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ORIGINAL RESEARCH

Psychometric Validation of the ViSIO-PRO and ViSIO-ObsRO in Retinitis Pigmentosa and Leber Congenital Amaurosis

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ABSTRACT

Introduction: Retinitis Pigmentosa (RP) and Leber Congenital Amaurosis (LCA) are rare inherited retinal degenerative disorders. The Visual Symptom and Impact Outcomes patient-reported outcome (ViSIO-PRO) and observer-reported outcome (ViSIO-ObsRO) instruments were developed in this population to assess visual function symptoms and impacts on vision-dependent activities of daily living (ADL) and distal health-related quality of life (HRQoL). This study aimed to explore the psychometric properties of the ViSIO-PRO and ViSIO-ObsRO in RP/LCA.

Methods: The 49-item ViSIO-PRO and 27-item ViSIO-ObsRO instruments were completed by 83 adult and adolescent patients and 22 caregivers of child patients aged 3–11 years with RP/LCA, respectively, at baseline and 12–16-day follow-up. Concurrent measures were also administered at baseline. Psychometric analyses assessed item (question) properties, dimensionality, scoring, reliability, validity, and score interpretation.

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Results: Item responses were mainly evenly distributed across the response scale, and inter-item correlations were mostly moderate to strong (> 0.30) at baseline within hypothesized domains. Item deletion was informed by item properties, qualitative data, and clinical input and supported retention of 35 ViSIO-PRO items and 25 ViSIO-ObsRO items. Confirmatory factor analysis in line with pre-hypothesized domains supported a four-factor model assessing visual function symptoms, mobility, vision-dependent ADL, and distal HRQoL. A bifactor model supported calculation of total scores and four domain scores. Internal consistency was high for domain and total scores (Cronbach's alpha > 0.70) and test–retest reliability for total scores was strong between baseline and 12–16-day follow-up (intraclass correlation coefficients 0.66–0.98). Convergent validity was supported by strong correlations in a logical pattern with concurrent measures. Mean baseline scores differed significantly between severity groups. Distribution-based methods provided initial insights to guide interpretation of scores.
Conclusions: Findings supported item reduction and established scoring of the instruments. Evidence of reliability and validity as outcome measures in RP/LCA was also reported. Further research is ongoing to explore responsiveness of the ViSIO-PRO and ViSIO-ObsRO instruments and interpretation of change scores.

Keywords: Clinical outcome assessment; Inherited retinal disease; Leber congenital amaurosis; Observer-reported outcome; Patient-reported outcome; Psychometrics; Retinitis pigmentosa

Key Summary Points

Why carry out this study?

Previous research evaluating the appropriateness of clinical outcome assessments (COAs) identified that there are no disease-specific instruments to assess the visual function symptoms and impacts of Retinitis Pigmentosa (RP)/Leber Congenital Amaurosis (LCA). The Visual Symptom and Impact Outcomes patient-reported outcome (ViSIO-PRO) and observer-reported outcome (ViSIO-ObsRO) instruments were developed through qualitative research with RP/LCA patients and caregivers/parents of children. The purpose of this study was to evaluate the psychometric properties of the instruments for use in RP/LCA.

What was learned from the study?

This study provides evidence that the ViSIO-PRO and ViSIO-ObsRO are valid and reliable instruments that capture the most relevant and important concepts of visual functioning and associated impacts on vision-dependent activities of daily living (ADL) and distal health-related quality of life (HRQoL) in an RP/LCA population, across a range of genotypes.

The findings strongly support the ViSIO-PRO and ViSIO-ObsRO to be appropriate instruments for inclusion as outcome assessments in future RP/LCA clinical trials and research studies. Further research will explore whether the instruments are able to detect changes over time in an RP/LCA population.

INTRODUCTION

Retinitis Pigmentosa (RP) and Leber Congenital Amaurosis (LCA) are rare inherited retinal degenerative disorders (IRD) caused by a variety of autosomal dominant, autosomal recessive, or X-linked-associated gene mutations that lead to impairments in the rod and cone photoreceptors and subsequent progressive visual function symptoms [1, 2]. Gene mutations associated with RP/LCA are commonly seen in the *RHO*, *USH2A*, *RPGR*, and *RP2* genes, with rarer mutations seen in genes such as *RPE65* and *RLBP1*, among others [3]. Patients typically lose night vision in adolescence, peripheral vision in young adulthood, and central vision in later life, in addition to a variety of other visual impairments [4]. These visual function symptoms experienced as part of RP/LCA can have a significant impact on patients' vision-dependent activities of daily living (ADL) and health-related quality of life (HRQoL) [5–8].

Previous research has assessed the appropriateness of existing patient-reported outcome (PRO) instruments used to assess functional vision in other ophthalmologic conditions, for use in *RLBP1* RP/LCA [9]. The findings demonstrated that existing PRO instruments do not provide a comprehensive assessment of the patient experience of *RLBP1* RP (and likely RP/LCA more broadly) and contain items that lack relevance or are difficult for patients to interpret due to being insufficiently specific (i.e., items do not account for the range of lighting conditions and familiarity of environment conditions that act as moderating factors for visual function symptoms). As a result, the Visual Symptom and Impact Outcomes patient-reported outcome (ViSIO-PRO) and observer-reported outcome (ViSIO-ObsRO) instruments have been developed to assess the visual function symptoms and impacts on vision-dependent ADL and distal HRQoL concepts in patients with RP/LCA, in line with best-practice guidelines for clinical outcome assessment (COA) development and regulatory guidance [10–12]. Specifically, development of the instruments has been informed by the prior research and two rounds of qualitative concept elicitation (CE) and cognitive debriefing (CD) interviews that explored the patient experience of RP/LCA and qualitatively evaluated the ViSIO-PRO and ViSIO-ObsRO instruments, to provide evidence of their content validity in this population [5, 7, 8].

In addition to content validity, PRO and ObsRO instruments should provide evidence of scoring and psychometric properties including reliability, construct validity, ability to detect change, and score interpretation, within the target population [13]. A non-interventional observational study was conducted with adult and adolescent patients and caregivers of child patients with RP/LCA, to evaluate the

Table 1 Schedule of assessments

Assessment	Timepoint 1: baseline	Timepoint 2: 12–16 days following baseline
Adults and adolescent patients with RP/LCA		
ViSIO-PRO	x	x
VFQ-25 [15, 16]	x	
EQ-5D-5L [17, 18]	x	x
PGI-S [19]	x	x
Caregivers of child patients aged 3–11 with RP/LCA		
ViSIO-ObsRO	x	x
VFQ-25	x	
EQ-5D-5L (proxy version) [17, 18]	x	x
CGI-S [19]	x	x

ViSIO-PRO Visual Symptom and Impact Outcomes patient-reported outcome, *ViSIO-ObsRO* Visual Symptom and Impact Outcomes observer-reported outcome, *VFQ-25* Visual Function Questionnaire 25, *EQ-5D-5L* Euro-Qol-5 dimension-5L, *PGI-S* Patient Global Impression of Severity, *CGI-S* Caregiver Gglobal Impression of Severity
Wording of PGI−S: "Please rate how severe your vision problems have been over the past 7 days?"
Wording of CGI−S: "Please rate how severe your child's vision problems have been over the past 7 days?"

Table 2 Study eligibility criteria

Inclusion criteria	
1	Patient/[the patient they care for] has a clinical and molecular diagnosis of Retinitis Pigmentosa (RP)/Leber Congenital Amaurosis (LCA) confirmed by genetic testing
2	For adults with RP/LCA: Patient is at least 18 years of age For adolescents with RP/LCA: Patient is between the ages of 12 and 17 inclusive For children with RP/LCA: Patient is between the ages of 3 and 11 inclusive For parents/caregivers: Participant is the parent/caregiver of a patient aged 3 to 11
3	Patient/[the patient they care for] has clinically confirmed visual impairment, assessed by visual acuity worse than 20/60 in the best eye, or significant visual field loss or loss of visual sensitivity
4	For adult and adolescent patients and parents/caregivers: Patient/[participant] must, in the opinion of the recruiting clinician, be willing and able to complete all aspects of the study, including completion of a number of questionnaires over the telephone on two occasions
5	For adult patients and parent's/caregivers: Participant is willing and able to participate in the study and provide written informed consent For adolescent patients: Patient is willing and able to participate in the study and provide written informed assent, and a parent/caregiver is willing and able to provide written informed consent for the patient they provide care for
6	For adult and adolescent patients and parents/caregivers: Patient/[participant] is an English (in USA and Canada), German (in Germany), Danish (Denmark), or French (in France) speaker able to fully understand the language
Exclusion criteria	
1	Participant (patient or parent/caregiver) has great difficulty hearing or speaking
2	Patient has a confirmed diagnosis of Usher Syndrome
3	Patient has a history of any ophthalmic disease other than RP/LCA that would preclude the patient from providing adequate measures of visual function. Examples of ophthalmic conditions that might not disqualify a patient include uncomplicated posterior vitreous detachment, peripheral retinal lesions not at risk for a retinal break, incipient cataract, aphakia, dry eye disease, infectious conjunctivitis, strabismus
4	Participant (patient or parent/caregiver) has an uncontrolled psychiatric condition (e.g., schizophrenia, bipolar disorder) or has severe physical, neurological, or cognitive deficits rendering the participant unable to understand the nature, scope, and possible consequences of the study or likely to have difficulty participating in the study
5	Patient has ocular inherited retina pathologies other than RP or LCA

