Quality of life in patients with CRB1-associated retinal dystrophies: a longitudinal study

Karuntu, J.S.; Nguyen, X.T.A.; Talib, M.; Schooneveld, M.J. van; Wijnholds, J.; Genderen, M.M. van; ... ; Boon, C.J.F.

Received: 22 May 2023 | Accepted: 30 August 2023

DOI: 10.1111/aos.15769

Acta Ophthalmologica

ORIGINAL ARTICLE

Quality of life in patients with *CRB1*-associated retinal dystrophies: A longitudinal study

Jessica S. Karuntu[1] | **Xuan-Thanh-An Nguyen**[1] | **Mays Talib**[1] | **Mary J. van Schooneveld**[2] | **Jan Wijnholds**[1,3] | **Maria M. van Genderen**[4,5] | **Nicoline E. Schalij-Delfos**[1] | **Caroline C. W. Klaver**[6,7,8,9] | **Magda A. Meester-Smoor**[6] | **L. Ingeborgh van den Born**[11] | **Carel B. Hoyng**[8] | **Alberta A. H. J. Thiadens**[6] | **Arthur A. Bergen**[10] | **Ruth M. A. van Nispen**[12] | **Camiel J. F. Boon**[1,2]

[1]Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Ophthalmology, Amsterdam UMC, Academic Medical Center, Amsterdam, The Netherlands
[3]The Netherlands Institute for Neuroscience (NIN-KNAW), Amsterdam, The Netherlands
[4]Bartiméus, Diagnostic Centre for complex visual disorders, Zeist, The Netherlands
[5]Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, The Netherlands
[6]Department of Ophthalmology, Erasmus Medical Center, Rotterdam, The Netherlands
[7]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
[8]Department of Ophthalmology, Radboud University Medical Center, Nijmegen, The Netherlands
[9]Institute for Molecular and Clinical Ophthalmology, Basel, Switzerland
[10]Department of Clinical Genetics, Amsterdam UMC, Academic Medical Center, Amsterdam, The Netherlands
[11]Rotterdam Eye Hospital, Rotterdam, The Netherlands
[12]Department of Ophthalmology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

Correspondence
Camiel J. F. Boon, Department of Ophthalmology, Amsterdam University Medical Centers, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: camiel.boon@amsterdamumc.nl

Funding information
Bontius Stichting; Curing Retinal Blindness Foundation; Stichting Blindenhulp; Stichting Retina Fonds; Stichting Steunfonds Uitzicht, Grant/Award Number: UZ2021-03

Abstract

Purpose: To assess the longitudinal vision-related quality of life among patients with *CRB1*-associated inherited retinal dystrophies.

Methods: In this longitudinal questionnaire study, the National Eye Institute Visual Function Questionnaire (39 items, NEI VFQ-39) was applied at baseline, two-year follow-up, and 4-year follow-up in patients with pathogenic *CRB1* variants. [Correction added on 20 November 2023, after first online publication: The preceding sentence has been updated in this version.] Classical test theory was performed to obtain subdomain scores and in particular 'near activities' and 'total composite' scores. The Rasch analysis based on previous calibrations of the NEI VFQ-25 was applied to create visual functioning and socio-emotional subscales.

Results: In total, 22 patients with a *CRB1*-associated retinal dystrophy were included, […] with a median age of 25.0 years (interquartile range: 13–31 years) at baseline and mean follow-up of 4.0 ± 0.3 years. [Correction added on 20 November 2023, after first online publication: The preceding sentence has been updated in this version.] A significant decline at 4 years was observed for 'near activities' (51.0 ± 23.8 vs 35.4 ± 14.7, $p = 0.004$) and 'total composite' (63.0 ± 13.1 vs 52.0 ± 12.1, $p = 0.001$) subdomain scores. For the Rasch-scaled scores, the 'visual functioning' scale significantly decreased after 2 years (−0.89 logits; $p = 0.012$), but not at 4-year follow-up (+0.01 logits; $p = 0.975$). [Correction added on 20 November 2023, after first online publication: In the preceding sentence, "…after 4 years…" has been corrected to "…after 2 years…" in this version.] The

Jessica S. Karuntu and Xuan-Thanh-An Nguyen shared first authors.

'socio-emotional' scale also showed a significant decline after 2 years (−0.78 logits, $p=0.033$) and 4 years (−0.83 logits, $p=0.021$).
Conclusion: In the absence of an intervention, a decline in vision-related quality of life is present in patients with pathogenic *CRB1* variants at 4-year follow-up. Patient-reported outcome measures should be included in future clinical trials, as they can be a potential indicator of disease progression and treatment efficacy.

KEYWORDS
CRB1, inherited retinal dystrophy, National Eye Institute Visual Function Questionnaire, patient-reported outcome measure, quality of life

1 | INTRODUCTION

Inherited retinal dystrophies (IRDs) are a spectrum of hereditary degenerations of the retina, which can result in photoreceptor loss. Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) are among the more severe phenotypes within IRDs. LCA usually presents within the first year of life with nystagmus, severe visual impairment, and (nearly) non-detectable responses on electroretinography. RP is caused by a degeneration of photoreceptors, initially rod photoreceptors followed by cone photoreceptors. Accordingly, patients suffer from reduced night vision and progressive loss of the peripheral visual field. As cone photoreceptors deteriorate and macular function is lost in later stages, patients notice a loss of visual acuity, limited contrast sensitivity, and loss of colour discrimination. Both LCA and RP patients are significantly affected by their IRD in daily life and substantially limited in their everyday activities.

LCA and RP can both be caused by relatively common pathogenic variants in the crumbs cell polarity complex component 1 (*CRB1*) gene. Studies have shown that patients with *CRB1*-associated IRD are likely to be classified as having low vision by the median age of 18 years and being blind by the median age of 40 years (Talib et al., 2017; Talib et al., 2021a). With the current advances in gene augmentation research and the advent of gene therapy for LCA caused by mutations in *RPE65* (Maguire et al., 2021), treatment for *CRB1*-associated IRDs seems feasible. Experiments in mice and retinal organoids using adeno-associated viral vectors for *CRB1-CRB2* have shown encouraging results to facilitate upcoming gene therapy trials for *CRB1*-associated IRDs. Such trials require sensitive and clinically relevant outcomes, which have been identified using retrospective studies and a prospective natural history study. The latter has described the progression and course of *CRB1*-associated IRDs based on ophthalmological examinations including visual acuity, perimetry, microperimetry, full-field stimulus threshold (FST) testing, and multimodal imaging (Nguyen et al., 2021; Talib et al., 2021b).

