Optimizing a New Patient-Reported Outcome Instrument for Proliferative Diabetic Retinopathy: A Psychometric Study

PCR166

Christopher Hartford, MPH,[1] Steven Sherman, MPH,[2] Aviva Gillman, MSc,[3] Sophie Cleanthous, PhD,[3] Jasmin Tinsley, BSc,[3] Stefan J. Cano, PhD,[3] Diana Rofail, PhD,[2] Diana V. Do, MD[4]
[1]Regeneron Pharmaceuticals, Inc., Sleepy Hollow, New York, USA; [2]Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA; [3]Modus Outcomes, a THREAD Company, London, UK; [4]Byers Eye Institute, Stanford University School of Medicine, Palo Alto, California, USA

BACKGROUND & PURPOSE

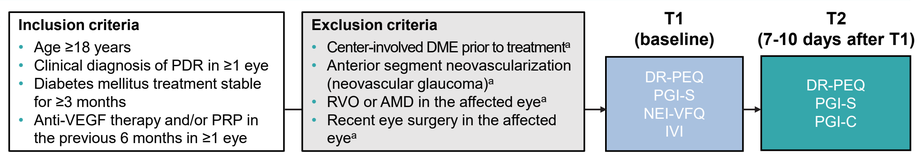
- Diabetic retinopathy (DR) is a major microvascular complication of diabetes and is a leading cause of vision loss[1,2]
- DR can have a profound impact on patient vision, daily functioning, quality of life (QoL), and independence[3,4]
- The DR-Patient Experience Questionnaire (DR-PEQ) is a patient-reported outcome (PRO) instrument developed with qualitative input directly from patients and ophthalmologists to assess the symptoms of disease worsening and the effect of treatment on a wide range of symptoms, functional aspects, and QoL in patients with proliferative DR (PDR)[5]
- The DR-PEQ was developed in line with US Food and Drug Administration guidance, which emphasizes incorporating the patient perspective into the development of PRO measures for use in clinical trials to capture treatment benefits that are meaningful and known only to the patient[6,7]
- This study aimed to psychometrically validate and refine the DR-PEQ (comprising 85 items, 4 domains, and 5 subscales)[5] to optimize the measurement of patient QoL and treatment outcomes in PDR

METHODS

- This was a noninterventional, cross-sectional psychometric validation study of the DR-PEQ instrument conducted between February-November 2024 (**Figure 1A**)
- Participants were from the US, aged ≥18 years with PDR treated with intravitreal anti–vascular endothelial growth factor (VEGF) therapy and/or pan-retinal photocoagulation (PRP) in the past 6 months
- Participants completed an online survey at 2 time-points: T1 (baseline) and T2 (7-10 days later)
  - At T1, participants completed the DR-PEQ, the Patient Global Impression of Severity (PGI-S) questionnaire, the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ) and the Impact of Vision Impairment (IVI)
  - At T2, these same participants completed the DR-PEQ and PGI-S for a second time, along with the Patient Global Impression of Change (PGI-C) (**Figure 1A and 1B**)
  - Global impression scales were used to anchor understanding of the impact of PDR on patients; NEI-VFQ and IVI were used as reference ophthalmology-specific QoL instruments
  - Psychometric analysis used Rasch Measurement Theory (RMT) and Classical Test Theory (CTT)

Figure 1. Study (A) Design and (B) Instruments

(A)



(B)

Instrument	Items (scales)	Response scales
DR-PEQ[5]	85 (5)	5-pt difficulty; 5-pt frequency
PGI-S[8,9]	1 (4)	5-pt difficulty; 4-pt frequency; 4-pt severity
NEI-VFQ[10]	25 (12)	6-pt difficulty; 5-pt severity; 5-pt frequency; 5-pt true to false
IVI[11]	28 (3)	4-pt frequency; additional for N/A (1-15)
PGI-C[8,9]	1 (3)	6-pt difficulty; 6-pt increased frequency; yes/no change

[a]If the participant had PDR in both eyes they were included in the study if ≥1 eye met the eligibility criteria and none of the exclusion criteria. If the participant had PDR in both eyes, the eye with worse BCVA was selected as the study eye. AMD, age-related macular degeneration; anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DME, diabetic macular edema; DR-PEQ, Diabetic Retinopathy–Patient Experience Questionnaire; IVI, Impact of Vision Impairment; N/A, not applicable; NEI-VFQ, National Eye Institute Visual Function Questionnaire; PDR, proliferative diabetic retinopathy; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; pt, point; RVO, retinal vein occlusion.