Table 3 Overview of statistical analyses

Analysis	Description
Stage 1: Item properties	
Quality of completion	• The quality of completion of the ViSIO-PRO and ViSIO-ObsRO instruments was evaluated to identify any problematic items. Missing data at the form-level and item-level were described at baseline and 12–16-day follow-up
Item response distributions	• Response distributions for each ViSIO-PRO and ViSIO-ObsRO item were examined to assess the frequency and percentage of each endorsed response and identify any response options that were overly favored. This was assessed at baseline and 12–16-day follow-up for the total sample
	• Percentages of minimum and maximum responses were also calculated to examine floor and ceiling effects for all items. A floor effect was defined as a high percentage of patients endorsing the response option that represents the most severe health state (i.e., "I cannot/did not do this at all because of my vision"/"Very often"/"I cannot work or go to school because of my vision" for the ViSIO-PRO or "My child cannot/did not this at all because of their vision"/"Very often" for the ViSIO-ObsRO), and a ceiling effect was defined as a high percentage of patients endorsing the response option which represents the least severe health state (i.e., "No difficulty"/"Never" for the VISIO-PRO or "No, not at all"/"Never" for the ViSIO-ObsRO). An item with a substantial proportion of patients scoring floor/ceiling was flagged for further consideration:
	○ Cutoff thresholds for floor and ceiling effects for the ViSIO-PRO were prespecified as $> 20\%$ (or $> 25\%$ for items 43–48)
	○ Cutoff thresholds for floor and ceiling effects for the ViSIO-ObsRO were stated as $> 30\%$ (or $> 40\%$ for items 1, 2, 24–26)
Stage 2: Dimensionality and scoring	
Inter-item correlations	• Inter-item correlations were examined for each pair of items in the ViSIO-PRO and ViSIO-ObsRO instruments at baseline and 12–16-day follow-up, to ensure each item measured a distinct concept without any redundancy. Items that correlated very highly with one another (> 0.90) were flagged for review
Exploratory and confirmatory factor analysis	• Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) was performed on all items in the ViSIO-PRO using the PRO psychometric analysis population at baseline
	• EFA was conducted to explore the underlying factor structure of the 49-item ViSIO-PRO independent of the hypothesized conceptual framework, due to inter-relatedness of concepts assessed in the instrument. The results from the EFA provided an indication of underlying factors of the ViSIO-PRO
	• CFA was then conducted to assess the fit of the observed responses with a multiple domain framework, using RMSEA (< 0.10) [19], CFI (≥ 0.95) [22], and Standardized Root Mean Square Residual (SRMR) (< 0.10) [19] model-fit statistics
	• EFA and CFA were not conducted on the ViSIO-ObsRO due to the small sample size

Table 3 continued

Analysis	Description
Rasch analysis	• Rasch analysis was conducted within each of the four ViSIO-PRO domains to inform scoring and examine the presence of any local dependencies between items within each domain, which may indicate conceptual overlap or item redundancy, to further inform possible item deletion [23, 24]
	• Rasch analysis was not conducted on the ViSIO-ObsRO due to the small sample size
Bifactor model	• g a total score) and four specific factors was fit to investigate essential unidimensionality of all items in the ViSIO-PRO. Essential unidimensionality is an important consideration to support calculating a total ViSIO-PRO score in addition to domain scores [25, 26]
	• Bifactor modeling was not conducted on the ViSIO-ObsRO due to the small sample size
Stage 3: Reliability and validity of scores	
Reliability	
Internal consistency reliability	• Internal consistency reliability was evaluated to assess the homogeneity of items belonging to the same domain, using Cronbach's alpha coefficient (> 0.70 for good internal consistency) [27]
	• The impact of item and domain removal on internal consistency reliability was examined by calculating Cronbach's alpha with each item or domain removed from their respective scores to assess the impact (alpha-if-item-deleted method). If removal of an item caused the alpha value to increase substantially, this could indicate that the item does not fit well within its assigned domain
	• Corrected item-total correlations were also calculated by computing the polyserial correlation of each item with the sum of the remaining items within its corresponding score
	• Internal consistency was assessed at baseline in the PRO psychometric analysis population for the ViSIO-PRO and ObsRO psychometric analysis population for the ViSIO-ObsRO, for all scores that included more than two items
Test–retest reliability	• Test–retest reliability (TRT) was evaluated by examining the stability of scores between baseline and 12–16-day follow-up [14]. This analysis was performed using the PRO TRTAP for the ViSIO-PRO and the ObsRO TRTAP for the ViSIO-ObsRO
	• Intraclass correlation coefficients (ICCs) were calculated and evaluated using prespecified cutoff criteria: < 0.50 indicating poor reliability, 0.50–0.75 indicating moderate reliability, 0.75–0.90 indicating good reliability, and > 0.90 indicating excellent reliability [28]
	• Person's correlation coefficients were also calculated for each ViSIO-PRO and ViSIO-ObsRO TRTAP
Construct validity	

Table 3 continued

Analysis	Description
Convergent validity	• Convergent validity was evaluated by calculating Spearman's correlations with concurrent measures using data collected at baseline in the PRO psychometric analysis population for the ViSIO-PRO and ObsRO psychometric analysis population for the ViSIO-ObsRO. Correlations with the following measures were examined: ○ EQ-5D-5L dimensions (i.e. mobility, usual activities, self-care, pain, anxiety/depression); ○ EQ-5D-5L VAS; ○ VFQ-25; ○ PGI-S (or CGI-S); ○ VA score • Convergent validity evaluates the relationships with other measures that assess similar or related concepts. Scores assessing similar or related concepts were expected to have strong correlations ($\geq$ 0.50) thereby demonstrating convergent validity. Scores assessing unrelated concepts were expected to show small ($<$ 0.30) or negligible correlations thereby demonstrating discriminant validity [29]
Known-groups analysis	• The known-groups method was used to evaluate differences in domain and total scores on the ViSIO-PRO and ObsRO among groups of patients expected to differ by visual function severity. Known groups were defined using scores on the PGI-S item and age • Known-group comparisons were assessed using baseline data in the PRO psychometric analysis population for the ViSIO-PRO and ObsRO psychometric analysis population for the ViSIO-ObsRO • Mean ViSIO-PRO or ViSIO-ObsRO scores were calculated at baseline, with one-way analyses of variance (ANOVAs) used to test the mean score differences between groups. The prespecified criterion for known-groups validity was considered to be met if statistically significant differences ($p < 0.05$) in mean ViSIO-PRO or ViSIO-ObsRO scores were observed between the known groups, and scores increased monotonically as expected. Between-group effect sizes (ES) were also calculated as a measure of the magnitude of differences in scores between groups. The following prespecified cutoffs were used to interpret the magnitude of each ES: small (ES 0.20), moderate (ES 0.50), and large (ES 0.80) [29]
Stage 4: Interpretation of scores	
Distribution-based methods	• Distributional properties of the ViSIO-PRO domain and total scores were used to provide an indication of the amount of change beyond measurement error that may be considered meaningful [13, 30] • The minimal important difference was estimated by calculating 0.5 of the SD at baseline and the standard error of measurement (SEM)

Table 3 continued

Analysis	Description
Exploratory analyses	• Exploratory analyses were conducted to determine whether there were any differences in scores across the different RP/LCA genotypes of patients recruited into the study. Comparison of ViSIO-PRO mean scores was performed for any subgroups with sufficient sample sizes • A one-way ANOVA was performed to test for differences in mean scores between genotype subgroups • Due to the small sample size, exploratory analyses were not performed on the ViSIO-ObsRO

psychometric properties of the ViSIO-PRO and ViSIO-ObsRO instruments.