These clinical measurements are useful for detecting possible treatment effects, but do not reflect patient experiences in their daily life and activities. For instance, patients may have an improved visual acuity on psychophysical measurements without a meaningful treatment effect from a patient's perspective. Additionally, clinical measurements are often variable and fail to address daily obstacles associated with the retinal dystrophy.

Assessing patient context and quality of life is a critical part of treatment evaluation, but has been relatively scarcely addressed in therapeutic trials for IRDs to date. Without proper measurements for patient experiences, clinical trials may fail in capturing the most meaningful outcome. Patient-reported outcome measures (PROMs) are recognised and encouraged by the US Food and Drug Administration (FDA) as clinical trial outcome measures (Research et al., 2006; Varma et al., 2010). An IRD PROM should ideally be based on patient input and should be reliable, validated, and able to detect changes, before it can be used for clinical trials. The National Eye Institute developed a 25-item questionnaire called the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), which assesses difficulties with visual activities and condition-specific symptoms for a wide range of chronic eye diseases (Mangione et al., 2001). Fourteen additional items were added in an appendix to enhance the reliability of the various domains and resulted in the NEI VFQ-39 (Clemons et al., 2003).

The NEI VFQ-25 and NEI VFQ-39 are well-established questionnaires that focus on different domains specific to a patient's day-to-day functioning and well-being (Mangione et al., 2001). Thus far, several clinical gene therapy trials have used the NEI VFQ-25 as PROM (Dimopoulos et al., 2018; Russell et al., 2017; Weleber et al., 2016). However, these questionnaires do not meet the requirements of the FDA for a PROM as they are not specifically developed for IRD patients. Moreover, the analysis of the NEI VFQs is flawed according to current methodology standards, as it is based on classical test theory, which assumes equal difficulty per question (Khadka et al., 2012; Marella et al., 2010; Stelmack et al., 2002). Instead, expert consensus suggests using questionnaires based on item response theory, such as the Rasch analysis, which is based on the notion that some questions are more difficult than other questions and which enables estimates from ordinal responses on an invariant scale (Boone, 2016). One method to maintain the use of the NEI VFQ is to apply the Rasch analysis to calibrate item measures to an invariant scale as was done by Goldstein et al. (2022).

The present study reports on the physical and social functioning and well-being of patients with a

CRB1-associated IRD based on the NEI VFQ-39 over the course of 4 years in order to provide an insight into the quality of life using the pre-calibrated item measures of the NEI VFQ to meet current psychometric standards.

2 | METHODS

2.1 | Subjects

Participants were recruited from the RD5000 database, a Dutch registry of patients with IRDs (van Huet et al., 2014), and from the Delleman archive for inherited ophthalmic disorders at Amsterdam University Medical Centers. This study is part of a larger cohort study, which investigated the natural history of *CRB1*-associated IRDs (Nguyen et al., 2021; Talib et al., 2021b). As such, inclusion criteria have been described earlier, but shortly include the following: (1) biallelic pathogenic variants in the *CRB1* gene and (2) a Snellen best-corrected visual acuity (BCVA) of 1.3 logMAR (equivalent to 20/400) in the better-seeing eye (Talib et al., 2021b). Initially, 22 patients were included of which 10 patients originated from a Dutch genetic isolate that has been previously described (van den Born et al., 1994). This study adhered to the tenets of the Declaration of Helsinki and has obtained approval from the Erasmus Medical Center Medical Ethics Committee and from the Leiden University Medical Center Ethics Review Board. Informed consent was given by all patients and obtained from their caretakers if applicable.

2.2 | Clinical assessment

For this study, we focused on BCVA, microperimetry, and the NEI VFQ-39 (Nguyen et al., 2021; Talib et al., 2021b). Refraction and BCVA were determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts. BCVA was initially noted in decimal as is common in the Netherlands and later converted to logMAR values. Microperimetry was used to determine mesopic macular sensitivity with the Macular Integrity Assessment System (MAIA, CenterVue) and a standard 37-stimuli grid. The follow-up function was used at every follow-up visit. Some patients were not able to complete all measurements due to young age. All patients were asked to complete the NEI VFQ-39 before each visit at baseline, at the two-year follow-up, and at the 4-year follow-up. During the second follow-up, the questionnaire was not completed by two patients due to their young age, and during the final follow-up, one questionnaire was not completed by one elderly patient due to the COVID-19 pandemic.

2.3 | NEI VFQ-39 questionnaire

The NEI VFQ-39 is a 25-item questionnaire with 14 supplemental items and consists of the following subdomains: 'general health', 'general vision', 'ocular pain', 'near activities', 'distance activities', 'social functioning', 'mental health', 'role differentiation', 'dependency', 'colour vision', and 'peripheral vision'. The addition of 14 supplemental items provides more information on specific subdomains, making it a more robust questionnaire. Per classical test theory, composite scores for each domain of the NEI VFQ-39 were calculated as the sum of all items for each patient at each time point, resulting in separate scores per subdomain, and a total composite score which was calculated as an average of all subdomain scores (excluding 'general health'). A higher score reflects a better quality of life relating to that specific subdomain. The subdomain scores range from 0 to 100 units. Of specific interest were the subdomain 'near activities' and total composite score for the other analyses.