RESULTS

- A total of 217 patients with DR were recruited and participated in the study between March 2024 and November 2024
  - The DR-PEQ was completed by 217 participants at T1 and by 215 participants at T2
- Baseline demographics are shown in **Table 1**

Table 1. Baseline Demographics

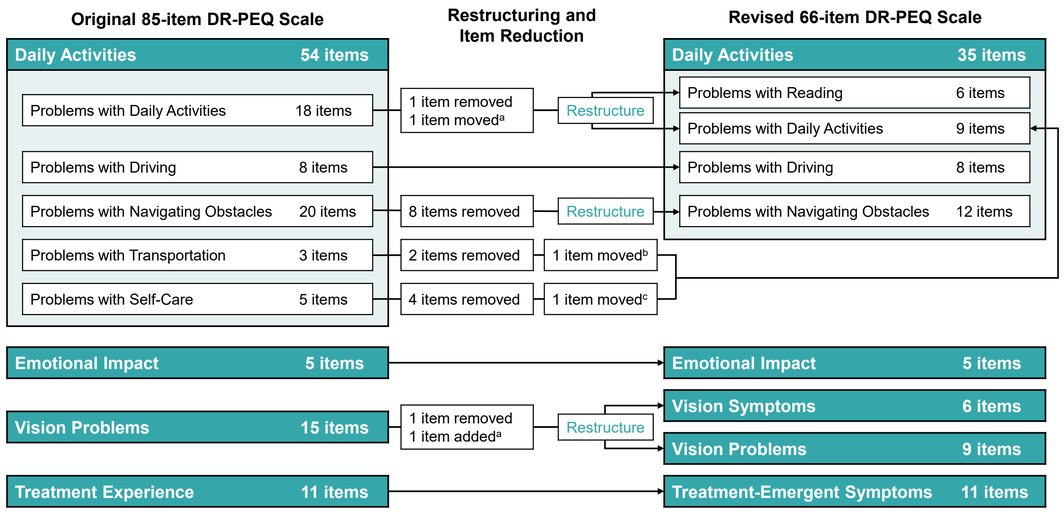
Participants (N=217)					
Demographics/health variables		**n (%)**	**Health variables**		**n (%)**
Sex[a]	Male Female	107 (49.3) 106 (48.8)	**PDR**[b]	Unilateral Bilateral	208 (95.9) 9 (4.1)
Age group (years)[a]	18-34 35-54 55-74 ≥75	23 (10.6) 61 (28.1) 104 (47.9) 29 (13.4)	**Time since PDR diagnosis (years)**[b]	<1 ≥1-2 ≥3-4 ≥5-6 ≥7	8 (3.7) 95 (43.8) 44 (20.3) 45 (20.7) 25 (11.5)
Race/ethnicity[a]	White/Caucasian Black/African Am. Am. Indian/Alaskan Native Native Hawaiian/Pacific Isl. Asian Am. Biracial Hispanic/Latino	100 (46.1) 44 (20.3) 16 (7.4) 15 (6.9) 6 (2.8) 1 (0.5) 46 (21.2)	**Time since treatment**[b]	>1 week to <1 month[c] ≥1-3 months ≥4-6 months >6 months[d]	113 (52.1) 41 (18.9) 60 (27.6) 3 (1.4)
Employment[a]	Full-time Part-time Retired Disabled Student Homemaker Prefer not to answer	8 (3.7) 66 (30.4) 86 (39.6) 8 (3.7) 3 (1.4) 40 (18.4) 6 (2.8)	**Self-reported general health**[b]	Excellent Very good Good Fair Poor Prefer not to answer	0 (0) 4 (1.8) 27 (12.4) 98 (45.2) 51 (23.5) 37 (17.1)
BCVA (PDR eye)[b]	≥20/40 >20/40 to ≥20/100 <20/100 to ≥20/200 <20/200 to ≥20/400 <20/400	36 (16.6) 71 (32.7) 14 (6.5) 79 (36.4) 17 (7.8)	**Most recent treatment**[b]	**Anti-VEGF** Aflibercept Ranibizumab Bevacizumab Faricimab Brolucizumab	 54 (24.0) 41 (18.2) 13 (5.8) 7 (3.1) 1 (0.4)
Treatment type[b]	Anti-VEGF PRP Both	87 (40.1) 105 (48.4) 25 (11.5)		**PRP** <1200 PRP spots >1200 PRP spots	 42 (18.7) 58 (25.8)