METHODS

Study Design

This was a non-interventional observational study to evaluate the psychometric properties of the newly developed ViSIO-PRO and ViSIO-ObsRO instruments. Participants completed the ViSIO-PRO or ViSIO-ObsRO, along with Patient Global Impression of Severity (PGI-S) or Caregiver Global Impression of Severity (CGI-S) items and the EQ-5D-5L or EQ-5D-5L (parent/caregiver proxy version) over the telephone at two separate timepoints, 12–16 days apart [14]. All participants also completed the Visual Functioning Questionnaire-25 (VFQ-25) at baseline only (Table 1).

Participant Sample

One-hundred-and-twenty participants were targeted for this study. The target sample size was determined by best-practice guidelines for psychometric validation studies (i.e., minimum sample size of 100 patients overall for factor analysis, or at least 5 patients per item in the instrument under assessment), while considering that RP/LCA is a rare disease. Participants were recruited from clinical sites in France, Denmark, Germany, Canada, and the USA. Centralized ethical approval and oversight for this study was provided by Copernicus Group Independent Review Board (CG-IRB) to conduct the study in the USA and Denmark. Local ethical approval was provided at the specialist clinical sites in France, Germany, and Canada. Documentation of informed consent was obtained prior to any research activities being conducted. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments [20].

Eligibility Criteria

All participants were required to meet the eligibility criteria outlined in Table 2 to be enrolled into the study.

Overview of Instruments

ViSIO-PRO

The 49-item ViSIO-PRO instrument is designed to assess impacts on vision-dependent ADL, mobility, and distal HRQoL by measuring the level of difficulty experienced by patients with RP/LCA when in specific situations or performing a variety of ADLs that significantly rely on visual function. There are two versions of the ViSIO-PRO: a self-administered version and an interviewer-administered version for those who are unable to self-complete due to their vision. Both are identical other than differences in the instructions provided. During the observational study, all participants completed the

Table 4 Demographic characteristics of adults, adolescents, and parent/caregiver participants (n = 105)

Demographic characteristics	Adults/adolescents (n = 83)	Caregiver/patient (n = 22)*	Total (n = 105)
Age of patient/child, (years)			
Mean	37.8	7	31.4
Minimum, maximum	12, 79	3, 11	3, 79
Gender, n (%)			
Male	49 (59.0)	7 (31.8)	56 (53.3)
Female	34 (41.0)	15 (68.2)	49 (46.7)
Country, n (%)			
USA	26 (31.3)	1 (4.5)	27 (25.7)
Canada	17 (20.5)	0	17 (16.2)
France	19 (22.9)	12 (54.5)	31 (29.5)
Denmark	16 (19.3)	8 (36.3)	24 (22.9)
Germany	5 (6.0)	1 (4.5)	6 (5.7)
Ethnicity, n (%)			
Hispanic or Latino (of any race)	2 (2.4)	2 (9.1)	4 (3.8)
Non-Hispanic or Latino	65 (78.3)	10 (45.5)	75 (71.4)
Missing data**	16 (19.3)	10 (45.5)	26 (24.8)
Race, n (%)			
Caucasian	74 (89.2)	18 (81.8)	92 (87.6)
Black/African American	2 (2.4)	1 (4.5)	3 (2.9)
Asian	0	0	0
Multiracial	2 (2.4)	0	2 (1.9)
Other	5 (6.0)	3 (13.6)	8 (7.6)
Marital status, n (%)[a]			
Never married	25 (38.5)	2 (9.1)	27 (31.0)
Married	33 (50.8)	19 (86.4)	52 (59.8)
Widowed	2 (3.1)	0	2 (2.3)
Divorced	5 (7.7)	0	5 (5.7)
Missing data	0	1 (4.5)	1 (1.1)
Working status, n (%)			
Working full-time	28 (33.7)	14 (63.6)	42 (40.0)
Working part-time	7 (8.4)	4 (18.2)	11 (10.5)
Looking for work	0	0	0

Table 4 continued

Demographic characteristics	Adults/adolescents (n = 83)	Caregiver/patient (n = 22)*	Total (n = 105)
Full-time homemaker	2 (2.4)	3 (13.6)	5 (4.8)
Student	23 (27.7)	0	23 (21.1)
Not working due to your RP/LCA	10 (12.0)	0	10 (9.5)
Retired	11 (13.3)	0	11 (10.5)
Other	2 (2.4)	1 (4.5)	3 (2.9)
Living status, n (%)[b]			
Live alone	11 (13.3)	0	11 (10.5)
Live with husband/wife/partner	41 (49.4)	21 (95.5)	62 (59.0)
Live with children	7 (8.4)	22 (100.0)	29 (27.6)
Live with parents/other family members	27 (32.5)	0	27 (25.7)
Live with friends	1 (1.2)	0	1 (1.0)
Other	2 (2.4)	0	2 (1.9)
Highest education level, n (%)			
Elementary school	13 (15.7)	1 (4.5)	14 (13.3)
Some high school	9 (10.8)	2 (9.1)	11 (10.5)
High school diploma or GED	16 (19.3)	4 (18.2)	20 (19.0)
Some years of college	7 (8.4)	2 (9.1)	9 (8.6)
Certificate program	1 (1.2)	1 (4.5)	2 (1.9)
University/college degree (2 or 4 year)	19 (22.9)	10 (45.5)	29 (27.6)
Graduate or professional degree	12 (14.5)	2 (9.1)	14 (13.3)
Other	6 (7.2)	0	6 (5.7)

*All caregiver/patient characteristics are in relation to the parent/caregiver unless otherwise stated
**Missing data due to ethnicity data not allowed to be collected in Denmark
[a]Participants were asked to check "all that apply," so percentages may not sum 100%
[b]Demographics for adult (18+ years) participants and caregivers/parents only (adult and caregiver/parent, $n = 87$)

interviewer-administered version of the ViSIO-PRO to ensure standardization across the sample. All items require patients to answer on the basis of the "past 7 days" and each ViSIO-PRO item is assessed on a 4- or 5-point verbal descriptor frequency or severity response scale. An additional response option is also provided for most items, for patients to select if they have not been in a specific situation or performed the activity within the past 7 days for reasons other than their vision, rendering the item not applicable.

Items within the ViSIO-PRO are grouped under four hypothesized domains assessing visual function symptoms (items 1–13), impacts on vision-dependent ADL (items 14–27),

Table 5 Clinical characteristics of adult, adolescent, and child patients (n = 105)

Clinical characteristics	Adults/ Adolescents (n = 83)	Children (n = 22)	Total (n = 105)
Genotype of patient/child, n (%)			
RPE65 LCA/RP	17 (20.5)	9 (41)	26 (24.8)
RLBP1 RP	12 (14.5)	0	12 (11.4)
RPGR X-linked RP	10 (12.0)	2 (9.1)	12 (11.4)
CEP290	7 (8.4)	2 (9.1)	9 (8.6)
RDH12	5 (6.0)	2 (9.1)	7 (6.7)
EYS	5 (6.0)	0	5 (4.8)
BBS1	4 (4.8)	0	4 (3.8)
PDE6B	3 (3.6)	0	3 (2.9)
Rhodopsin gene (*RHO*)	3 (3.6)	1 (4.5)	4 (3.8)
RP1	2 (2.4)	0	2 (1.9)
RP2	2 (2.4)	0	2 (1.9)
PRPH2	2 (2.4)	0	2 (1.9)
USH2A	2 (2.4)	0	2 (1.9)
CRB1	2 (2.4)	0	2 (1.9)
PRPF31 RP	1 (1.6)	0	1 (1.0)
LCA5	1 (1.6)	0	1 (1.0)
CNGA1	1 (1.6)	0	1 (1.0)
IMPDH1	1 (1.6)	0	1 (1.0)
CRX	1 (1.6)	0	1 (1.0)
MERTK	1 (1.6)	0	1 (1.0)
RPB4	1 (1.6)	0	1 (1.0)
LRAT	0	2 (9.1)	2 (1.9)
TULP1	0	2 (9.1)	2 (1.9)
A1PL1	0	1 (4.5)	1 (1.0)
NR2E3	0	1 (4.5)	1 (1.0)
VA score of the left eye, n (%)			
Mild (> 60 letters)	24 (28.9)	4 (18.2)	28 (26.7)
Moderate (36–60 letters)	11 (13.3)	10 (45.5)	21 (20)
Severe (5–35 letters)	19 (22.9)	3 (13.6)	22 (20.1)
Very severe (< 5 letters)	18 (21.7)	0	18 (17.2)

