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Patient-reported outcome measures in inherited retinal degeneration gene therapy trials

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Abstract

Patient-reported outcome (PRO) measures have the potential to uniquely capture patient experience and serve as an outcome measure in inherited retinal degeneration (IRD) gene therapy trials. An IRD-specific patient-reported outcome measure may yield valuable information that has not been obtained from inherited retinal dystrophy gene therapy trials published to-date. Existing PRO measures have inherent limitations for use in IRD gene therapy trials. Developing an applicable patient-reported outcome measure for such trials needs to incorporate patient input from the target population, demonstrate sound psychometric properties, and be made in accordance with U.S. Food and Drug Administration (FDA) guidelines,. This review will discuss the currently available PRO instruments, their limitations for IRD therapeutic trials, and suggestions for future PRO development in IRD populations. The PRO instruments highlighted were identified in PubMed search of English-language journals and previously published review articles.

Keywords

patient-reported outcomes; gene therapy; inherited retinal degeneration; clinical trial; PRO; retinal dystrophy

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INTRODUCTION

Inherited retinal degenerations (IRDs) are generally slowly progressing diseases that are caused by pathogenic variants in a given gene. Notably, patients with rod-cone dystrophy often complain of lack of peripheral vision, limited contrast sensitivity, and poor low-light vision which can all lead to substantial limitations in daily life (1–4). Certain IRDs may follow a common progression pattern, such as degeneration beginning in the periphery, then progressing centrally, and causing a tunnel vision effect. Depending on the type of IRD, either rods or cones may be disproportionally affected resulting in variable deficits in night, peripheral, central, or color vision. Despite some commonalities, the effects of retinal dystrophies are unique to the individual patient.

Often clinical tests are limited in their ability to describe patients' vision impairment in the context of the real world(4–6). For example, a patient may have 20/20 visual acuity, but be unable to walk through an unfamiliar room due to a severely constrained visual field or due to the background illumination. Common clinical measures--visual acuity, visual field, contrast sensitivity, and electroretinogram (ERG) -- do not always reflect patient experience (3–5). Furthermore, these tests have challenges in the reliability of repeated measurements(7–12).

Until recently those diagnosed with IRDs had no treatment options. Today, therapeutic advances, such as gene therapy, are providing new possibilities for IRD treatment, and clinical trials to evaluate the efficacy and safety of these therapies are active in centers around the world. With the rapid advancements of these therapies, experts have already identified the need for standardized outcome measures and testing protocols(13).

Most importantly, as new treatments are developed, it is critical to evaluate whether or not the changes or improvements are meaningful to the patient(14). This, combined with the limitations in existing functional outcome measures, calls for the development of a sensitive, reliable, and validated measure to capture patient-reported outcomes (PROs) for use in IRD therapeutic trials.

The present review includes discussion of existing literature and clinical trials. Patient-reported outcome measures in this review were identified in a PubMed search using keywords of "patient-reported outcome", "questionnaire", "retinal dystrophy", "inherited retinal disease", "retinitis pigmentosa". The search was limited to PubMed indexed English-language journals and PROs identified in previous reviews that are disease-specific to a condition of inherited retinal degeneration.

In this review, we will discuss the use of PRO instruments, status of current PROs, and recommendations for PRO development. There will be particular emphasis on three key features of PRO development described by the FDA and their particular importance in IRD gene therapy populations. A validated PRO measure is an instrument that has undergone a qualitative analysis of in-depth patient interviews as well as thorough quantitative statistical analysis to determine the measure's reliability and ability to detect change in the target population. After a review of the existing PRO literature, we have found the existing

instruments do not fully meet the needs of a PRO for gene therapy clinical trials therapy and suggest the development of a novel PRO for this application.

Why use PRO Instruments?

Patient-reported outcome measures offer a means of capturing patients' experience of how their vision condition affects their daily life. These measures are commonly administered as questionnaires that can be used as a screening tool for visual impairment or as a functional outcome measure, and their application results in an enhanced communication between the patient and provider by uncovering aspects of vision and living that might otherwise would be ignored.