Not all categories shown. [a]Collected by phone during the screening interview. [b]Patient-reported data collected in the DHIF (after screening). [c]Discrepancy of most recent treatment due to time lag between screening and DHIF completion. Most participants did not complete the survey immediately after screening. A 1-2–week gap could be the difference between 2 categories in this variable, e.g., if a participant had received treatment 3.5 weeks prior to the survey at time of screening. [d]The date of the most recent treatment was collected twice, once at screening and once in the DHIF during the survey. All participants had received their most recent treatment within the 6 months prior to screening, however 3 participants provided dates >6 months ago in the DHIF. They were not removed from the analysis.
Am., American; anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; DHIF, Demographic and Health Information Form; Isl., islander; PDR, proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation.

Analysis and Restructuring of the Original DR-PEQ

- The 4 domains of the original 85-item DR-PEQ and areas for psychometric improvement are shown in **Figure 2**
  - Initial RMT findings indicated good to excellent targeting across most scales, good reliability, and minimal DIF (**Table 2**)
  - Convergent validity analyses displayed strong correlations both within the DR-PEQ scales and the corresponding PGI-S item, and between the DR-PEQ scales and NEI-VFQ and IVI measures
  - Several domains, however, showed unclear item hierarchies and item dependencies
    - The Problems with Transportation and Problems with Self-Care domains exhibited conceptual overlap with Problems with Daily Activities. Additionally, Problems with Self-Care exhibited high ceiling effects and Problems with Transportation exhibited poor discrimination (**Table 2**)
  - This prompted restructuring to improve scale precision and conceptual clarity, including the creation of the Problems with Reading domain. Items from Problems with Transportation and Problems with Self-Care were either merged into other domains or removed entirely to streamline and enhance clarity (**Figure 2**)
- The RMT and CTT analyses resulted in the removal of 19 items from the original 85-item DR-PEQ and scale reordering (**Figure 2**)
  - Items recommended for removal were cross-checked against the original concept elicitation and cognitive debriefing data to ensure that nothing of importance to patients with PDR was removed[4,5]

Figure 2. Revision of the Original DR-PEQ



[a]1 item (Recognizing faces) was removed from Problems with Daily Activities and added to the new Vision Problems scale. [b]1 item (Problems using Transportation) was removed from Problems with Transportation and added to the new Problems with Daily Activities subscale. [c]1 item (Organizing Medication) was removed from Problems with Self-Care and added to the new Problems with Daily Activities scale.

RMT and CTT Analyses of the Revised DR-PEQ

- Summary RMT and CTT analyses are shown in **Table 2**
  - The revised DR-PEQ demonstrated good targeting (5 scales; items appropriate for 86%-99% of participants), cohesive scales (matching expected and observed scores; 0%-6% item misfit), clear item hierarchy, and high reliability with or without extremes (0.91-0.98 or 0.89-0.98)
  - All revised scales displayed good evidence for scaling assumptions (corrected item-total correlation [CITC] range ≥0.30), targeting, unidimensionality, and reliability
  - The minimum CITCs were higher for the revised versus original Daily Activities scale, and at least as high for all other revised scales apart from Vision Symptoms
  - Floor and ceiling effects were minimal for all scales apart from Problems with Driving (19.4% and 6%, respectively)
  - CTT results also showed good discrimination between groups of disease severity (all differences $P<0.001$), BCVA (differences $P\leq0.003$), age (differences $P<0.001$ except for treatment experience, $P=0.078$), and general health (differences $P\leq0.005$) (data not shown)

Table 2. Summary RMT and CTT Analyses of the Original and Revised DR-PEQ Scales and Subscales of A) Daily Activities, and B) Emotional Impact, Vision Problems, and Treatment-Emergent Symptoms

(A)

