5]

Both bevacizumab[6,7] and slow-release dexamethasone intravitreal implant (DEX implant)[8,9] have been shown to be effective in reducing swelling due to DME and improving visual acuity. However, few studies have reported the effects of these treatments from the patient's perspective. Okamoto and colleagues[10] found short-term VRQoL improvements (using the 25 item version of National Eye Institute Vision Functioning Questionnaire [NEI VFQ-25]), following a single injection of bevacizumab for persistent post vitrectomy DME, and Ramu and associates[11] similar vision and VRQoL outcomes for both fixed or pro re nata (PRN) treatment schedules for DEX implant in refractory DME.

However, both studies were only conducted over a short time-period (3 and 12 months, respectively) so the longer-term treatment effect of either bevacizumab or DEX implant on VRQoL is unknown. Moreover, most studies reporting VRQoL after treatment for DME[12,13] have used traditional summary scoring methods, which have inherent limitations.[14,15] Importantly, recent studies using Rasch analysis, a form of item response theory, have found the NEI VFQ-25 to be multidimensional, suggesting its measurement precision may be compromised.[16–18]

In contrast to the NEI VFQ-25, the Impact of Vision Impairment Questionnaire (IVI) is a VRQoL instrument, which has been shown to be reliable and responsive to interven-

tions[19–22] and has been rigorously validated using Rasch analysis.[23,24] Rasch analysis addresses the limitations of summary scoring as it provides a method for transforming ordinal scores into an interval level estimate.[25,26] In addition, Rasch analysis provides detailed insight into dimensionality; item 'fit' to the underlying construct; and targeting of items to the population.[27] Therefore, we used the IVI to determine the impact of DEX implant and bevacizumab on VRQoL in patients with DME in the BEVORDEX study, in the patients overall at 24 months. We also analyzed the IVI results in a subgroup of patients, who received either DEX implant or bevacizumab only, to compare impact of VRQoL between the two treatments.

Methods

The BEVORDEX study was a 2-year clinical trial that directly compared sustained release intravitreal DEX implant (Ozurdex; Allergan, Inc., Irvine, CA, USA) versus intravitreal injections of bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) for center-involving DME. As previously described,[28] the study was conducted in accordance with the Declaration of Helsinki and was approved by relevant Health Research Ethics Committees. Safety data were reviewed by an independent safety monitoring committee. Patients gave written informed consent before being randomized to receive study treatment. Both eyes of patients were enrolled if inclusion criteria were met; the right eye received the randomized treatment and the left eye the other treatment.

Protocol Synopsis

The eligibility requirements for patients and eyes, clinical evaluation, clinical data collection methods, and study schedules have been detailed elsewhere.[28,29] Briefly, baseline measurements included best-corrected logMAR and best-corrected visual acuity (BCVA) with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts measured using standardized procedures by certified staff. Central macular thickness (CMT) was measured from the central 1-mm subfield from spectral-domain ocular coherence tomography (OCT; Cirrus; Carl Zeiss, Meditec, Jena, Germany). Bevacizumab 1.25 mg (Avastin) or DEX implant 0.7 mg (Ozurdex) was injected into the vitreous under sterile conditions as an outpatient procedure. All eyes were considered for retreatment at appropriate intervals (4 weekly for bevacizumab or 16 weekly for DEX implant); treatment was either administered or withheld in accordance with prospectively defined criteria.

Patients with both eyes enrolled had each eye treated at separate visits.

The Impact of Vision Impairment Questionnaire

The IVI was either self- or interviewer-administered at baseline and 24 months. The IVI was developed as a measure of patients' perception of vision-related restriction on their activity and quality of life, particularly in the context of low vision rehabilitation.[30] The questionnaire was revised using Rasch analysis to improve measurement characteristics.[23,24] The revised version used in the current study has 28 items, with three to four response options for each item. Patients can rate their perceived impact of vision limitation from "not at all," "a little," "a fair amount," to "a lot," which are allocated number scores from 0 to 3. There is an additional response, "don't do this for other reasons" for 15 of the items, which was categorized as "missing." In this paper, Rasch analysis supported the use of the three IVI scales; reading and accessing information, mobility and independence, and emotional well-being.[23,24]