Table 5 continued

Clinical characteristics	Adults/ Adolescents (n = 83)	Children (n = 22)	Total (n = 105)
N/A (blind)	3 (3.6)	1 (4.5)	4 (3.8)
Missing data	8 (9.6)	4 (18.2)	12 (11.4)
VA score of the right eye, n (%)			
Mild (> 60 letters)	26 (31.3)	4 (18.2)	30 (28.6)
Moderate (36–60 letters)	12 (14.5)	10 (45.5)	22 (21.0)
Severe (5–35 letters)	23 (27.7)	3 (13.6)	26 (24.8)
Very severe (< 5 letters)	13 (15.7)	0	13 (12.4)
N/A (blind)	4 (4.8)	1 (4.5)	5 (4.8)
Missing data	5 (6.0)	4 (18.2)	9 (8.6)
Visual field Goldmann V4e score, left eye, n (%)[a]			
Mild	17 (20.5)	0	17 (16.2)
Moderate	0	0	0
Severe	3 (3.6)	0	0
Very severe	21 (25.3)	6 (27.3)	27 (25.7)
Missing data	42 (50.6)	16 (72.7)	58 (55.2)
Visual field Goldmann V4e score, right eye, n (%)[a]			
Mild	15 (18.1)	0	15 (14.3)
Moderate	1 (1.2)	0	1 (1.0)
Severe	3 (3.6)	1 (4.5)	4 (3.8)
Very severe	23 (27.7)	6 (27.3)	29 (27.6)
Missing data	41 (49.4)	15 (68.2)	56 (53.3)
Visual field Goldmann V4e score, both eyes, n (%)[b]			
Mild	0	0	0
Moderate	0	0	0
Severe	0	0	0
Very severe	13 (15.7)	6 (27.3)	19 (18.1)
Missing data	70 (84.3)	16 (72.7)	86 (81.9)
Pharmacological treatments received, n (%)			
Voretigene neparvovec (Luxturna)	8 (9.6)	6 (27.3)	14 (13.3)
ASO therapy	4 (4.8)	0	4 (3.8)

Table 5 continued

Clinical characteristics	Adults/ Adolescents (n = 83)	Children (n = 22)	Total (n = 105)
Not applicable	71 (85.5)	16 (72.7)	87 (82.9)

ASO antisense oligonucleotide
Visual acuity (VA) score defined by early treatment diabetic retinopathy study (ETDRS) letter score (if every letter read correctly on that line and all lines above it on the chart)
[a]Visual Field Goldmann V4e scores are defined by the following categories: mild (> 44), moderate (36 to < 44), severe (22 to < 36), and very severe (0 to < 22). These categories were defined by clinical experts
[b]Visual Field Goldmann V4e score for both eyes is the sum total degrees (calculated by kinetic perimetry)

impacts on mobility (items 28–35), and impacts on distal HRQoL (items 36–49).

ViSIO-ObsRO

The 27-item ViSIO-ObsRO instrument is designed to assess impacts on vision-dependent ADL, mobility, and distal HRQoL experienced by children with RP/LCA (aged 3–11 years), on the basis of informant report (i.e., a caregiver of a child aged 3–11 years with RP/LCA). The ViSIO-ObsRO instrument requires parents/caregivers of children with RP/LCA to report the observed level of difficulty or frequency that a problem is experienced when their child is in specific situations or performing vision activities, over the "past 7 days." Items are assessed on a 2- and 3-point verbal descriptor response scale. Three different response scales are used. An additional response option is provided for all items, for the parent/caregiver to select if they have not observed their child do that activity in the past 7 days, rendering the item not applicable.

Items within the ViSIO-ObsRO are grouped under the same four hypothesized domains as the ViSIO-PRO, assessing visual function symptoms (items 1–2), impacts on vision-dependent ADL (items 3–10), impacts on mobility (items 11–18) and impacts on distal HRQoL (items 19–27).

Translations of the ViSIO-PRO and ViSIO-ObsRO were informed by best-practice guidelines for translation, cultural adaptation, and linguistic validation, as outlined in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force report, before their inclusion in this study [21].

Validation Instruments

Concurrent measures were administered alongside the ViSIO-PRO and ViSIO-ObsRO instruments during the observational study, to support psychometric validation analysis. An overview of the additional study instruments used for validation are presented in Supplementary File 1. All instruments are scored so that higher scores indicate worse functioning or well-being, with the exception of the VFQ-25 and EQ-5D-5L VAS.

Statistical Methods

A series of tests and analyses were performed throughout the study, each designed to evaluate different aspects of an item or score's performance. All planned statistical analyses were detailed in a psychometric analysis plan. Table 3 details the main statistical methods used in this study. A description of the analysis populations is provided in Supplementary File 2.

RESULTS

Demographic Characteristics

Eighty-three patients with RP/LCA (including 65 adults and 18 adolescents) and 22 caregivers of children aged 3–11 years with RP/LCA participated in the observational study (Table 4).

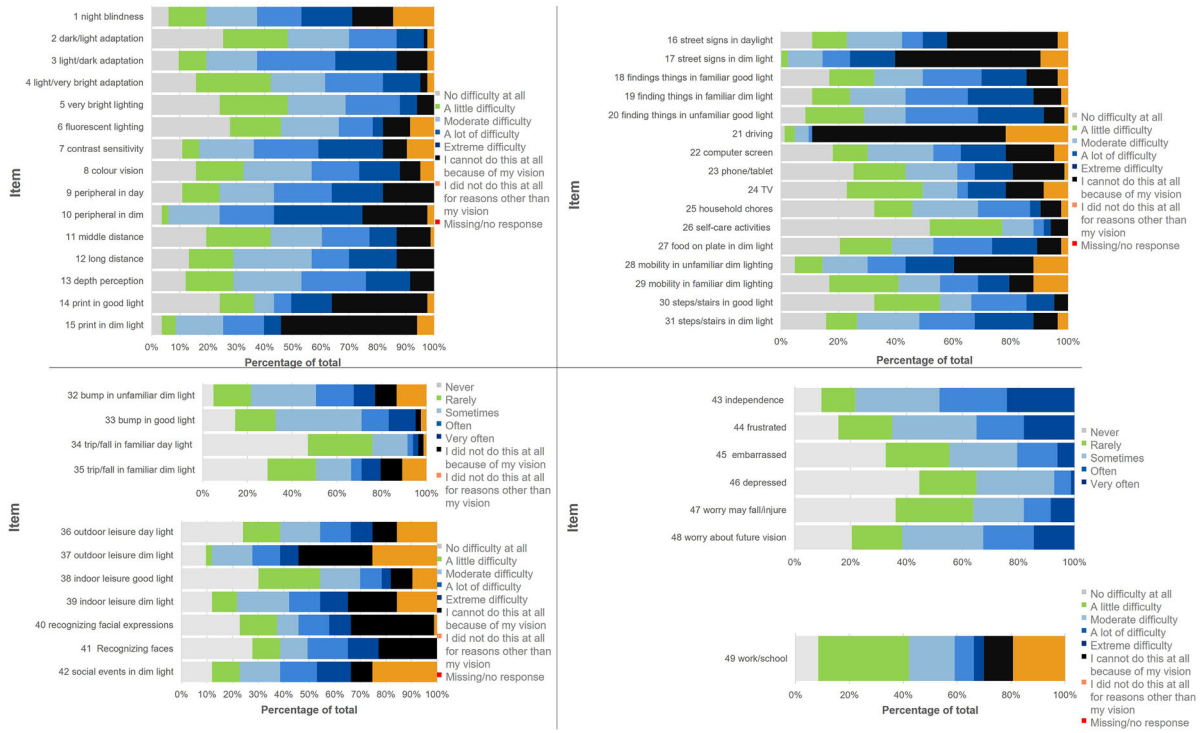

Fig. 1 Item response distributions for the ViSIO-PRO at baseline

Clinical Characteristics

Overall, there was a good range of different RP/LCA genotypes within the sample across adults and adolescents including a range of VA severity levels (Table 5).

Stage 1: Item Properties

Quality of Completion

Quality of completion for the ViSIO-PRO was excellent at both timepoints, with no items missed at baseline and only one item missed by one patient at 12–16-day follow-up. Four patients did not participate in the 12–16-day follow-up, due to starting treatment within the 12–16-day timeframe.

For the ViSIO-ObsRO, quality of completion was excellent across all timepoints, with no items missed at baseline or 12–16-day follow-up.