2.4 | Modification and calibration of item measures of the NEI VFQ-25

The NEI VFQ-25 is a well-known and often-used questionnaire; however, it also has inherent problems with multidimensionality, item fit validity, and differential item functioning (Khadka et al., 2012; Marella et al., 2010; Stelmack et al., 2002). To resolve these problems and to bypass the Rasch analysis on this small test sample, Goldstein et al. suggested using modified versions and calibrated item measures (Goldstein et al., 2022). In brief, the NEI VFQ-25 was modified to two separate questionnaires: NEI VFQ-VF and NEI VFQ-SE, focusing on visual function and on socio-emotional functioning, respectively. A third modification led to the NEI VFQ-25C, which excludes general health and eyesight quality and serves as an overall measure. Goldstein et al. combined the data of 3342 patients with retinal diseases (mostly age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion) into a single data set, which was used for the Rasch analysis and the method of successive dichotomisation to estimate person and item measures. For this study, the calibrated item measures based on the NEI VFQ-25 provided by Goldstein et al. were used to estimate person measures ranging from −3 to +3, which translate to low and high perceived visual function, respectively (Goldstein et al., 2022). There are currently no calibrated item measures for the NEI VFQ-39 available.

2.5 | Statistical analysis

Data were analysed in SPSS (version 25.0.0; IBM Corp) and in R software using the R package 'msd'. Normal-distributed data are presented as mean ± standard deviation (SD), and non-normal-distributed data are presented as median and interquartile range (IQR). Changes in scores were assessed using a linear mixed model. *p*-Values of ≤0.05 were considered statistically significant, unless *p*-values were corrected for multiple testing.

3 | RESULTS

3.1 | Baseline measurements

We identified 22 patients with a *CRB1*-associated IRD. Most patients ($n=20$; 90%) had (early-onset) RP, followed by cone-rod dystrophy ($n=1$; 5%) and macular dystrophy ($n=1$; 5%). Study participants ranged in age at first visit from 6 to 74 years, with a median age of 25.0 years (IQR: 13.0–31.0 years) (Table 1). At the time of the first visit, the estimated mean disease duration was 19.0 ± 10.6 years based on the age of the first symptoms. Median BCVA was relatively low with 1.0 logMAR (0.6–1.2 logMAR), equivalent to 20/200 Snellen. Retinal sensitivity on mesopic microperimetry was performed on 13 patients at baseline with median sensitivity of 6.9 dB (2.7–12.8 dB). At baseline measurement, the NEI VFQ-39 was not completed by six patients, due to a variety of reasons including young age ($n=3$), incomplete questionnaire ($n=2$), and the development of acute glaucoma after topical use of mydriatics ($n=1$).

TABLE 1 Baseline characteristics of patients with *CRB1*-associated retinal dystrophies included in this study.

Baseline characteristics	Number (%) or median (IQR)
Gender	
Male	13 (41%)
Female	9 (59%)
Age at first visit	25.0 (13.0–31.0 years)
Follow-up time	4.0 ± 0.3 years
IRD diagnosis	
(Early-onset) RP	20 (90%)
Cone-rod dystrophy	1 (5%)
Macular dystrophy	1 (5%)
Estimated duration of disease at the time of first visit	19.0 ± 10.6 years
Part of genetic isolate	
Yes	10 (45%)
No	12 (55%)
logBCVA ODS	1.0 logMAR (0.6–1.2 logMAR)
Retinal sensitivity on microperimetry[a]	6.9 dB (2.7–12.8 dB)

Abbreviations: IRD, inherited retinal dystrophy; logMAR, logarithm of the minimum angle of resolution; RP, retinitis pigmentosa.

[a]$n=13$, 3 missing at baseline.

3.2 | Follow-up after 2 and 4 years

Disease progression in patients was evaluated on a biennial basis up to 4 years (4.0 ± 0.3 years) with mean follow-up times of 2.0 ± 0.1 years and 2.0 ± 0.3 years between the first two and the last two visits, respectively. At 2 years, the median BCVA of both eyes at 0.9 logMAR (0.6–1.1 logMAR; i.e. 20/160 Snellen) did not significantly differ from baseline ($p=0.069$), whereas at 4 years; median BCVA (1.1 logMAR; IQR: 0.8–1.3; i.e. 20/240 Snellen) significantly decreased compared to baseline ($p=0.003$). Microperimetry was performed on 20 patients during the 2-year follow-up with two patients being too young to perform reliably. During the 4-year follow-up, microperimetry was performed on 19 patients with one patient being too young and two patients being unable to visit the hospital due to the COVID-19 pandemic. Median retinal sensitivity changed significantly from baseline over 2 and 4 years, from 6.9 dB (2.7–12.8 dB) to 4.3 dB (1.4–9.9 dB, $p=0.001$) and 3.7 dB (0.0–7.9 dB, $p=0.004$), respectively.

3.3 | Composite scores NEI VFQ

Individual questions on the NEI VFQ were clustered into the following generally accepted domains: 'general health', 'general vision', 'ocular pain', 'near activities', 'distance activities', 'social functioning', 'mental health', 'role differentiation', 'dependency', 'colour vision', and 'peripheral vision'. Finally, a final score was produced by compressing all domain scores into one score 'total composite score' (Table S1). Overall, there was a downward trend in most domains from baseline until final visit, especially those that relate best to IRD symptoms, such as 'general vision', 'near and distance activities', and 'peripheral vision' (Figure 1). However, after correction for multiple testing, none of these downward trends was statistically significant. The other domains remained stable over 4 years.

3.4 | Relationship between BCVA and microperimetry vs. scores for near activities (V_{NA}) and total score (V_{TOT})

We were interested in studying the relationship between the scores on the VFQ-39, for near activities (V_{NA}) and total score (V_{TOT}), and functional measurements of BCVA and macular sensitivity on microperimetry. Using a linear mixed model, we found significant positive relationships between BCVA and the composite score for 'near activities' (V_{NA}), where every 0.002 increase in visual acuity ($p=0.004$) and every 0.086 dB increase in microperimetry ($p=0.002$) resulted in a unit increase in V_{NA} (Figure 2a,b). In addition, with every 0.002 increase in visual acuity ($p=0.008$) and every 0.095 dB on microperimetry ($p=0.0003$), total composite score (V_{TOT}) increases one unit (Figure 2c,d).