Psychometric Assessment of the Impact of Vision Impairment Questionnaire

The psychometric properties of the IVI questionnaire were assessed using Rasch analysis in Winsteps (version 3.91.0; Beaverton, OR, USA)[31] with the Andrich rating scale model,[32] with different rating scale structures to allow for the two out of 28 items having three response choices rather than four. Rasch analysis has been described in detail previously; in brief, we assessed whether category thresholds were ordered, scale precision and targeting were adequate, measurement was unidimensional and that items 'fit' the underlying trait of VRQoL (Supplementary Table S1). Baseline and 24 month IVI data were "stacked" and item measures anchored to pretreatment values in order to keep pre- and post measurement in the same frame of reference. This involves entering the two sets of IVI responses for each patient as separate "cases," which were then analyzed simultaneously as one data file.[33] The resulting scores are "person measures," expressed in logits (log of the odds units), and in this study ranged from −4.95 to +4.90. Higher scores indicate better VRQoL. In brief, the IVI had good psychometric properties with ordered thresholds (demonstrating appropriate use of the range of questionnaire response categories) and excellent precision, as demonstrated in person reliability and separation values. However, principal components analysis revealed evidence of multidimensionality with an eigenvalue of four and three misfitting items. Therefore, based on the standardized residual loadings for items, the IVI was split into three scales for analysis, namely reading and accessing information or "reading" (9 items), mobility and independence or "mobility," (11 items) and emotional well-being (8 items). The reading and emotional well-being scales had no misfitting items and good precision. However, the mobility scale was not well targeted for this sample, as the participants were on average, above the average level of item difficulty (difference of 1.54 logits between person and item mean score). Similarly, the person separation index was 1.71, which suggests this scale had less than adequate precision. In addition, one item (13), displayed borderline misfit (infit MnSq 1.36), but was retained for the analysis.

In this paper, we use 'VRQoL' to describe the over-arching construct of QoL, and reading, mobility, and emotional to describe the three subtraits of VRQoL measured by the IVI.

Statistical Analysis

The Statistical Package for the Social Sciences (v. 22.0; SPSS, Inc., Chicago, IL, USA) was used to analyses the data. Descriptive statistical analysis of demographic, clinical, and IVI data was performed using Student's *t*-tests. The IVI person measures in logits were analyzed using paired *t*-tests to assess change over time. Pearson's correlation coefficient *r* was used to explore the relationship between VRQoL and BCVA. Change in BCVA was assessed for the study eye or, in patients with both eyes enrolled, the most improved study eye. The most-improved study eye was either the better or equal seeing eye[34] at the 24-month visit in 21/24 patients with both eyes enrolled. Of 43 eyes whose BCVA was used, 19 were treated with DEX implant and 24 with bevacizumab.

Due to the wide range of BCVA changes in a relatively small sample, the patients were divided into two groups according to BCVA gain (one with vision gain of $\leq$15 letters, and the other $>$15 letters) to compare VRQoL changes. Fifteen letters is equivalent to approximately three lines and is likely to be associated with VRQoL improvements.[35,36] The subgroup of

Table 1. IVI Scores for 43 Patients at Baseline and 24 Months

IVI (Logits)	Baseline	24 mo	Change	*P* Value of Change
Reading ($n = 43$)	0.14 (SD 1.93)	1.58 (SD 2.06)	1.44 (SD 1.90)	**<0.001**
Mobility ($n = 43$	1.05 (SD 1.77)	2.04 (SD 1.78)	0.99 (SD 1.51)	**<0.001**
Emotional ($n = 42$)	0.34 (SD 2.13)	1.82 (SD 2.18)	1.49 (SD 2.49)	**<0.001**

Significant *P* values in bold.

patients with single eye enrolment was used to evaluate whether there was any difference in VRQoL between the bevacizumab and DEX implant treatments, using *t*-tests.

Results

Demographic and Clinical Characteristics of Patients

A total of 48 patients completed the 24 months of the study and 43/48 (90%) answered the IVI questionnaire at both time points. The mean age of these 43 patients ($n = 17$, 40% male) was 62 (SD 10.80) years at study entry, ranging from 36 to 86 years. A total of 24/43 (56%) patients had both eyes enrolled (subsequently, 3/24 of patients with both eyes enrolled had one eye withdrawn by the Principal Investigator), while 19/43 (44%) received treatment to only one eye. The mean BCVA of the 64 study eyes of the above 43 patients increased from 57 (SD 12; range, 7–19) logMAR letters at baseline to 65 letters (SD 16; range, 0–91) at 24 months. This represented an average increase of 8 letters (SD 15; range, −56 to +44). There was a mean decrease in CMT for the 64 study eyes by the 24-month study visit of 166 μm (SD 134; range, −478 to +95 μm). There was no correlation between BCVA and CMT change (Pearson $r = 0.09$). The fellow eyes not enrolled in the study ($n = 19$) had a mean improvement of 2 logMAR letters (SD 16; range, −40 to +35).