Property	Daily Activities (overall)	Problems with Daily Activities (restructured)	Problems with Reading (new)	Problems with Driving	Problems Navigating Obstacles (restructured)	Problems with Transportation (removed)	Problems with Self-Care (removed)
RMT Analyses							
Targeting[a] **(% coverage)**	Excellent (99% → no change)	Excellent → very good (97% → 89%)	Excellent (97%)	Excellent (100% → no change)	Very good (89% → no change)	Excellent (100%; mean –1.71)	Sub-optimal (61%; mean –4.90)
Item misfit[b]	12 items (22%) → 6 items (17%)	7 items (39%) → 1 item (11%)	No item misfit	0% → no change	8 items (40%) → 5 items (42%)	2 items (67%)	1 item (20%)
Item dependency[c]	102 pairs (7%) → 51 pairs (9%)	5 pairs (28%) → no dependency	No dependency	4 pairs (14%) → no change	12 pairs (6%) → 3 pairs (5%)	1 pair (33%)	0 pairs (0%)
Item hierarchy[d]	Unclear → clearer	Unclear → clear	Clear	Clear → no change	Unclear → clearer	Unclear	Unclear
Reliability (PSI)[e]	0.98/0.99 → 0.98/0.98	0.97/0.97 → 0.93/0.92	0.92/0.92	0.93/0.93 → no change	0.96/0.97 → 0.94/0.95	0.52/0.68	0.90/0.87
DIF[f]	3 items → 5 items (age, BCVA)	4 items → no DIF	4 items (age, BCVA)	1 item → no change (age)	2 items → 5 items (age, BCVA)	No DIF	No DIF
CTT Analyses							
CITC[g]	0.50-0.93 → 0.72-0.93	0.71-0.94 → 0.72-0.94	0.74-0.86	0.86-0.95 → no change	0.67-0.93 → 0.68-0.90	0.96-0.98	0.62-0.90
Skewness[h]	0.48 → no change	0.45 → 0.87	–0.04	0.13 → no change	0.45 → no change	0.65	0.98
Floor[i]	0% → no change	0.9% → 0.5%	0%	19.3% → no change	0% → no change	9.2%	0%
Ceiling[i]	0.5% → no change	2.8% → 13.8%	2.8%	6% → no change	6.2% → 6.9%	25.3%	38.2%
PCA factor 1 loadings[j]	0.52-0.93 → 0.73-0.93	0.75-0.95 → 0.84-0.96	0.82-0.90	0.90-0.96 → no change	0.70-0.94 → 0.72-0.92	0.98-0.99	0.73-0.94
Cronbach's alpha[k]	0.99 → 0.99	0.98 → 0.97	0.93	0.98→ no change	0.98 → 0.97	0.99	0.93
ICC (no change)[l]	0.89 → 0.91	0.91 → 0.83	0.95	0.94 → no change	0.93 → no change	0.94	0.94

(B)

Property	Emotional Impact	Vision Problems (restructured)	Vision Symptoms (new)	Treatment Experience/Treatment-Emergent Symptoms
RMT Analyses				
Targeting[a] **(% coverage)**	Good (86%) → no change	Excellent (99%) → no change	Excellent (96%)	Good (92%) → no change
Item misfit[b]	1 item (20%) → no change	1 item (7%) → 1 item (11%)	No item misfit	No item misfit → no change
Item dependency[c]	1 pair (10%) → no change	2 pairs (2%) → no dependency	No dependency	1 pair (2%) → no change
Item hierarchy[d]	Unclear → no change	Unclear → clearer	Clear	Unclear → no change
Reliability (PSI)[e]	0.91/0.89 → no change	0.96/0.96 → 0.93/0.93	0.93/0.93	0.91/0.91 → no change
DIF[f]	No DIF → no change	No DIF → no change	No DIF	1 item (diabetes type) → no change
CTT Analyses				
CITC[g]	0.80-0.86 → no change	0.65-0.83 → 0.66-0.81	0.64-0.75	0.71-0.78 → no change
Skewness[h]	0.35 → no change	0.11 → 0.04	0.30	0.93 → no change
Floor[i]	2.3% → no change	0% → no change	0.9%	0% → no change
Ceiling[i]	11.5% → no change	0.5% → 0.9%	3.2%	4.6% → no change
PCA factor 1 loadings[j]	0.87-0.92 → no change	0.70-0.86 → 0.73-0.86	0.85-0.91	0.76-0.82 → no change
Cronbach's alpha[k]	0.94 → no change	0.96 → 0.94	0.95	0.94 → no change
ICC (no change)[l]	0.89 → no change	0.92 → 0.90	0.92	0.80 → no change