Item Response Distributions

For the ViSIO-PRO, baseline scores were relatively evenly distributed across the full response scale (Fig. 1). However, item 21 (driving) was heavily skewed to the higher end of the scale, i.e., great difficulty with driving. Some floor and ceiling effects were observed for a number of items and flagged for discussion (Supplementary File 3).

For the ViSIO-ObsRO, although responses were well distributed at baseline across the full response scale for most items (Fig. 2), there were several items with responses skewed towards the bottom of the scale, indicating that patients did not have difficulty or had minimal difficulty with the concept being assessed. ViSIO-ObsRO items showing floor or ceiling effects were flagged for discussion (Supplementary File 3). Full item response distribution tables for the ViSIO-PRO and ViSIO-ObsRO instruments are provided in Supplementary File 4.

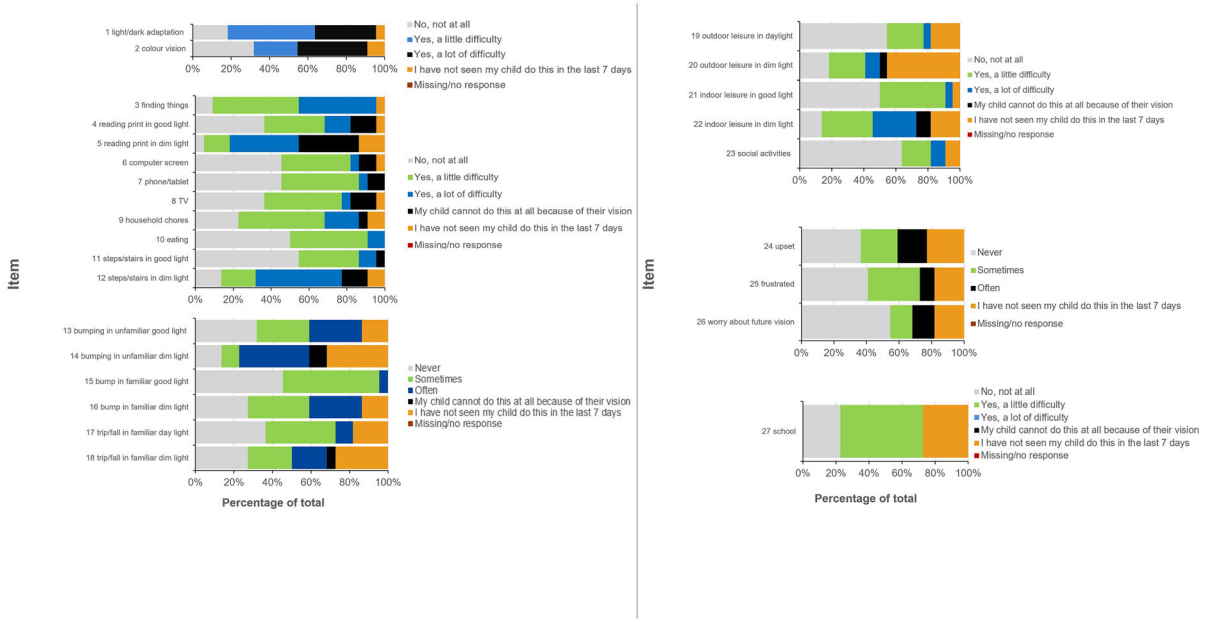

Fig. 2 Item response distributions for ViSIO-ObsRO at baseline

Stage 2: Dimensionality and Scoring

Inter-Item Correlations

Inter-item correlations between item pairs within the four specified subdomains were mostly moderate to strong (> 0.30) [31]. High item-pair correlations (≥ 0.90) were observed for some items in the visual function symptoms, vision-dependent ADL, and distal HRQoL domains. Weak correlations were found for four item pairs in the vision-dependent ADL domain (range 0.03–0.29), two item pairs in the mobility domain (range 0.16–0.22), and several item pairs within the distal HRQoL domain (range 0.00–0.28). Inter-item correlation matrices for each ViSIO-PRO domain are presented in Supplementary File 5.

Twenty-four ViSIO-ObsRO item pairs demonstrated high inter-item correlations (≥ 0.90; Supplementary File 5). However, these results should be interpreted with caution due to highly skewed item response distributions (Fig. 2).

Factor Analysis

Exploratory factor analysis (EFA) for the ViSIO-PRO identified two-factor or three-factor solutions, but item-domain groupings did not align conceptually with item content. Several items were removed, on the basis of the item response distributions and floor and ceiling effect results, while considering earlier qualitative findings and clinical relevance/importance (for further details on item deletion, see Supplementary File 6).

A confirmatory factor analysis (CFA) was then conducted to assess the factor structure with these selected items removed (Supplementary File 6). CFA results broadly supported a four-factor model reflecting the a-priori hypothesized domain structure with adequate model-fit (CFI 0.914, RMSEA 0.088, SRMR 0.112). Items excluded in the CFA were subsequently excluded from the finalized ViSIO-PRO except from item 21 (driving), which is scored separately from the remaining items.

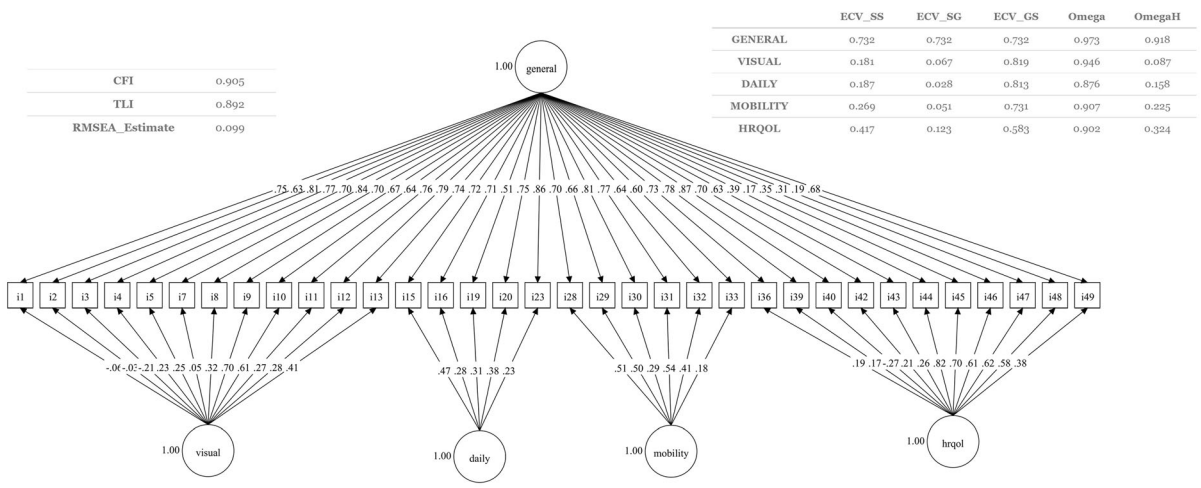

Fig. 3 Bifactor modeling for the ViSIO-PRO. *CFI* comparative fit index, *TLI* Tucker–Lewis index, *RMSEA* root mean square error of approximation, *ECV_SS* explained common variance of the specific factor with respect to itself, *ECV_SG* explained common variance of the specific factor with respect to the general factor, *ECV_GS* explained common variance of the general factor with respect to the specific factor, *Omega* omega reliability estimate, *OmegaH* hierarchical omega reliability estimate. Note, items are represented in the square boxes, factors are represented in the circles and the arrows indicate standardized factor loadings

Rasch Analysis

Rasch analysis was conducted within each of the four ViSIO-PRO domains. The presence of local dependencies informed further deletion of six items (Supplementary File 6).

Bifactor Model

A bifactor model with one general factor (representing a total score) and four specific factors was fit to investigate essential unidimensionality of all ViSIO-PRO items (Fig. 3). The general factor explained common variance (ECV) equal to 0.73—thus falling slightly below the recommended threshold to meet essential unidimensionality of 0.80 or higher [32]. However, as this result is likely due to the small sample size, it was still deemed acceptable to calculate a total score of all items.

The sample size for the ViSIO-ObsRO (n = 22) was not large enough to perform factor analysis, Rasch analysis, or bifactor modeling.

Item Deletion

Following all stage 1 and 2 psychometric analyses, the study team and expert clinicians discussed possible item deletion. Decisions were made on the basis of stage 1 and 2 results, findings from the previous qualitative interviews [5, 7, 8], and input from the expert clinicians. Given the small ViSIO-ObsRO sample size and the limited analyses performed, a cautious approach towards item deletion was taken. Fourteen items were removed from the ViSIO-PRO and two items from the ViSIO-ObsRO. Rationale for item deletion is provided in Supplementary File 6.