3.5 | Inter-visit progression

Overall progression was determined by comparing baseline measurements with the measurements taken at the final visit, revealing a significant drop in score of 15 units in V_{NA} ($p=0.005$) and of 10 units in V_{TOT} ($p=0.001$). Interestingly, these declines appear to occur between the first and second visits, with V_{NA} decreasing with 13 points after the first 2 years ($p=0.008$) and V_{TOT} with nine points ($p=0.004$). There was no significant decrease

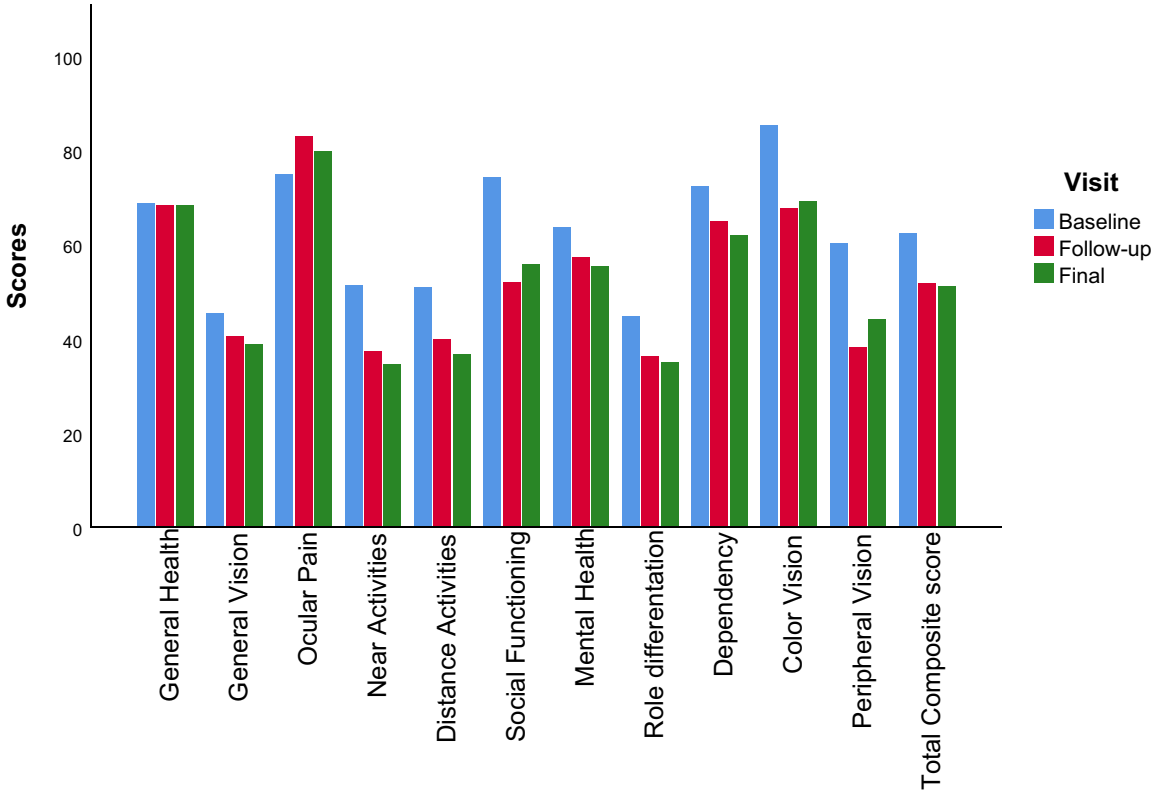

FIGURE 1 Bar chart demonstrating the different subdomains of the National Eye Institute Visual Function Questionnaire and the mean scores given by patients with *CRB1*-associated retinal dystrophies at each visit.

in V_{NA} and V_{TOT} between the 2-year follow-up and 4-year follow-up, $p=0.684$ and $p=0.626$, respectively.

3.6 | MSD person measures

The calibrated item measures were developed specifically for the VFQ-25, and using these, we found a mean±SD person measure of 0.428±0.360 logit. The calculated person measures were plotted against their standard errors of the person measure (Figure S1). Extreme person measures, that is greater visual function, generally demonstrate lower precision, that is higher standard errors. Like the authors of the original paper, we also found a slight increase in standard error for higher person measures when using the calibrated item measures (Goldstein et al., 2022). Figure 3 plots the estimated person measures against the NEI VFQ-25 composite scores, demonstrating a near-linear relationship with a correlation of $R^2=0.905$. This indicates that the visual ability of a patient, as estimated with the person measures, is well-described by the composite scores of the NEI VFQ-25.

3.7 | Quality of life based on visual function and socio-emotional impact

Goldstein et al. suggested domain-specific versions for the NEI VFQ-25 based on visual function, NEI VFQ-VF, and on socio-emotional impact, NEI VFQ-SE. We investigated the quality of life based on three modified versions of the NEI VFQ-25. Overall quality of life based on the VFQ-25C score declined significantly after two (−0.756; $p=0.006$) and 4 years (−0.839; $p=0.002$) after baseline. Visual function as measured with VFQ-VF was significantly decreased after 2 years (−0.889; $p=0.012$), although this decrease did not reach statistical significance over 4 years (0.010; $p=0.975$). Scores on the socio-emotional domain as determined by the NEI VFQ-SE were also significantly lower after two (−0.776; $p=0.033$) and 4 years (−0.831; $p=0.021$).

4 | DISCUSSION

In this study, we investigated the quality of life in patients with *CRB1*-associated retinal dystrophies based on the NEI VFQ-25 questionnaire and its appendix, and compared it to the functional measures BCVA and retinal sensitivity on microperimetry. Currently, many research groups are developing therapies for retinal dystrophies, including RP (Botto et al., 2022; Schneider et al., 2022). Many of the functional outcome measures assessed in these studies may not reflect a patient's experience. Thus, PROMs are becoming increasingly important outcome measures. Being able to reliably assess key quality of life aspects in RP patients and correlating this knowledge to the disease course may help in the design of future clinical trials.