The baseline average IOP of the 64 study eyes was 14.53 mm Hg (SD 2.53); with mean of 14.6 mm Hg (SD 2.74) for eyes assigned to DEX implant treatment and 14.5 mm Hg (SD 2.32) in eyes to be treated with bevacizumab. During the study, 21/33 of eyes treated with DEX implant (64%) had an IOP rise of greater than or equal to 5mm Hg from baseline at a subsequent study visit, and 8/33 (24%) required topical treatment to lower IOP. In comparison, 9/31(29%) eyes treated with bevacizumab had a IOP rise of greater than or equal to 5 mm Hg from baseline, and none required treatment.

VRQoL improved significantly overall, with increases of 1.44, 0.99, and 1.49 logits, for the reading, mobility, and emotional well-being scales respectively, from baseline to 24 months, ($P < 0.001$, Table 1).

Relationship Between Change in Vision and VRQoL

In order to explore relationship of improved vision and VRQoL, we used the vision gain in the study eye in patients with a single eye enrolled, and in the group of 24/43 patients who both eyes treated the vision gain in the most improved study eye. The vision in the better seeing eye has been found to correspond to binocular vision when both have been measured.[36]

When we stratified the 43 patients according to number of letters gained, patients gaining greater than 15 letters had 2.2-logits increase in reading scores at 24 months compared with 1.0 logits in those than those who gained less than or equal to 15 letters; however, the *P* value was 0.050, which indicated that the difference was of borderline significance. The gain in mobility and emotional well-being was similar for both stratified groups (Table 2).

The change in reading and emotional scores for all patients showed a low correlation with change in BCVA, ($r = 0.32$ and 0.34, $P < 0.05$, respectively), with a nonsignificant correlation with the mobility scale; ($r = 0.29$, $P = 0.059$). However, when we stratified patients into two groups according to number of letters gained (≤15 and >15), the relationship between the change in IVI scores and BCVA differed. In the greater than 15 letter gain group, there was a strong correlation between VA gain and the three IVI scales (range, $r = 0.79$–0.80; $P = 0.001$). However, in the less than or equal to 15 letter group there was no significant correlation with VA gain in any of the IVI scales (range, $r = -0.09$ to -0.13; $P > 0.05$).

Comparison of IVI Scores Between the Bevacizumab and DEX Implant Treatment Groups

Patients (24/43) who had both eyes enrolled were assigned a different treatment for each eye. Therefore, to compare VRQoL changes between the two treatments, only the subgroup of patients with a single eye enrolled (19/43) was analyzed. There

Table 2. IVI and BCVA Results in Patients Stratified for Vision Gain

BEVORDEX Patients Stratified for BCVA	>15 Letters Gain, $n = 15/43$	≤15 Letters Gain, $n = 29/43$	*P* Value of Difference
IVI baseline (logits)			
Reading	−0.16 (SD 1.73)	0.30 (SD 2.03)	0.47
Mobility	1.27 (SD 1.99)	0.93 (SD 1.67)	0.55
Emotional	0.17 (SD 2.08)	0.43(SD 2.18)	0.70
IVI, Mean change baseline to 24 mo			
Reading	2.21 (SD 2.07)	1.03 (SD 1.71)	**0.050**
Mobility	1.20 (SD 1.85)	0.87 (SD 1.32)	0.501
Emotional	2.07 (SD 2.90)	1.35 (SD 2.06)	0.357
BCVA, mean change (logMAR letters)	23 (SD 7.8)	6 (SD 10.4)	**<0.0005**
BCVA baseline	48 (SD 15)	60 (SD 9)	**0.01**
BCVA 24 mo	71 (SD 15)	66 (SD 14)	0.27

Significant *P* values in bold.

Table 3. Change in IVI Scores in Patients With Single Eye Enrolled (n = 19)

IVI Mean Change Baseline to 24 mo	DEX Implant n = 9/19	Bevacizumab n = 10/19	P Value*
Reading	1.41 (SD 2.09)	1.48 (SD 1.72)	0.96
Mobility	1.18 (SD 1.88)	1.06 (SD 0.93)	0.87
Emotional	2.11(SD 2.55)	0.95 (SD 2.77)	0.35

* Difference in baseline IVI and IVI change between treatment groups.

was no significant difference between average VA changes in the study eye in this small patient subgroup between the two treatments, namely a 2.4 letter gain (SD 21.67) in the DEX implant group, and a 9.3 (SD 7.06) gain in the bevacizumab group, respectively (P = 0.36). The VRQoL improvement was similar in both treatment groups (Table 3).