Conceptual Framework

Thirty-five items were retained in the ViSIO-PRO and 25 items in the ViSIO-ObsRO for further psychometric validation (final conceptual framework provided in Tables 6 and 7, respectively).

Scoring Algorithm

A scoring algorithm for the ViSIO-PRO was established on the basis of the EFA, CFA, Rasch analyses, bifactor modeling, and findings from the previous qualitative research supporting the conceptual relevance of the domains and items. For the ViSIO-ObsRO, the scoring algorithm was based on findings for the ViSIO-PRO and

Table 6 Conceptual framework for the ViSIO-PRO including corresponding domains and subdomains

Domain	Subdomain	Concept	Item
Visual function symptoms	Night blindness		1. Difficulty seeing outside with street lighting on a dark night
	Light/dark adaptation		2. Difficulty adjusting from darkness to good lighting
			3. Difficulty adjusting from good lighting to darkness
			4. Difficulty adjusting from good lighting to very bright lighting
	Vision in bright lighting		5. Difficulty seeing in very bright lighting once you have already adjusted to the lighting
	Contrast sensitivity		6. Difficulty seeing furniture in dimly lit rooms with dark floors
	Difficulty seeing color		7. Difficulty telling the difference between different colors in good lighting
	Loss of peripheral vision		8. Difficulty noticing objects off to the side when walking outdoors in daylight
			9. Difficulty noticing objects off to the side when walking outdoors in dim lighting
	Distance vision	Middle distance	10. Difficulty seeing things that are on the other side of the room in good lighting
		Long distance	11. Difficulty seeing things that are far away in daylight
	Depth perception		12. Difficulty judging how far away things are from you in daylight
Vision-dependent ADL	Reading normal print		13. Difficulty reading normal-size print in a dimly lit room
	Reading street signs		14. Difficulty reading street signs when walking outside in daylight
	Finding things in familiar environment		15. Difficulty finding an object in a dimly lit room in your own home
	Finding things in unfamiliar environments		16. Difficulty finding things when moved from their usual place in a room with good lighting
	Driving*		17. Difficulty driving in dim lighting
	Viewing digital screens		18. Difficulty seeing things on a mobile phone or tablet

Table 6 continued

Domain	Subdomain	Concept	Item
Mobility	Navigating/mobility in unfamiliar environments		19. Difficulty walking in unfamiliar outdoor places by yourself without help from someone else in dim lighting
	Navigating/mobility in dark or dim light		20. Difficulty walking in familiar outdoor places by yourself without help from someone else in dim lighting
	Going up/down steps and stairs		21. Difficulty going down steps or stairs, or stepping off a curb by yourself without help from someone else in good lighting
			22. Difficulty going down steps or stairs, or stepping off a curb by yourself without help from someone else in dim lighting
	Bumping into objects/people		23. Bumping into objects or people when walking in unfamiliar places in dim lighting
			24. Bumping into objects when they were moved from their usual spot when walking in a room with good lighting
Distal HRQoL	Leisure activities		25. Difficulty doing outdoor leisure activities in daylight
			26. Difficulty doing indoor leisure activities in a dimly lit room
	Social functioning	Recognizing facial expressions	27. Difficulty seeing reactions on people's faces in a room with good lighting
		Going to social events	28. Difficulty going to social events in dim lighting
	Interpersonal relationships	Independence	29. Relying on others for help
	Emotional well-being	Frustration	30. Felt frustrated
		Embarrassment	31. Felt embarrassed
		Depression	32. Felt depressed
		Worry	33. Felt worried that you may fall or be injured
			34. Felt worried about changes to your vision in future
	Work and school		35. Difficulty at work or school

*Impacts on driving will not contribute to domain or total scores

Table 7 Conceptual framework for ViSIO-ObsRO including corresponding domains and subdomains

Domain	Subdomain	Concept	Item
Visual function symptoms	Light/dark adaptation		1. Difficulty adjusting to new light conditions
	Difficulties seeing color		2. Difficulty telling the difference between different colors
Vision-dependent ADL		Finding things	3. Difficulty finding things
		Reading normal print	4. Difficulty identifying letters, numbers, or small pictures in a room with good lighting
			5. Difficulty identifying letters, numbers, or small pictures in a dimly lit room
		Viewing digital screens	6. Difficulty seeing things on a computer screen
			7. Difficulty seeing things on a mobile phone or tablet
			8. Difficulty when watching TV
		Household chores	9. Difficulty when tidying up toys or clothes
		Eating	10. Difficulty finding food on their plate
Mobility		Going up/down steps and stairs	11. Difficulty when going down steps or stairs, or stepping off a curb in good lighting without help from someone else
			12. Difficulty when going down steps or stairs, or stepping off a curb in dim lighting without help from someone else
		Bumping into objects/people	13. Bump into objects or people when walking in unfamiliar environments in good lighting
			14. Bump into objects or people when walking in unfamiliar environments in dim lighting
			15. Bump into objects or people when walking in familiar places in good lighting
			16. Bump into objects or people when walking in familiar places in dim lighting
Distal HRQoL	Leisure activities		17. Difficulty doing outdoor leisure activities in daylight
			18. Difficulty doing outdoor leisure activities in dim lighting
			19. Difficulty doing indoor leisure activities in good lighting
			20. Difficulty when doing indoor leisure activities in a dimly lit room
	Social functioning/ independence	Taking part in social activities	21. Difficulty taking part in social activities without help from a parent or carer
	Emotional well-being	Upset	22. Become upset
		Frustration	23. Become frustrated
		Worry	24. Become worried about changes to vision in future
			24a. Person who informed on well-being
	Work and school		25. Difficulty doing school work or homework
			25a. Person who observed difficulties

Table 8 Rescaling method for ViSIO-PRO items 29–34

Response option	0	1	2	3	4
Rescaled	0	1.25	2.5	3.75	5

Table 9 Rescaling methods for ViSIO-ObsRO items 1, 2, and 22–24

Response option	0	1	2
Rescaled	0	1.5	3

conceptual relevance informed by previous qualitative research.

All ViSIO-PRO items are rated using either a 4-point or 5-point verbal descriptor scale. An additional "not applicable" response option is included for items 1–28 and 35 (Table 6), but does not contribute to the scoring of the ViSIO-PRO and instead can be reported descriptively (i.e., treated as equivalent to missing data). Items responded to using a 4-point verbal descriptor scale (items 29–34) are rescaled to a 5-point scale prior to calculating a domain or total score, so that every item is scored using the same 0–5 scale (Table 8).

Similarly, all ViSIO-ObsRO items are rated using a 2-point or 3-point verbal descriptor response scale and include an additional "not applicable" response option that does not contribute to the scoring of the ViSIO-ObsRO. Items assessed using a 2-point verbal descriptor response scale (items 1, 2, and 22–24 in Table 7 are rescaled to a 3-point so that every item is scored using the same 0–3 scale; Table 9).

For the ViSIO-PRO and ViSIO-ObsRO, an overall total score and domain scores for the four domains (Tables 6, 7) in each instrument can be calculated.

Domain scores: Domain scores are calculated by summing scores for all items within a domain and dividing by the number of items completed within that domain. Thus, each domain score is an average or mean of the item scores for the items included in that domain.

Total score: All items included in these four domains can be combined into a single total score, calculated by averaging the mean domain scores. Each domain and total score can range from 0–5 to 0–3 for the ViSIO-PRO and ViSIO-ObsRO, respectively, where higher total scores reflect worse visual functioning or HRQoL.

Item 17 (driving in dim lighting) does not contribute to any ViSIO-PRO domain score or the total score due to a high proportion of patients with RP/LCA not being able to drive. However, this ViSIO-PRO item was retained on the basis of evidence from previous research, to assess and monitor change in driving ability over time [7, 8].

Stage 3: Reliability and Validity of Scores

Reliability

ViSIO-PRO All Cronbach's alpha coefficients for the ViSIO-PRO total and domain scores were ≥ 0.80, indicating high internal consistency reliability (Table 10) [33]. The impact of ViSIO-PRO item/domain removal provided further support for internal consistency reliability, with no domains and only few items showing marginal increases using the alpha-if-item deleted method (Supplementary File 7 for all internal consistency reliability findings). The ViSIO-PRO items also had strong item–total correlations. Only item 40 (recognizing facial expressions) showed a correlation < 0.40 (with the distal HRQoL domain; Supplementary File 8 for all item–total correlations).

Intraclass correlation coefficients (ICCs) for the ViSIO-PRO total score and domain scores all surpassed 0.75 across each TRTAP (Table 10), indicating excellent test–retest reliability (TRT; Supplementary File 9).