Despite the variety of clinical tests used to diagnose and monitor IRDs, researchers and clinicians still struggle to relate the results of clinical tests to a patient's experience. Here we will highlight three prominent challenges facing reliance on the results of current visual and retinal function tests in the IRD population.

First, each clinical test individually does not capture the breadth of visual dysfunction and there is no gold standard test that can fully characterize the impact an IRD has on a patient. As a result, physicians often order a large number of clinical tests for IRD patients. Although recommendations have been made for standardizing testing and outcome measures, patient burden from several hours of testing can be significant, and often the tests yield findings that fail to address domains that are relevant to their condition and its treatment(13).

Second, clinical test results can be incongruent with what the patient is experiencing. For example, patients may report changes to their vision, yet their visual acuity shows no change. Further investigation and testing may help explain patient symptoms, as seen with contrast sensitivity testing in patients with Stargardt's disease and normal visual acuity(15). Ultimately, a patient's quality of life should be the most important consideration in evaluating treatment efficacy, and thus PRO instruments have the potential to be the most comprehensive measure of a clinically meaningful treatment effect.

Third, the outcome of often-used tests such as visual acuity, visual field, contrast sensitivity, and electroretinography can show substantial test-retest variability in the IRD population(8–10)and some claim that these supposedly objective measures could be influenced by patients' moods or feelings about their general health(11, 16). This presents a challenge in interpreting and analyzing test results over time in IRD patients. In preparation for their clinical trials, groups have attempted to quantify the degree of variability in clinical tests for *ABCA4*(12, 17), *RS1*(7), *CHM*(18), *RPE65*(19) to inform the use of these data to define meaningful change beyond variability in these measures.

High quality PRO instruments are designed to offer reliable measures in their target population, which can mitigate the potentially inconsistent data obtained from clinical testing measures. In IRD gene therapy research, PRO tools have provided meaningful data to demonstrate treatment efficacy. In August 2017, published results of a Phase 3 trial of voretigene neparvovec (trade name: Luxterna) showed patient improvement in two non-

standard outcome measures—results of a mobility task and a PRO instrument, the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) —that measures visual functioning in a variety of domains.(20) In response to this report and previous findings, Luxturna was approved for treatment of RPE65-mediated IRD in December 2017(21).

Current Status of PRO Tools in Gene Therapy Trials

Research to-date places a heavy reliance on a small number of tested and validated PRO questionnaires. While well-established instruments such as the NEI VFQ-25 are high-quality and valuable tools, they were not designed for use in IRD populations nor for gene therapy trials. As will be discussed further in this article, use of a PRO instrument as an outcome measure requires careful consideration of the appropriateness of a particular instrument for the target population.

Despite these issues, to our knowledge, the only validated PRO instrument that has been used in published gene therapy trials for IRDs is the NEI VFQ-25. Of the peer-reviewed publications of clinical trials in *RPE65*, *XLRS*, and *CHM*; three studies have included the NEI VFQ-25 as an outcome measure(20, 22, 23). An additional three studies have anecdotally included patient commentary on the perceived changes in their vision from treatment (24–26). While patient interviews yield information on PROs, without standardizing the method of collecting patient experience and validating the questionnaire, the utility of patient commentaries is limited.

Of the 54 gene therapy trials listed in 2018 in the National Clinical Trials (NCT) database, 17 note the use of a PRO instrument. Only 7 of these trials specify use of a questionnaire that has been validated for use in other conditions in the NCT listings (NEI VFQ-25, SF-36). We note that in ongoing clinical trials it is possible that not all information on the trial's methods is publicly available.

While results from PROs are not required for U.S. Food and Drug Administration (FDA) approval, they are highly recommended by the FDA to be incorporated in a clinical trial. They have been identified as valuable outcome measures in other fields such as intraocular lenses (27) and the FDA has produced guidelines for PRO tool development (28).