"No change" denotes no change in values from the original DR-PEQ to the revised DR-PEQ; "→" denotes the change from original to revised DR-PEQ; "new" denotes scale added to the revised DR-PEQ, and "removed" denotes original DR-PEQ scale removed in the revised DR-PEQ. Amber shading denotes improvement from the original to revised DR-PEQ, blue shading denotes scales that were merged or removed. [a]Estimated using the percentage of individual sample measurements covered by the scale range (higher percentages denote better outcomes). [b]Estimated on the basis of the percentage of items with fit residuals outside recommended range of −2.5 to 2.5. [c]Estimated on the percentage of item pairs that are locally dependent based on >0.3 residual correlations indicating >9% shared variance (higher percentages denote worse outcomes). [d]Based on whether the relative item location denotes a hierarchy between the items relative to the construct under measurement. [e]PSI was reported on a scale from 0 to 1; 0=all error; 1=no error. [f]Presence of DIF indicates a significant difference between how one group responds to an item compared with another with the same person ability. [g]CITC ≥0.30 demonstrate supportive evidence of scaling assumption. [h]Skewness statistic should range from –1 to +1; numbers outside this range indicate skewness. [i]Floor and ceiling percentages should be <15%; higher values indicate targeting issues. [j]PCA factor loadings are expected to be >0.30 to support unidimensionality. [k]Cronbach`s alpha >0.70 indicates good reliability. [l]ICC >0.70 indicates good test-retest reliability. DIF, differential item functioning; ICC, intraclass correlation coefficient; PCA, Principal Component Analysis; PSI, person separation index.

LIMITATIONS

- Recruitment of a predominantly White sample, under-recruitment of bilateral PDR cases relative to the protocol target, and inclusion of only participants with online access to complete the surveys all may limit the generalizability of findings to the broader PDR population
- The refined DR-PEQ could need further reduction of items to reduce the patient burden (average completion 12 min 32 sec at T1)

CONCLUSIONS

- The refined DR-PEQ exhibits strong psychometric properties, potentially supporting its use as a reliable, valid, and comprehensive tool for assessing the patient experience of PDR-related symptoms and impacts on QoL, and facilitating meaningful evaluation of patient QoL and treatment benefits
- The modular design of the DR-PEQ also allows for targeted assessment of domains most relevant to investigators' research questions

REFERENCES

1. Faselis C et al. *Curr Vasc Pharmacol*. 2020;18:117–124.
2. World Health Organization. World report on vision. 2019. https://www.who.int/publications/i/item/world-report-on-vision. Accessed September 24, 2025.
3. Fenwick EK et al. *Br J Ophthalmol*. 2018;102:948–953.
4. Sherman SA et al. *Ophthalmol Ther*. 2023;12(1):431–446.
5. Rofail D et al. *Adv Ther*. 2023;40(4):1773–1786.
6. US Food & Drug Administration. Guidance for Industry: Patient-reported outcome measures: Use in medical product development to support labeling claims. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims. Accessed September 25, 2025.
7. US Food and Drug Administration. Patient-focused drug development: selecting, developing, or modifying fit-for-purpose clinical outcome assessments. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome. Accessed September 25, 2025.
8. Hurst H, Bolton J. *J Manipulative Physiol Ther*. 2004;27(1):26–35.
9. Viktrup L et al. *BMC Urol*. 2012;12:30.
10. Mangione CM et al. *Arch Ophthalmol*. 2001;119:1050–1058.
11. Weih LM et al. *Invest Ophthalmol Vis Sci*. 2002;43:927–935.

ACKNOWLEDGMENTS & DISCLOSURES

- Christopher Hartford and Steven Sherman are employees of and stockholders in Regeneron Pharmaceuticals, Inc. Diana Rofail is an employee of and stockholder in Regeneron Pharmaceuticals, Inc., and holds stock in Roche. Aviva Gillman was an employee of Modus Outcomes, a THREAD Company, at the time of this analysis. Sophie Cleanthous, Jasmin Tinsley, and Stefan J. Cano are employees of Modus Outcomes, a THREAD Company. Diana V. Do is a consultant to Boehringer Ingelheim, Genentech, Kodiak Sciences, Kriya, and Regeneron Pharmaceuticals, Inc.; has received research funding from Boehringer Ingelheim, Genentech, Kriya, and Regeneron Pharmaceuticals, Inc.; and has stock options from Kodiak Sciences
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, New York). The sponsor participated in the design and conduct of the study, analysis, of the data, and preparation of this presentation
- Writing assistance was provided by Kelly Bryant, PhD, of Core (a division of Prime, London, UK), funded by Regeneron Pharmaceuticals, Inc. according to Good Publication Practice guidelines

Poster presented by Christopher Hartford, MPH, email: christopher.hartford@regeneron.com, at ISPOR Europe 2025, November 9-12, 2025, Glasgow, Scotland