We also compared IVI scores of patients in the single eye enrolled group whose eyes were phakic (i.e., eyes with natural lens) at baseline (13/19). Of the 13 eyes, 5 were treated with DEX implant, and 8 with bevacizumab. We found no significant difference in reading or emotional well-being scores between the two treatments. However, there was a trend for greater mobility improvement in bevacizumab-treated patients, compared with DEX implant patients (0.96 and 0.02 logits, respectively, P = 0.072; Table 4).

Discussion

Using Rasch-transformed data from the IVI questionnaire, our findings suggest that treatment of DME with both bevacizumab and DEX implants results in substantial and similar improvements in VRQoL.

The study by Ramu and colleagues,[11] who compared fixed versus PRN dosing schedule for DEX implant in refractory DME, reported similar increase in the NEIVFQ-25 composite score, as well the two other questionnaires used in the study corresponding to similar VA outcomes for both regimens. Okamoto and colleagues[10] found that patients in an observational study, who received a single bevacizumab injection for persistent post vitrectomy DME, had a transient, but significant increase of 13% in the mental health domain of the 25-item NEI VQF, and this correlated with improved letter contrast sensitivity, rather than BCVA which did not improve.

Previous large clinical trials have reported improved VRQoL in patients following other anti-VEGF treatment (such as ranibizumab) compared with laser or sham in DME.[12,13] However, in these studies improvements were not consistent across all NEIVFQ subscales and were predominantly related to visual functioning. This contrasts with our study, where we found significant improvements across all three VRQoL domains, including emotional well-being.

In our study, the relationship between change in BCVA and change in VRQoL was not linear, as a strong positive correlation was only observed in the group who gained greater than 15 letters. This, together with findings of Okamoto and colleagues,[10] suggests that changes in other aspects of visual function such as contrast sensitivity, reading speed, or central visual fields could be driving the VRQoL improvements seen in patients in our study who gained less than or equal to 15 letters, and future studies assessing the impact of VRQoL in DME patients should include these relevant clinical measurements, in addition to BCVA.

Our finding that VRQoL improvements were similar for both bevacizumab and DEX implant treatment was surprising considering the differing treatment regimen and side-effect profiles of the two treatments. Although the frequency of bevacizumab treatments given during the study decreased from an average of nine injections over the first 12 months to four during the second 12 months, substantially fewer DEX implant treatments were required overall (an average of 2–3 and 2 injections in first and second years, respectively).[29] This suggests that number of injections may not be a contributing factor to patients' VRQoL or, alternatively, that our IVI instrument did not have the sensitivity to detect treatment-related burden such as inconvenience, and so on. Our sample size comparing these two groups was very small and we may not have had the power to detect a difference between the two treatment groups. Future studies in larger sample sizes with additional patient-reported outcome measures are required to answer this question definitively.

There was also a trend for worse VA results for all phakic eyes in the main study treated with DEX implants, most likely related to the known side effect of development and progression of cataract.[29] However, no significant difference in improvement in VRQOL was found between treatments in our subgroup (n = 13) of phakic eyes, although comparison was problematic due to the small sample size. Both these results, if replicated in future larger samples, may suggest that DEX implant should be a second, rather than a first line treatment for DME in patients with phakic eyes.

Our study is the first to report on VRQoL changes in patients with DME treated with DEX implant and/or bevacizumab over a 24-month randomized clinical trial. Previous studies in either of these treatments used in DME, and reporting VRQOL, have been of 3 or 12 months duration only.[10,11] A major strength of our study is the use of the Rasch-validated IVI questionnaire and the fact that we conducted Rasch analysis anew on our study sample. The use of interval level person measures in our parametric testing is likely to have increased measurement precision, thus increasing the likelihood of detecting a change over time.[25,37] Another strength is that the questionnaire (from 90% of the study patients who finished the study) represents a complete set of baseline and 24-month data from each of the 43 patients, no data were imputed, in contrast to other studies.[13]

Limitations include the small sample size, precluding subgroup, and multivariate regression analysis, which could have revealed confounding factors influencing our results. Also, the mobility scale had some psychometric issues including suboptimal precision and targeting of items to our patient group. Lack of precision is problematic because it suggests that the scale did not have discriminatory ability and therefore the results on mobility must be interpreted with some caution. Another limitation of our study is that we did not include the commonly used NEI-VFQ questionnaire, which makes our results difficult to compare with other, similar studies. However, given that the NEI-VFQ has been found to function best with just two subscales, socioemotional and visual functioning,[38,39] it would still be difficult compare such results with studies reporting all 12 subscales.