ViSIO-ObsRO Cronbach's alpha coefficients for the ViSIO-ObsRO total score and domain scores were ≥ 0.70, indicating good internal consistency reliability (Table 11; Supplementary File 7). Using the alpha-if-item deleted method, all ViSIO-ObsRO Cronbach's alpha coefficients were high and only marginally increased with the removal of select items/domains (Supplementary File 7). For item–total correlations,

Table 10 Reliability of ViSIO-PRO scores

Score	Internal consistency reliability: Cronbach's alpha (n = 83)	Test–retest reliability: ICC (95% confidence intervals)		
		TRTAP 1 (n = 57)	TRTAP 2 (n = 65)	TRTAP 3 (n = 33)
Visual function symptoms domain	0.93	0.96 (0.93–0.98)	0.95 (0.92–0.97)	0.96 (0.92–0.98)
Vision-dependent ADL domain	0.84	0.91 (0.85–0.94)	0.92 (0.88–0.95)	0.93 (0.86–0.97)
Mobility domain	0.89	0.89 (0.82–0.94)	0.90 (0.83–0.94)	0.92 (0.84–0.96)
Distal HRQoL domain	0.86	0.95 (0.90–0.97)	0.92 (0.87–0.95)	0.96 (0.92–0.98)
Total score	0.89	0.96 (0.93–0.98)	0.96 (0.93–0.97)	0.98 (0.96–0.99)

TRTAP 1 adult and adolescent patients with data for the ViSIO-PRO at both baseline and timepoint 2 with the same response on the PGI-S at both timepoints, *TRTAP 2* adult and adolescent patients with data for the ViSIO-PRO at both baseline and timepoint 2 with a less than 10-point change on the EQ-5D-5L VAS between timepoints, *TRTAP 3* adult and adolescent patients with data for the ViSIO-PRO at both baseline and timepoint 2 with a less than 0.037-point change on the EQ-5D-5L UK index score between timepoints

ViSIO-ObsRO items performed well, with most correlating highly with their corresponding domains (Supplementary File 8). However, four items in the distal HRQoL domain (items 21, 23, 26, and 27) had item–total correlation coefficients < 0.40 (0.08–0.36).

ICCs for the ViSIO-ObsRO total and domain scores all surpassed 0.50 indicating moderate to excellent TRT reliability across each TRTAP (Table 11; Supplementary File 9).

Construct Validity

Convergent and Discriminant Validity Convergent validity was supported by a logical pattern of correlations between the ViSIO-PRO total score and scores from concurrent measures expected to be closely related, including the PGI-S (r = 0.77), VA scores (r = 0.54–0.60), and VFQ-25 composite score (r = −0.93). Moderate to strong correlations (r = 0.23 to −0.89) were also reported between the ViSIO-PRO domain scores and scores assessing similar concepts. These patterns of results were also observed for the ViSIO-ObsRO total score in respect to the CGI-S (r = 0.76), VA score (r = 0.54), and VFQ-25 composite score (r = −0.89).

Weak correlations between the ViSIO-PRO and ViSIO-ObsRO domain scores and scores from measures assessing dissimilar concepts indicated discriminant validity, for example, low correlations between the vision-dependent ADL domain in both the ViSIO-PRO and ViSIO-ObsRO and the EQ-5D-5L anxiety/depression score (0.10 and −0.05, respectively). Weak correlations were observed between the ViSIO-PRO and ViSIO-ObsRO scores and pain domains of concurrent measures, consistent with evidence that pain is not considered a symptom of RP/LCA [4–8], and none of the ViSIO-PRO or ViSIO-ObsRO scores assesses pain. For all convergent and discriminant validity outputs, see Supplementary File 10.

Known-Groups Validity There was a statistically significant difference in mean ViSIO-PRO scores when groups were defined by PGI-S response ($p < 0.001$), with monotonically increasing mean scores with greater severity (Table 12) and large between-group ES. Statistically significant differences in mean ViSIO-PRO scores by age group ($p < 0.001$) were also observed with higher scores among patients in the older age groups as expected, consistent with the degenerative nature of RP/LCA. Known-groups comparisons for the ViSIO-PRO domains followed a similar pattern with monotonically increasing mean scores by PGI-S and age (Supplementary File 11).

Table 11 Reliability of ViSIO-ObsRO scores

Score	Internal consistency reliability: Cronbach's alpha (n = 22)	Test–retest reliability: ICC (95% confidence intervals)		
		TRTAP 1 (n = 14)	TRTAP 2 (n = 16)	TRTAP 3 (n = 10)
Visual function symptoms domain	N/A*	0.57 (0.07–0.84)	0.70 (0.33–0.89)	0.57 (−0.10 to 0.88)
Vision-dependent ADL domain	0.92	0.80 (0.47–0.93)	0.96 (0.89–0.99)	0.95 (0.81–0.99)
Mobility domain	0.95	0.68 (0.26–0.89)	0.83 (0.49–0.94)	0.75 (0.24–0.93)
Distal HRQoL domain	0.76	0.69 (0.21–0.90)	0.54 (0.05–0.82)	0.69 (0.10–0.92)
Total score	0.71	0.66 (0.22–0.88)	0.85 (0.63–0.95)	0.80 (0.36–0.95)

TRTAP 1 parents/caregivers of patients aged 3–11 years old completed the ViSIO-ObsRO at both baseline and timepoint 2 with the same response on the CGI-S at both timepoints, *TRTAP 2* parents/caregivers of patients aged 3–11 years old completed the ViSIO-ObsRO at both baseline and timepoint 2 with a less than 10-point change on the EQ-5D-5L VAS between timepoints, *TRTAP 3* parents/caregivers of patients aged 3–11 years old completed the ViSIO-ObsRO at both baseline and timepoint 2 with a less than 0.037-point change on the EQ-5D-5L UK index score between timepoints, *ICC* intraclass correlation coefficient

*Cronbach's alpha was not calculated for domains consisting of fewer than three items

Due to the small ObsRO sample size, a small number of parents/caregivers of child patients were in each of the CGI-S response categories and age groups, limiting interpretation. As expected, higher mean scores were observed in the CGI-S "Severe/Very severe" group compared with the "Mild/Moderate" group, with statistically significant differences between severity groups for the ViSIO-ObsRO total (Table 13) and most domain scores (Supplementary File 11). Mean scores did not differ significantly by age.

Stage 4: Preliminary Exploration of Interpretation of Scores

Distribution-Based Methods

Distribution-based estimates of meaningful change ranged between 0.30 and 0.65 for all ViSIO-PRO scores (Table 14) and 0.15–0.49 for all ViSIO-ObsRO scores (Table 15), indicating that changes above those magnitudes would be indicative of a true score change beyond measurement error.

Exploratory Analyses

Mean ViSIO-PRO domain and total scores at baseline were examined by genotype-defined subgroups with sufficient sample sizes (*RLBP1* RP, *RPE65* RP/LCA, and X-linked/*RPGR* RP). All other genotypes were grouped together due to smaller sample sizes ($n < 10$).

There were no clear differences between RP/LCA genotypes based on ViSIO-PRO scores, with the exception of statistically significant differences across subgroups for the mobility domain score. The *RLBP1* RP subgroup showed the highest mean scores across all domains and the total score, indicating worse visual functioning or HRQoL compared with other genotypes, although a higher mean age could be observed in the *RLBP1* RP subgroup compared with the other genotypes (Supplementary File 12).

Exploratory analyses were not performed for the ViSIO-ObsRO due to small sample size.

DISCUSSION

The ViSIO-PRO and ViSIO-ObsRO are the first known RP/LCA-specific instruments developed for use with adult/adolescent patients with RP and LCA and caregivers of children with RP/LCA. Qualitative evidence supporting the content validity of the instruments has been demonstrated previously, across a range of RP/LCA genotypes [5, 7, 8]. However, according to regulatory guidance, to be considered fit-for-

Table 12 Known-groups comparison for the ViSIO-PRO total score at baseline

Anchor	Group	*N*	Mean (SD)	Median	Between-groups effect size	*p* value
PGI-S response*	None (reference)	6	1.14 (0.60)	1.36		< 0.001
	Mild/Moderate	39	1.86 (0.71)	1.81	1.02	
	Severe/Very severe	38	3.17 (0.73)	3.27	2.84	
Age	12–17 years old (reference)	18	1.61 (0.62)	1.57		< 0.001
	18–35 years old	25	1.95 (0.70)	2.11	0.51	
	36–60 years old	28	3.06 (0.82)	3.21	1.93	
	61+ years old	12	3.03 (1.17)	3.42	1.62	

*PGI-S item wording: Please rate how severe your vision problems have been over the past 7 days?