Similar to previous RP studies, our patient cohort showed a significant general decline in quality of life over the course of 4 years (Altinbay & Taskin, 2021; Levinson et al., 2017; Sugawara et al., 2010). Furthermore, we found a strong correlation between the deterioration of BCVA and macular sensitivity, and a decreasing total quality of life score (V_{TOT}). More

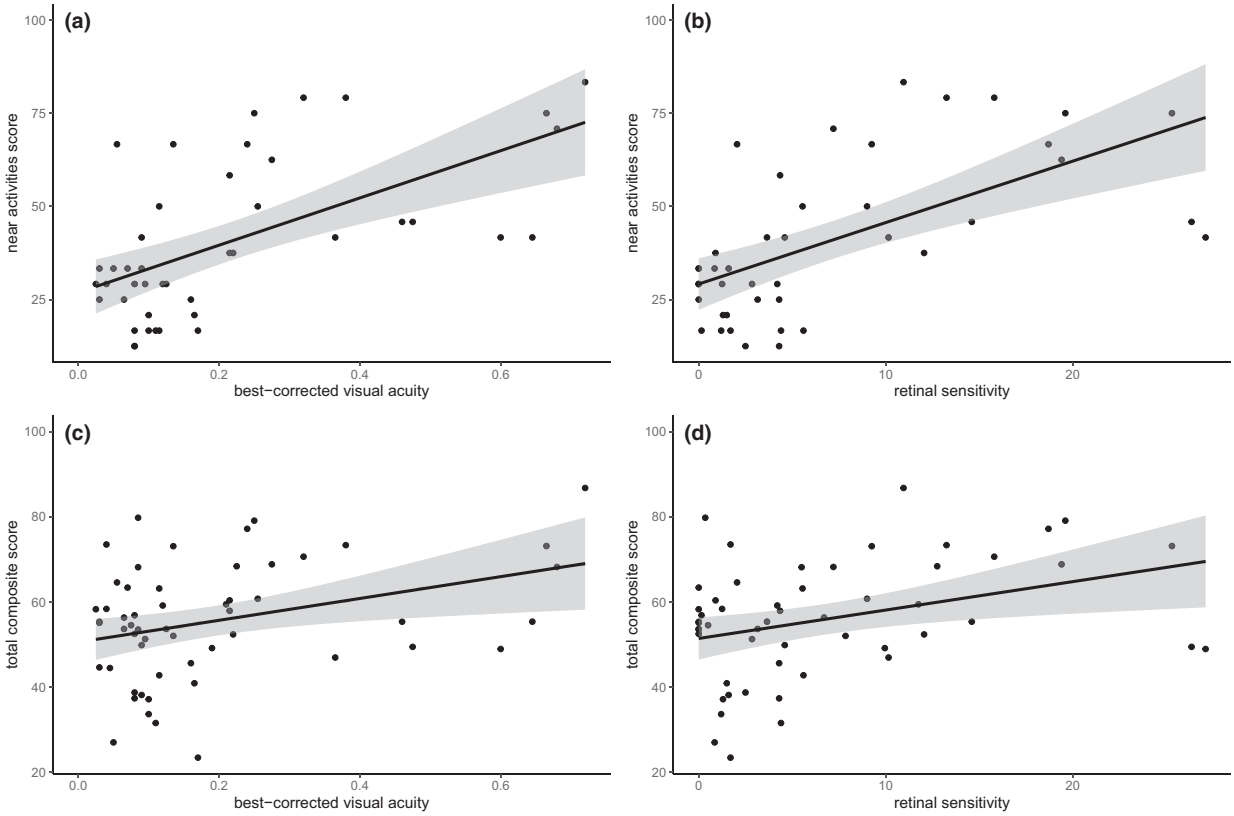

FIGURE 2 Significant positive relationships between BCVA, macular sensitivity, and scores for 'near activities' and 'total composite score' based on linear mixed model analysis. (a) Significant relationship between BCVA and NEI VFQ-25 score for 'near activities' (V_{NA}) ($n=43$). (b) Significant relationship between retinal sensitivity as measured on microperimetry and V_{NA} ($n=43$). (c) Significant relationship between BCVA and total composite score of NEI VFQ-25 ($n=55$). (d) Significant relationship between retinal sensitivity and total composite score of NEI VFQ-25 ($n=53$). Significance is denoted as $p \leq 0.05$.