Published FDA guidelines highlight four properties for evaluation of a PRO as an outcome measure: validity, reliability, ability to detect change, and interpretability (28). This review will focus on the first three criteria. Validity (i.e. content-related, criterion-related, predictive) refers to the capacity of the PRO instrument to describe the trait it intends to measure. Reliability (i.e. test-retest, internal consistency, inter-interviewer reproducibility) describes the consistency of the measurements taken using the PRO instrument. The instruments' ability to detect change (i.e. effect size, standard error) reflects the sensitivity of the test.

Inherited Retinal Dystrophy-Specific PRO Measures

Khadka, Senthil, and colleagues have evaluated the content, measurement, psychometric, and validation properties of the existing ophthalmologic questionnaires relative to FDA guidelines (29, 30). In their study of IRD PRO instruments, 11 IRD-specific PRO

instruments were identified (9 for retinitis pigmentosa, 1 for Stargardt's disease, and 1 for Congenital Stationary Night Blindness) and few had been adequately validated. To our knowledge, these disease-specific PROs have not been incorporated into past or existing gene therapy trials. We will discuss the merits of each of the PRO instruments and discuss the limitations to their application in IRD gene therapy clinical trials.

Perceived Visual Function Questionnaire.—As mentioned earlier, clinical function tests may not always reflect a patient's subjective experience. To address this concern, Lodha and colleagues developed a PRO instrument and compared PRO responses with visual acuity, visual field, and contrast sensitivity testing in patients with retinitis pigmentosa (RP) (2). They identified correlations between PRO items related to near vision with visual acuity and contrast sensitivity when these factors were combined (r=0.609). Similarly, they found a correlation between global vision items and combined visual field and visual acuity (r=0.545). This study is informative in its contribution to the understanding of the intersection of patient reports and clinical testing. However, the study gives little information regarding how PRO items were derived and psychometrically validated.

Activities of Daily Vision & Daily Task Performance Questionnaire.—Szlyk and colleagues have developed two PRO instruments designed to evaluate the functional tasks and activity limitations experienced by patients with RP (3, 31). The first PRO instrument they developed combined two existing questionnaires and added additional questions intended to be specific to RP-related difficulties (3). Using factor analysis, they categorized tasks into 6 categories and created a composite score. Additionally, their analysis generated a predictive model to evaluate the relative correlations of visual acuity, visual fields, and ERG to patient-reported functional abilities. Their findings suggest that acuity scores significantly correlated ($p<0.01$) with 28/33 PRO items (r=0.22–0.57), while 18/33 items correlated with V-4-e (r=0.20–0.47) and 23/33 with II-4-e (r=0.21–0.45) Goldmann visual field areas. ERG data added minimally to the correlation between PRO items and visual acuity and visual fields(3). In a follow-up to their previous work, the group sought to evaluate how well patient perception of their functional abilities matched their actual functional ability (31). Using the Activities of Daily Vision questionnaire and adding 20 RP-specific items identified by expert opinion, their results showed a significant correlation ($p<0.01$) between 29 of the 32 questionnaire items and a functional assessment by a low-vision specialist (r=0.13–0.70). In addition, they observed significant correlations ($p<0.01$) between questionnaire domains (reading/mobility/peripheral detection) and logMAR visual acuity ($r_s=-0.55/-0.40/-0.38$), visual field ($r_s=0.42/0.47/0.55$), contrast sensitivity ($r_s=0.62/0.54/0.52$) and ERG. While both studies are informative, the methods for generating PRO items using in-depth interviews with patients with IRDs and the extent to which the PROs were psychometrically validated are unclear.