Table 4. Change in IVI Scores in Patients With Single Eye Enrolled and Phakic at Baseline (n = 13)

IVI Mean Change Baseline to 24 mo	DEX Implant n = 5/13	Bevacizumab n = 8/13	P Value
Reading	0.53 (SD 1.07)	1.08 (SD 1.73)	0.54
Mobility	0.02 (SD 0.57)	0.96 (SD 0.94)	0.072
Emotional	1.13 (SD 1.59)	0.81 (SD 3.02)	0.83

P value, difference in baseline IVI and IVI change between treatment groups.

Conclusions

We have shown that both DEX implant and bevacizumab treatment result in significant and similar improvements in VRQoL in patients with DME over a 24-month period.

Acknowledgments

Supported by grants from the National Health and Medical Research Council (NHMRC; Canberra, ACT, Australia), which was supplemented by an unrestricted educational grant from Allergan Pharmaceuticals (Irvine, CA, USA), and a NHMRC Clinical Fellowship (MCG).

Disclosure: **C. Aroney**, None; **S. Fraser-Bell**, Allergan (F); **E.L. Lamoureux**, None; **M.C. Gillies**, Allergan (C, F), Bayer (C, R), Novartis (C); **L.L. Lim**, Abbvie (C, R), Allergan (C), Bayer (C, R), Novartis (C); **E.K. Fenwick**, None