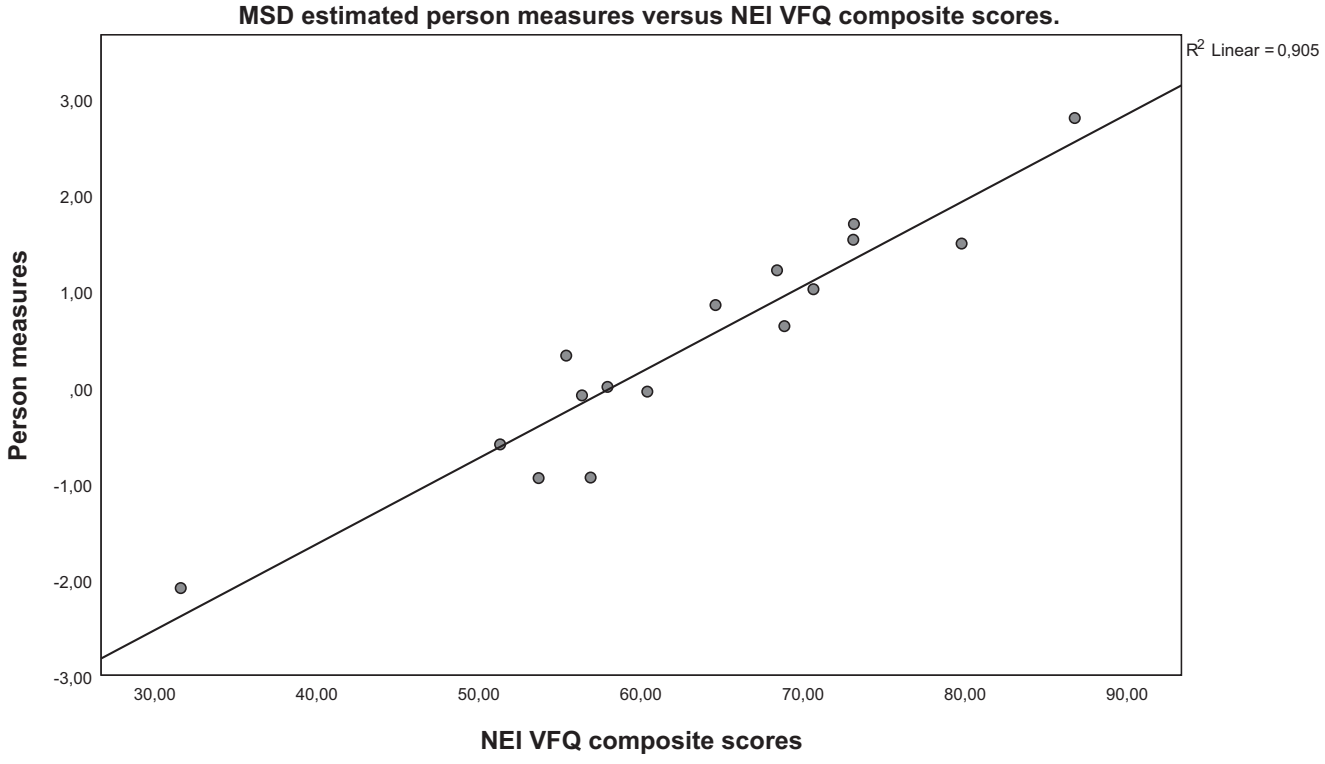

FIGURE 3 Near-linear relationship between estimated person measures and composite score of the NEI VFQ-25, $R^2=0.905$.

specifically, BCVA and macular sensitivity were found to be closely related to quality of life score for 'near activities' (V_{NA}). Interestingly, some earlier reports did not find a correlation between NEI VFQ-25 scores and visual acuity in RP, and visual field loss has been proposed as a better estimate of quality of life

(Altinbay & Taskin, 2021; Sugawara et al., 2010). Instead of visual field loss, we investigated macular sensitivity on microperimetry as an even more sensitive outcome measure in the present *CRB1*-IRD cohort. Here, we found another strong relationship between the deterioration of macular sensitivity and a decreasing quality of life based on V_{NA} and V_{TOT} (Nguyen et al., 2021). This finding is corroborated by another study with 30 RP patients with a relatively high visual acuity of >0.2 logMAR (equivalent to 20/32 Snellen) who performed microperimetry on the Nidek MP1 microperimeter (Sugawara et al., 2011). The NEI VFQ-39 scores deteriorated over time, but we found that the greatest significant decline occurred between baseline and second visit. The reason for the disparity in decline between the first 2 years and the second 2 years remains uncertain.

Although the NEI VFQ-39 has been shown as a marginally more informative questionnaire in IRD patients compared to the NEI VFQ-25 (Schofield et al., 2022), the latter has been a popular ophthalmic PROM since its first introduction in 2001 due to its simplicity and widespread use, which facilitates international comparison (Mangione et al., 2001). However, to accommodate for its simplicity, the NEI VFQ-25 does not meet current psychometric standards as it lacks unidimensionality, has poor item fit validity, and has crude differential item functioning (Khadka et al., 2012; Marella et al., 2010; Stelmack et al., 2002). The Rasch analysis has been proposed as a modern psychometric technique to enable estimates on an invariant scale from ordinal responses. However, this form of item response theory can only be applied on sufficiently large patient cohorts. As IRDs are relatively rare and we have focused specifically on *CRB1*-associated IRDs, our cohort is too small for the Rasch analysis. So, we applied the Rasch-calibrated item measures provided by Goldstein et al. to analyse the quality of life in this cohort.

In addition to providing calibrated item measures, Goldstein et al. suggest adopting domain-specific versions to resolve the problem of multidimensionality of the NEI VFQ-25 (Goldstein et al., 2022). Two of these versions focus on visual function (VFQ-VF) and socio-emotional impact (VFQ-SE), and a third version excludes overall health and eyesight quality (VFQ-25C). Using these versions, we found that visual function as measured with the VFQ-VF decreased significantly after 2 years, but not after 4 years. Interestingly, these significant decreases did not follow the visual function parameters BCVA, which decreased significantly after 4 years, but not after 2 years. This finding implies that patients are able to notice deterioration in experienced quality of life earlier, than BCVA as an objective visual function parameter can. Additionally, the socio-emotional impact of the *CRB1*-associated IRD was substantially higher after 2 years ($p=0.033$) and after 4 years ($p=0.021$) compared to the baseline visit. Likewise, macular sensitivity on microperimetry was significantly decreased after 2 and 4 years. Thus, macular sensitivity reflects visual function and socio-emotional impact as measured on the domain-specific VFQ-VF and VFQ-SE.

Our study has some limitations, mainly related to the content validity of the calibrated item measures and the NEI VFQ-25. The calibrated items and the resulting modified versions of the NEI VFQ-25 were estimated based on different patient populations with retinal disease diagnoses ranging from low-vision and age-related macular degeneration to retinal vein occlusion and diabetic retinopathy. As such, the calibrations may not be entirely applicable for inherited retinal dystrophies, and we suggest a calibration of item measures based on data sets of IRD patient cohorts. Moreover, the heterogeneity of our patient population, including adults and children, and IRD diagnoses of RP, cone-rod dystrophy, and macular dystrophy may hinder the generalisability of our findings, although the great majority of patients constituted of adult RP patients. As our patient cohort was too small for an individual Rasch analysis, the most suitable option for analysis was using the calibrated item measures. In doing so, we aim to provide some guidance in applying this method for future clinical IRD trials with relatively small patient cohorts. Regarding content validity of the questionnaire, the NEI VFQ-25 and the appendix focus on difficulties caused by general visual impairment, rather than consequences specifically caused by an IRD. Patients with a *CRB1*-associated IRD do not only experience progressive loss of visual acuity but also constriction of visual fields, nyctalopia, photophobia, and loss of colour and contrast discrimination (Talib et al., 2017). These symptoms each result in a different set of obstacles, which are currently not investigated in the NEI VFQ-25 or in the NEI VFQ-39. On the other hand, ocular pain is a separate item on these questionnaires, but is not a regular symptom of an IRD and is thus not relevant to our study population.