Independent Mobility Questionnaire & Mobility Difficulties Questionnaire.—Turano 1999 developed a PRO targeted to assess mobility in RP patients based on expert opinion and a literature review(5). One hundred and forty-five patients completed the questionnaire but VA, VF, and contrast sensitivity data were available from only 32 patients. From these PRO data, they created a "person-measure" to describe the overall ability of the

patient. When comparing the clinical data, Turano et al reported that 57% of the variability in person-measure scores could be attributed to VA, contrast sensitivity, and VF converted to a functional retinal area. The strength of this PRO is the development process specifically addressing mobility in patients with RP as well as thorough psychometric analysis of the PRO data. The limitations of this PRO include its sole focus on mobility, its reliance on clinical testing that was performed in a small subpopulation of patients, and the lack of patient input in generating the questionnaire items. In a subsequent study, the group sought to examine how RP patients' mobility varies under different lighting conditions(6). Responses from 25 patients with RP on a 4-item questionnaire were significantly correlated with the walking speed of patients performing a mobility task when patients reported difficulty in more than one area ($p<0.01$). Furthermore, the group reported that contrast sensitivity and visual field extent accounted for 69% of the variance in walking speed. While short questionnaires provide certain advantages, this 4-item questionnaire was not validated and was limited to evaluating mobility in the context of varying lighting conditions.

Everyday Task Questionnaire.—In a continuation of their previous work, Lowe and Drasdo sought to broadly describe the patient experience with RP(32). Forty-eight patients with RP were sent a 16-item questionnaire and Snellen chart via mail. Patients were asked to complete the questionnaire and record their VA at home. Through these responses, they collected information regarding common features of RP, however the small sample size, and lack of validation present challenges for further application.

Vision-Related Activity of Daily Living & Field Expander Questionnaire.—In the course of studying visual field expander aids, two different groups created PRO instruments to collect information on patient experience (33, 34). While both studies were performed in small populations (16 and 10 patients), the questions were adapted to their RP low-vision aid users. The small sample size, specific focus of the questions, lack of validation, and insufficient information given regarding the PRO questionnaire all limit the generalizability of these PROs for use in other studies.

Stargardt's Macular Dystrophy Vision Questionnaire & Night Vision Questionnaire.—Apart from RP, only two PROs have been developed to target other IRDs. Miedziak et al studied 200 patients with Stargardt's disease to better characterize the condition(35). The group created a PRO tool based on existing instruments and patient input. While a strength of this PRO is its development in a large Stargardt's population, applying this PRO to all other IRDs would be inappropriate. Additionally, the validation methods of this PRO instrument are unclear. In a study of 101 Congenital Stationary Night Blindness (CSNB) patients, Bijveld et al attempted to specifically address night vision and created a PRO instrument that was based on existing low luminance questionnaires with some additional questions(1). While CSNB is an inherited retinal condition, the non-progressive nature of CSNB as well as the isolated symptom of night blindness are key distinguishers that limit the use of this PRO in a larger IRD population.

Guidelines for PRO Creation in IRD Gene Therapy Trials

Novel and existing PRO instruments used in clinical trials must be held to the same scientific standards as required for other outcome measures. Critically, the use of a particular PRO instrument must have demonstrated validity and reliability as well as appropriateness for its suggested application(14). To-date, no clinical trials have used publicly available PRO tools intended for use in the IRD gene therapy trials.

Development for intended population.—First, it is critical that a PRO instrument used in an IRD clinical trial has sound psychometric properties when applied to the target population. As Patrick et al and FDA colleagues have highlighted, the basic psychometric features of a PRO instrument are its reliability, validity, and ability to detect change (28, 36). In order for the application of a PRO to be appropriate for a clinical trial, each of these instrument features must be tested and proven in the IRD population targeted for clinical trials. The PRO should be developed for application to patients with a diagnosed retinal dystrophy who meet the eligibility criteria of the clinical trial (i.e. appropriate visual acuity, visual field, and ERG). While IRD clinical trials are largely enrolled based on identified pathogenic variants of genes (i.e. *RPE65*, *ABCA4*, etc.), given the similarity in clinical characteristics across many IRDs, we consider it appropriate to develop a PRO instrument in a non-gene specific IRD population first. As we gain further insight on these conditions—e.g., defined by genotype--and their responses to treatment, developing genotype-specific IRD PRO instruments may be warranted. At this time, a comprehensive PRO measure that evaluates all domains of visual dysfunction causing limitations, validated in a general IRD population (i.e. non gene-specific) has the greatest utility.