Table 13 Known-groups comparison for the ViSIO-ObsRO total score at baseline

Anchor	Group	*N*	Mean (SD)	Median	*p* value
CGI-S response*	None (reference)	1	0.00 (N.A.)	0.00	< 0.001
	Mild/Moderate	15	0.95 (0.31)	0.98	
	Severe/Very severe	6	1.72 (0.30)	1.69	
Age	3–5 years old	8	1.05 (0.48)	0.95	0.663
	6–11 years old	14	1.16 (0.55)	1.22	

*CGI-S item wording: Please rate how severe your child's vision problems have been over the past 7 days? Note, the between-group effect sizes were not calculated for the ViSIO-ObsRO due to insufficient sample sizes across the CGI-S response categories and age groups

purpose, there must also be adequate evidence supporting the psychometric properties of the ViSIO-PRO and ViSIO-ObsRO in their intended context of use [10–12].

To address this, the current study aimed to evaluate the psychometric properties of the ViSIO-PRO and ViSIO-ObsRO instruments using data collected from a non-interventional, observational study in France, Germany, Canada, Denmark, and the USA.

ViSIO-PRO

Results provide strong evidence for the psychometric validity and scoring of the ViSIO-PRO instrument, supporting its use in broader RP/LCA and as an appropriate outcome assessment in future clinical trials, other large research studies, or clinical practice.

Some floor and ceiling effects were observed; however, this was anticipated given differing severities across genotypes and the progressive nature of RP/LCA. Moderate to strong inter-item correlations were reported between items within each hypothesized domain. Strong correlations were not considered problematic, as item pairs with very strong correlations typically assessed similar concepts in different environmental conditions, an important feature of the ViSIO instruments. Strong correlations also likely reflect the nature of the condition, with visual functioning underpinning the majority of concepts assessed across ViSIO-PRO domains.

There was good representation of different RP/LCA genotypes in the sample, including

Table 14 Distribution-based estimates for the ViSIO-PRO domains and total scores

ViSIO-PRO scores	*N*	0.5 SD	SEM
Visual function symptoms	83	0.56	0.30
Vision-dependent ADL	82	0.65	0.53
Mobility	82	0.61	0.40
Distal HRQoL	83	0.52	0.39
Total score	83	0.51	0.34

SD standard deviation; 0.5 SD is based on the SD at baseline

SEM standard error of measurement. SEM is calculated as SD at baseline multiplied by the square root of 1 minus the reliability of the score (Cronbach's alpha)

Table 15 Distribution-based estimates of the ViSIO-ObsRO domains and total scores

ViSIO-ObsRO scores	*N*	0.5 SD	SEM
Visual function symptoms	22	0.45	0.49
Vision-dependent ADL	22	0.35	0.20
Mobility	22	0.33	0.15
Distal HRQoL	21	0.27	0.26
Total score	22	0.26	0.28

SD standard deviation; 0.5 SD is based on the SD at baseline

SEM standard error of measurement. SEM is calculated as SD at baseline multiplied by the square root of 1 minus the reliability of the score (Cronbach's alpha)

coverage of the topmost prevalent disease-causing genes (e.g., *RHO*, *PRPF31*, *PRPH2*, *EYS*, *USH2A*, *RPGR*, and *RP2*) [3, 34] and those treated with voretigene neparvovec (Luxturna). The findings are therefore considered adequate to support conclusions regarding the psychometric properties, dimensionality, and scoring of the ViSIO-PRO across multiple genotypes of RP/LCA. Item response distributions, dimensionality analyses, and previous qualitative interviews, alongside input from clinical experts informed the removal of several items, resulting in a 35-item instrument. Bifactor analysis showed adequate fit for a mean total score, in addition to four domain scores (visual function symptoms, vision-dependent ADL, mobility, and distal HRQoL). Domain and total scores performed well in tests of reliability, demonstrating good internal consistency reliability and TRT reliability. Construct validity was also supported, with significant differences in mean scores by severity and age group reported, with higher scores observed for older patients, in line with the degenerative nature of the disease. Exploratory analyses indicated that there were no clear differences in scores between RP and LCA genotypes, supporting the use of the ViSIO-PRO with patients with a broad range of RP/LCA genotypes; an important consideration for a condition with such an extensive and expanding number of gene mutations involved. This finding was consistent with the qualitative research that highlighted that similar visual function symptoms, impacts on vision-dependent ADL and mobility, and impacts on distal HRQoL were reported among patients with different gene mutations [5, 7, 8].

ViSIO-ObsRO

Analysis of the ViSIO-ObsRO was limited by the sample size due to challenges associated with recruiting children aged 3–11 years with a rare and progressive condition such as RP/LCA. However, initial evidence generated supports the psychometric validity of the ViSIO-ObsRO and established dimensionality and scoring, supporting its use in future clinical practice to demonstrate maintenance or rate of deterioration of visual functioning in pediatric populations.

Item responses at baseline were well distributed for most items; however, some demonstrated very high ceiling effects. Given the degenerative nature of RP/LCA and that severity of disease is often milder in pediatric populations, ceiling effects were expected and did not necessarily indicate problematic items [1, 35].

Due to the limited sample size, a more cautious approach was taken towards item deletion

and a scoring algorithm consistent with the ViSIO-PRO was applied. The resulting total score and four domain scores demonstrated good internal consistency and TRT reliability as well as good convergent, discriminant, and known-groups validity.

Limitations

For both the ViSIO-PRO and ViSIO-ObsRO instruments, analyses were limited by the small sample size for psychometric validation. Given the rarity of the disease, the study achieved a reasonable sample size and did include good representation of different RP/LCA genotypes; however, representation of certain genotypes in the sample was limited. Collection of additional data in future studies are recommended to further confirm validity across genotypes and cross-culturally in a larger sample.

Nevertheless, in this sample, a large variety of genotypes including *RPE65* RP, *RLBP1* RP, and *RPGR* X-linked RP were well represented. The study was conducted exclusively within a non-syndromic RP/LCA population, supporting use of the ViSIO instruments within this specific population across RP/LCA genotypes. This is unlike other PRO instruments developed, such as the Michigan Retinal Degeneration Questionnaire (MRDQ), which have not been specifically validated in RP/LCA but rather developed to capture the visual function symptoms occurring across a range of IRDs and, thus, may assess concepts that lack relevance or fail to comprehensively assess all concepts of importance to the RP/LCA population [36, 37].

The analyses were also limited by the lack of objective, clinical measures available for use as anchors in the psychometric analyses, specifically for the construct validity analyses. However, the anchors used were selected as they were expected to be sufficiently correlated with the ViSIO-PRO and ViSIO-ObsRO instruments and better reflected aspects of visual functioning and HRQoL compared with objective, clinical measures that differed in use across clinical sites or were reported as missing.

Finally, within the current dataset it was not possible to examine the ability of the instruments to detect changes over time, particularly in response to treatment. Future analyses using pre- and post-treatment data are planned with *RPE65* patients receiving voretigene neparvovec gene therapy. Data will be analyzed to provide initial insights to the sensitivity of the ViSIO-PRO and ViSIO-ObsRO to changes over time.

CONCLUSION

The findings support the 35-item ViSIO-PRO and 25-item ViSIO-ObsRO as valid and reliable measures across RP/LCA genotypes, to serve as outcome assessments in future clinical trials or track disease severity in clinical practice. Further evidence is required to establish the ability of the ViSIO-PRO and ViSIO-ObsRO to detect changes over time and to inform meaningful change thresholds.

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Compliance with Ethics Guidelines. Centralized ethical approval and oversight for this study was provided by Copernicus Group Independent Review Board (CG-IRB) to conduct the study in the US and Denmark (approval number: 20190129). Local ethical approval was provided by the Comité de protection des personnes (CPP) and Recherches et Collections Biologiques (RCB) in France (RCB ID: 2019-A01883-54, Réf. CPP: 19078-43420) and by specialist clinical sites in Germany (Universitätsklinikum Tübingen: 343/2019B01) and Canada (Newfoundland and Labrador Health Research Ethics Authority (HREA): #2019.186). See Supplementary File 13 for ethical approval information. Documentation of informed consent was obtained prior to any research activities being conducted. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The ViSIO-PRO and ViSIO-ObsRO are available for use under a formal licensing agreement. Please contact amanda.rosett@rws.com to request permission for use or for additional information.

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