At the time of assessment, the NEI VFQ-25 was widely used in ophthalmological clinical trials and accepted by the regulatory authorities as a means to evaluate vision-related quality of life. However, as the flaws of the NEI VFQ-25 questionnaire become more apparent and IRD research advances towards clinical applications, experts agree on the need for a specific IRD questionnaire that can evaluate meaningful changes for a patient (Lacy et al., 2020; Prem Senthil et al., 2017; Selvan et al., 2022). A few PROMs have been developed for specific IRDs, such as Stargardt macular dystrophy and congenital stationary night blindness, but these tools have not been validated and are of limited use in larger IRD populations (Bijveld et al., 2013; Miedziak et al., 2000). IRD patients experience many similar symptoms; thus, a non-gene-specific PROM may be useful for different IRD patient populations. Some questionnaires focus on a single domain, such as mobility for the Mobility Difficulties Questionnaire, Independent Mobility Questionnaire, or daily tasks for the Daily Task Performance Questionnaire and Everyday Task Questionnaire (Prem Senthil et al., 2017). While informative, these single-domain questionnaires cannot be used to give an overall perspective of a patient's quality of life. Other IRD PROMs do not meet the current quality criteria or were not based on in-depth interviews with patients (Lacy et al., 2020; Prem Senthil

et al., 2017). [Correction added on 20 November 2023, after first online publication: In the preceding sentence, "…PRO instruments…" has been corrected to "…PROMs…" in this version.] A novel questionnaire, the Michigan Retinal Degeneration Questionnaire (MRDQ) has been developed and psychometrically validated by Lacy et al. that conforms to the FDA guidelines for the use in IRD clinical trials (Research et al., 2006). The MRDQ items were derived from both expert and patient interviews, and seven relevant domains were identified: central vision, colour vision, contrast sensitivity, scotopic function, photopic peripheral vision, mesopic peripheral vision, and photosensitivity. Item response theory techniques were applied for psychometric validation, and test–retest variability was assessed. Since its introduction, the MRDQ has already been incorporated into several clinical trials for IRDs such as RP and LCA (NCT05203939, NCT05176717).

Investigating the vision-related quality of life in patients with gene-specific IRDs such as those caused by variants in the *CRB1* gene is important as it may form a key outcome measure for the upcoming gene therapy. This study is meaningful in that it investigated the use of calibrated item measures for the NEI VFQ-25 questionnaire in patients with IRDs and correlated these to visual function measures. The results from this study are useful for the design of future clinical trial designs for small IRD patient cohorts.

ACKNOWLEDGEMENTS

The authors thank Ferda Bijker, Miranda Slokker-Blommestein, and Christien Kiewiet de Jonge for their valuable assistance in this study, and Stefan Böhringer for his help with the statistical analyses.

FUNDING INFORMATION

This research was supported by UitZicht (specifically by Algemene Nederlandse Vereniging ter Voorkoming van Blindheid (ANVVB), Landelijke Stichting voor Blinden en Slechtzienden (LSBS), and the Oogfonds), Curing Retinal Blindness Foundation, Stichting Blindenhulp, Bontius Stichting, and Retina Fonds. Their contribution did not affect study design or research conduct.

ORCID

Jessica S. Karuntu https://orcid.org/0000-0003-4522-4721
Xuan-Thanh-An Nguyen https://orcid.org/0000-0001-8350-5896
Mays Talib https://orcid.org/0000-0001-7131-0004
Mary J. van Schooneveld https://orcid.org/0000-0003-1793-1154
Maria M. van Genderen https://orcid.org/0000-0002-9286-8397
Caroline C. W. Klaver https://orcid.org/0000-0002-2355-5258
Alberta A. H. J. Thiadens https://orcid.org/0000-0002-4911-9462
Camiel J. F. Boon https://orcid.org/0000-0002-6737-7932

REFERENCES

Altinbay, D. & Taskin, I. (2021) Evaluation of vision-related quality of life in retinitis pigmentosa patients with low vision. *Japanese Journal of Ophthalmology*, 65, 777–785.

Bijveld, M.M., van Genderen, M.M., Hoeben, F.P., Katzin, A.A., van Nispen, R.M., Riemslag, F.C. et al. (2013) Assessment of night vision problems in patients with congenital stationary night blindness. *PLoS One*, 8, e62927.

Boone, W.J. (2016) Rasch analysis for instrument development: why, when, and how? CBE life. *Science Education*, 15, rm4.

Botto, C., Rucli, M., Tekinsoy, M.D., Pulman, J., Sahel, J.-A. & Dalkara, D. (2022) Early and late stage gene therapy interventions for inherited retinal degenerations. *Progress in Retinal and Eye Research*, 86, 100975.

Clemons, T.E., Chew, E.Y., Bressler, S.B. & McBee, W. (2003) National eye Institute visual function questionnaire in the age-related eye disease study (AREDS): AREDS report No. 10. *Archives of Ophthalmology*, 121, 211–217.

Dimopoulos, I.S., Hoang, S.C., Radziwon, A., Binczyk, N.M., Seabra, M.C., MacLaren, R.E. et al. (2018) Two-year results after AAV2-mediated gene therapy for Choroideremia: the Alberta experience. *American Journal of Ophthalmology*, 193, 130–142.

Goldstein, J.E., Bradley, C., Gross, A.L., Jackson, M., Bressler, N. & Massof, R.W. (2022) The NEI VFQ-25C: calibrating items in the National eye Institute visual function Questionnaire-25 to enable comparison of outcome measures. *Translational Vision Science & Technology*, 11, 10.

Khadka, J., McAlinden, C. & Pesudovs, K. (2012) Validation of the National eye Institute visual function Questionnaire-25 (NEI VFQ-25) in age-related macular degeneration. *Investigative Ophthalmology & Visual Science*, 53, 1276.

Lacy, G.D., Abalem, M.F., Musch, D.C. & Jayasundera, K.T. (2020) Patient-reported outcome measures in inherited retinal degeneration gene therapy trials. *Ophthalmic Genetics*, 41, 1–6.

Levinson, J.D., Joseph, E., Ward, L.A., Nocera, J.R., Pardue, M.T., Bruce, B.B. et al. (2017) Physical activity and quality of life in retinitis Pigmentosa. *Journal of Ophthalmology*, 2017, 6950642.