References

1. Das A, McGuire PG, Rangasamy S. Diabetic macular edema: pathophysiology and novel therapeutic targets. *Ophthalmology*. 2015;122:1375–1394.
2. Yau J, Rogers S, Kawasaki R. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35:556–564.
3. Milne A, Johnson JA, Tennant M, Rudnisky C, Dryden DM. Diabetic retinopathy and health-related quality of life. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:267–272.
4. Fenwick EK, Xie J, Ratcliffe J, et al. The impact of diabetic retinopathy and diabetic macular edema on health-related quality of life in type 1 and type 2 diabetes. *Invest Ophthalmol Vis Sci* 2012;53:677–684.
5. Hariprasad SM, Mieler WF, Grassi M, Green JL, Jager RD, Miller L. Vision-related quality of life in patients with diabetic macular oedema. *Br J Ophthalmol*. 2008;92:89–92.
6. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol*. 2012;130:972–979.
7. Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372:1193–1203.
8. Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol*. 2010;128:289–296.
9. Boyer DS, Yoon YH, Belfort R Jr, et al. Three-year, randomized sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904–1914.
10. Okamoto Y, Okamoto F, Hiraoka T, Oshika T. Vision-related quality of life and visual function following intravitreal bevacizumab injection for persistent diabetic macular edema after vitrectomy. *Jpn J Ophthalmol*. 2014;58:369–374.
11. Ramu J, Yang Y, Menon G, et al. A randomized clinical trial comparing fixed vs pro-re-nata dosing of Ozurdex in refractory diabetic macular oedema (OZDRY study). *Eye (Lond)*. 2015;29:1603–1612.
12. Mitchell P, Bressler N, Tolley K, et al. Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema: randomized clinical trial. *JAMA Ophthalmol*. 2013;131:1339–1347.
13. Bressler NM, Varma R, Suñer IJ, et al. Vision-related function after ranibizumab treatment for diabetic macular edema: results from RIDE and RISE. *Ophthalmology*. 2014;121:2461–2472.
14. van Alphen A, Halfens R, Hasman A, Imbos T. Likert or Rasch? Nothing is more applicable than good theory. *J Adv Nurs*. 1994;20:196–201.
15. Massof RW. Likert and Guttman scaling of visual function rating scale questionnaires. *Ophthalmic Epidemiol*. 2004;11:381–99.
16. Pesudovs K, Gothwal VK, Wright T, Lamoureux EL. Remediating serious flaws in the National Eye Institute Visual Function Questionnaire. *J Cataract Refract Surg*. 2010;36:718–732.
17. Finger RP, Hoffmann AE, Fenwick EK, et al. Patients' preferences in treatment for neovascular age-related macular degeneration in clinical routine. *Br J Ophthalmol*. 2012;96:997–1002.
18. Marella M, Pesudovs K, Keeffe JE, O'Connor PM, Rees G, Lamoureux EL. The psychometric validity of the NEI VFQ-25 for use in a low-vision population. *Invest Ophthalmol Vis Sci*. 2010;51:2878–2884.
19. Lamoureux EL, Hooper CY, Lim L, et al. Impact of cataract surgery on quality of life in patients with early age-related macular degeneration. *Optom Vis Sci*. 2007;84:683–688.
20. Lamoureux EL, Pallant JF, Pesudovs K, et al. Assessing participation in daily living and the effectiveness of rehabiliation in age related macular degeneration patients using the impact of vision impairment scale. *Ophthalmic Epidemiol*. 2008;15:105–113.
21. Lamoureux EL, Maxwell RM, Marella M, Dirani M, Fenwick E, Guymer RH. The longitudinal impact of macular telangiectasia type 2 on vision-related quality of life. *Invest Ophthalmol Vis Sci*. 2011;52:2520–2524.
22. Finger RP, Guymer RH, Gillies MC, Keeffe JE. The impact of anti-vascular endothelial growth factor treatment on quality of life in neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:1246–1251.
23. Lamoureux EL, Pallant JF, Pesudovs K, Rees G, Hassell JB, Keeffe JE. The impact of vision impairment questionnaire: an assessment of its domain structure using confirmatory factor analysis and rasch analysis. *Invest Ophthalmol Vis Sci*. 2007;48:1001–1006.
24. Lamoureux EL, Pallant JF, Pesudovs K, Hassell JB, Keeffe JE. The Impact of Vision Impairment Questionnaire: an evaluation of its measurement properties using Rasch analysis. *Invest Ophthalmol Vis Sci* 2006;47:4732–4741.
25. Norquist JM, Fitzpatrick R, Dawson J, Jenkinson C. Comparing alternative Rasch-based methods vs raw scores in measuring change in health. *Med Care*. 2004;42(suppl):I25–I36.
26. Wright BD, Linacre JM. Observations are always ordinal; measurements, however, must be interval. *Arch Phys Med Rehabil*. 1989;70:857–860.
27. Lamoureux E, Pesudovs K. Vision-specific quality-of-life research: a need to improve the quality. *Am J Ophthalmol*. 2011;151:195–197.
28. Gillies MC, Lim LL, Campain A, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX Study. *Ophthalmology*. 2014;121:2473–2481.
29. Fraser-Bell S, Lim LL, Campain A, et al. Bevacizumab or dexamethasone implants for DME: 2-year results (The BEVORDEX Study). *Ophthalmology*. 2016;123:1399–1401.
30. Weih LM, Hassell JB, Keeffe J. Assessment of the impact of vision impairment. *Invest Ophthalmol Vis Sci*. 2002;43:927–935.
31. Linacre JM. Winsteps Rasch measurement program. Beaverton, Oregon; 2015. Available at: winsteps.com.
32. Andrich D. A rating formulation for ordered response categories. *Psychometrika*. 1978;43:561–573.

33. Wright B. Rack and stack: time 1 vs. time 2. *Rasch Measurement Transactions*. 2003;17:905–906.
34. Bressler NM, Chang TS, Suñer IJ, et al. Vision-related function after ranibizumab treatment by better- or worse-seeing eye: clinical trial results from MARINA and ANCHOR. *Ophthalmology*. 2010;117:747–756 e4.
35. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population. The Beaver Dam Eye Study. *Ophthalmology*. 1996; 103:1169–1178.
36. Rubin GS, Muñoz B, Bandeen-Roche K, West SK. Monocular versus binocular visual acuity as measures of vision impairment and predictors of visual disability. *Invest Ophthalmol Vis Sci*. 2000;41:3327–3334.
37. Garamendi E, Pesudovs K, Stevens MJ, Elliott DB. The Refractive Status and Vision Profile: evaluation of psychometric properties and comparison of Rasch and summated Likert-scaling. *Vision Res*. 2006;46:1375–1383.
38. Marella M, Pesudovs K, Keeffe JE, O'Connor PM, Rees G, Lamoureux EL. The psychometric validity of the NEI VFQ-25 for use in a low vision population. *Invest Ophthalmol Vis Sci*. 2010;5:2878–2884.
39. Pesudovs K, Gothwal VK, Wright T, Lamoureux EL. Remediating serious flaws in the National Eye Institute-Visual Function Questionnaire. *J Cataract Refract Surg*. 2010;36: 718–732.

Investigative Ophthalmology & Visual Science