Notably, many IRD clinical trials are conducted in children which presents additional challenges to the validity and reliability of these measures. Items addressed in a PRO must be comprehendible and relevant to the development level of the population.

Patient input.—The basis for generating applicable content and items in a PRO instrument is patient input. Patrick and colleagues have detailed the appropriate methodology for collecting and analyzing the qualitative data generated from patient input (37, 38). This involves a series of in-depth interviews and focus groups with patients to capture their perceptions of how their vision relates to basic domains of their daily life (e.g., functioning, emotional, social) with a series of open-ended questions. These interviews are qualitatively analyzed, and items are identified and sifted by software such as Atlas TI (Version 8.1.3 (522) Atlas.ti, Germany) . Based on identification of recurrent items, common themes and points of emphasis (items), along with obtaining guidance from a panel of experts in the field (retinal specialists, genetic counselors, occupational therapists, electrophysiologists, for example), a set of questions are developed that are designed to address all of the domains in a relevant, understandable, and comprehensive manner.

From this, specific PRO items can be generated to target the identified patient symptoms and experiences. After these items are drafted, researchers must solicit more feedback from patients in the form of a cognitive interview to ensure the items clearly and consistently capture their intended concepts. As emphasized by Patrick et al, expert opinion is not a

substitute for this process of direct patient input in establishing content validity of an instrument (36).

While many PROs are not validated in patients with severely limited vision, questions must be targeted and relevant to the low-vision IRD population. As these conditions are congenital and slowly progressing, patients may have lived with poor vision and/or subtle visual decline their entire life. Therefore, some common activities and experiences included in existing PRO instruments may not be relevant; for example, questions related to driving a car. Patient input is the only method of generating items that are targeting meaningful patient experiences and activities. For these reasons, we highly encourage patient involvement in the early development of content and questions via the in-depth and cognitive interview methods described in FDA guidelines and supporting literature(28, 37, 38).

Psychometric evaluation.—After the PRO instrument has been administered to a large sample of patients, statistical analysis must be performed on the collected data. FDA guidelines do not specify the methodology of statistical evaluation. However, internal consistency, test-retest reliability and the ability to detect change (responsiveness) are noted as critical items to address in a novel PRO instrument (28, 36). Given that IRDs are slowly progressing, patient reports should yield consistent findings over short time intervals (i.e. two weeks). The measure must elicit reproducible responses from patients and can be tested directly by repeat administration of the PRO instrument to a subset of patients to ensure reliability. We encourage careful consideration of this concept when designing a PRO for children as consistency in responses may be a particular concern.

The ability of a PRO instrument to detect change might be a particular challenge in developing a PRO for the IRD gene therapy population. While many gene therapy trial candidates may have very limited vision, floor effects in the distribution of PRO data raise substantial concerns. PRO items must be able to generate results that detect the subtle differences in ability and/or experience from person to person. Capturing such subtle differences requires careful thought in designing a response scale or metric for each intended question. The responses must have sensitivity to the rate and manner that IRD patients experience vision loss. When examining the same patient over time, the PRO instrument must be sensitive to change in both natural disease progression as well as sensitive enough to detect a possible treatment effect of improved visual function.

PRO statistical analysis conducted using factor analysis methods have been described as yielding first-generation instruments (39). Some have advocated the creation of second-generation instruments that are based on applying Rasch validation techniques (39, 40). The FDA does not advocate for the use of a particular statistical method to use in its guidelines.

Conclusion

With the proliferation of gene therapy trials that are intended for regulatory approval, use of validated PRO instruments for IRD-specific populations is imperative to fully understand treatment efficacy. To our knowledge, there is currently no PRO instrument developed for and validated in the population of potential IRD gene therapy candidates. We assert that such

a PRO tool will be a valuable clinical trial outcome measure and will provide meaningful information for patients and researchers.

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