Maguire, A.M., Bennett, J., Aleman, E.M., Leroy, B.P. & Aleman, T.S. (2021) Clinical perspective: treating RPE65-associated retinal dystrophy. *Molecular Therapy*, 29, 442–463.

Mangione, C.M., Lee, P.P., Gutierrez, P.R., Spritzer, K., Berry, S. & Hays, R.D. (2001) Development of the 25-item National eye Institute visual function questionnaire. *Archives of Ophthalmology*, 119, 1050–1058.

Marella, M., Pesudovs, K., Keeffe, J.E., O'Connor, P.M., Rees, G. & Lamoureux, E.L. (2010) The psychometric validity of the NEI VFQ-25 for use in a low-vision population. *Investigative Ophthalmology & Visual Science*, 51, 2878–2884.

Miedziak, A.I., Perski, T., Andrews, P.P. & Donoso, L.A. (2000) Stargardt's macular dystrophy–a patient's perspective. *Optometry*, 71, 165–176.

Nguyen, X.-T.-A., Talib, M., van Schooneveld, M.J., Wijnholds, J., van Genderen, M.M., Schalij-Delfos, N.E. et al. (2021) CRB1-associated retinal dystrophies: a prospective natural history study in anticipation of future clinical trials. *American Journal of Ophthalmology*, 234, 37–48.

Prem Senthil, M., Khadka, J. & Pesudovs, K. (2017) Assessment of patient-reported outcomes in retinal diseases: a systematic review. *Survey of Ophthalmology*, 62, 546–582.

Research U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research & U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. (2006) Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health and Quality of Life Outcomes*, 4, 79.

Russell, S., Bennett, J., Wellman, J.A., Chung, D.C., Yu, Z.F., Tillman, A. et al. (2017) Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*, 390, 849–860.

Schneider, N., Sundaresan, Y., Gopalakrishnan, P., Beryozkin, A., Hanany, M., Levanon, E.Y. et al. (2022) Inherited retinal diseases: linking genes, disease-causing variants, and relevant therapeutic modalities. *Progress in Retinal and Eye Research*, 89, 101029.

Schofield, D., Kraindler, J., Tan, O., Shrestha, R., Jelovic, D., West, S. et al. (2022) Patient-reported health-related quality of life in individuals with inherited retinal diseases. *Ophthalmology Science*, 2, 100106.

Selvan, K., Abalem, M.F., Lacy, G.D., Vincent, A. & Héon, E. (2022) The state of patient-reported outcome measures for pediatric patients with inherited retinal disease. *Ophthalmology and Therapy*, 11, 1031–1046.

Stelmack, J.A., Stelmack, T.R. & Massof, R.W. (2002) Measuring low-vision rehabilitation outcomes with the NEI VFQ-25. *Investigative Ophthalmology & Visual Science*, 43, 2859–2868.

Sugawara, T., Hagiwara, A., Hiramatsu, A., Ogata, K., Mitamura, Y. & Yamamoto, S. (2010) Relationship between peripheral visual field loss and vision-related quality of life in patients with retinitis pigmentosa. *Eye*, 24, 535–539.

Sugawara, T., Sato, E., Baba, T., Hagiwara, A., Tawada, A. & Yamamoto, S. (2011) Relationship between vision-related quality of life and microperimetry-determined macular sensitivity in patients with retinitis pigmentosa. *Japanese Journal of Ophthalmology*, 55, 643–646.

Talib, M., Van Cauwenbergh, C., De Zaeytijd, J., Van Wynsberghe, D., De Baere, E., Boon, C.J.F. et al. (2021a) CRB1-associated retinal dystrophies in a Belgian cohort: genetic characteristics and long-term clinical follow-up. *The British Journal of Ophthalmology*, 106, 696–704.

Talib, M., van Schooneveld, M.J., van Genderen, M.M., Wijnholds, J., Florijn, R.J., Ten Brink, J.B. et al. (2017) Genotypic and phenotypic characteristics of CRB1-associated retinal dystrophies: a long-term follow-up study. *Ophthalmology*, 124, 884–895.

Talib, M., van Schooneveld, M.J., Wijnholds, J., van Genderen, M.M., Schalij-Delfos, N.E., Talsma, H.E. et al. (2021b) Defining inclusion criteria and endpoints for clinical trials: a prospective cross-sectional study in CRB1-associated retinal dystrophies. *Acta Ophthalmologica*, 99, e402–e414.

van den Born, L.I., van Soest, S., van Schooneveld, M.J., Riemslag, F.C., de Jong, P.T. & Bleeker-Wagemakers, E.M. (1994) Autosomal recessive retinitis pigmentosa with preserved Para-arteriolar retinal pigment epithelium. *American Journal of Ophthalmology*, 118, 430–439.

van Huet, R.A.C., Oomen, C.J., Plomp, A.S., van Genderen, M.M., Klevering, B.J., Schlingemann, R.O. et al. (2014) The RD5000 database: facilitating clinical, genetic, and therapeutic studies on inherited retinal diseases. *Investigative Ophthalmology & Visual Science*, 55, 7355–7360.

Varma, R., Richman, E.A., Ferris, F.L., III & Bressler, N.M. (2010) Use of patient-reported outcomes in medical product development: a report from the 2009 NEI/FDA clinical trial endpoints symposium. *Investigative Ophthalmology & Visual Science*, 51, 6095–6103.

Weleber, R.G., Pennesi, M.E., Wilson, D.J., Kaushal, S., Erker, L.R., Jensen, L. et al. (2016) Results at 2 years after gene therapy for RPE65-deficient Leber congenital Amaurosis and severe early-childhood-onset retinal dystrophy. *Ophthalmology*, 123, 1606–1620.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Karuntu, J.S., Nguyen, X.-T.-A., Talib, M., van Schooneveld, M.J., Wijnholds, J., van Genderen, M.M. et al. (2023) Quality of life in patients with *CRB1*-associated retinal dystrophies: A longitudinal study. *Acta Ophthalmologica*, 00, 1–9. Available from: https://doi.org/10.1111/aos.15769