THE FORUM FOR COLLABORATIVE RESEARCH

OCULAR DISEASES FORUM 3

Ocular Diseases Forum 3

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THE FORUM
For Collaborative Research℠

Berkeley Public Health

CONTENTS

SESSION I: INTRODUCTIONS AND PROJECT OVERVIEW

The Ocular Disease Forum's third meeting opened with a welcome for participants, a review of the Forum's processes, and a discussion of goals and objectives for the meeting. Read about the Forum's operating principles and working process here.

The ODF is sponsored by Adverum, Alkeus Pharmaceuticals, Atsena Therapeutics, Boehringer Ingelheim, Fortrea, iCare, Lexitas, Merit, RV, and Tern Therapeutics.

Objectives for ODF3

Speaker: Claire Gelfman, Forum for Collaborative Research/CMG Consulting

Dr. Claire Gelfman outlined the goals for ODF3: to integrate lessons learned from AMD and geographic atrophy (GA) development, to explore how functional and structural endpoints can be harmonized across disease areas, and to refine strategies for regulatory engagement with the FDA and EMA.

SESSION II: ONGOING COLLABORATIONS AND CURRENT EFFORTS

International efforts to standardize and validate clinical endpoints for IRDs and creating consensus on measuring disease progression.

Ongoing Efforts: ERN-EYE

Speaker: Bart Leroy, Ghent University
Slides: Ongoing Efforts: ERN-EYE

Dr. Bart Leroy reviewed the activities of the European Reference Network for Rare Eye Diseases (ERN-EYE) and the policy advocacy group Act4RED. Dr. Leroy described the importance collaboration and information-sharing to improve clinical trial design., ERN-EYE and its partners aim to promote leaner, more innovative trial designs with realistic, patient-relevant endpoints.

Dr. Leroy used the example of the Phase 2/3 Illuminate study of sepofarsen, to discuss the limitations of traditional comparative approaches in small, heterogeneous rare-disease populations. The study exemplifies how adaptive analyses and more flexible endpoint strategies can yield interpretable results even with small sample sizes.

ERN-EYE's RealiseD program is developing validated patient-reported outcomes (PROs) and natural-history datasets for Leber congenital amaurosis, Stargardt disease, and achromatopsia. This program seeks to redefine therapeutic success by recognizing slowed decline or stable disease as meaningful, successful outcomes.

Dr. Leroy closed by advocating for alignment among science, policy, and patient experience. He also encouraged continued collaboration between ERN-EYE, the Forum, and U.S. partners on endpoint development, regulatory interaction, and patient-centered evidence generation.

Regulatory Endpoints and Trial Design for IRDs (REDI) Working Group: Ongoing Efforts

Speaker: Rachel Huckfeldt, Massachusetts Eye and Ear
Slides: Regulatory Endpoints and Trial Design for IRDs (REDI) Working Group: Ongoing Efforts

Dr. Rachel Huckfeldt reviewed the activities of the Regulatory Endpoints and Trial Design for IRDs (REDI) Working Group, detailing work to standardize endpoint evaluation and trial methodology.

The RUSH2A study of USH2A-related retinal degeneration continues to inform endpoint selection. Dr. Huckfeldt compared multiple candidate measures — visual acuity (VA), ellipsoid-zone (EZ) area, microperimetry, static perimetry, and full-field stimulus threshold testing (FST) — to assess their sensitivity, variability, and correlation with disease progression. Traditional measures such as VA and EZ area demonstrated limited dynamic range and significant floor effects, while microperimetry, static perimetry, and FST showed stronger longitudinal change and reproducibility. FST exhibited negligible floor effects, low test–retest variability, and the largest proportion of eyes exceeding the coefficient of repeatability (30 percent at two years and 47 percent at four years), making it a compelling functional endpoint for IRD trials.

New REDI initiatives include modeling functional-transition points, establishing an MCID (Minimal Clinically Important Difference) for FST, and developing composite endpoints that integrate structural and functional measures as well as patient-reported outcomes (PROs). Defining standardized, clinically meaningful changes remains a challenge for regulatory acceptance and endpoint qualification.

The REDI Working Group continues to coordinate with FDA, EMA, ERN-EYE, and the Forum to consolidate evidence across diseases and trials.

Open Discussion

Key Takeaways

- Tailoring endpoints to disease stage and treatment
- Redefining meaningful change
- Reliability of mean vs. pointwise sensitivity (perimetric endpoints)
- Structural endpoints, such as EZ area, as complements to functional endpoints
- Patient perspectives in endpoint development

Participants discussed the importance of disease-specific endpoints that reflect the heterogeneity and variable progression patterns of IRDs. While FST offers a sensitive and quantifiable functional endpoint for low-vision diseases, the group agreed that endpoints should be tailored to disease severity, therapeutic mechanism, and expected treatment effect. Regulators encouraged investigators to focus on data and stay flexible when determining trial endpoints.

A recurring theme was the need to better define what constitutes a “meaningful change.” Some participants said the often-used threshold of a 7 dB loss across 5 visual points is arbitrary and potentially misaligned with IRD pathophysiology. Signs or symptoms like this may not appear for years due to slow or nonlinear disease progression, so they are impractical for clinical trials. Natural-history studies will be critical for refining these thresholds and aligning functional change with disease biology.

Speakers also discussed the performance of perimetric endpoints. Both microperimetry and static perimetry show high point-to-point variability, but averaging across multiple loci can substantially improve reliability. Mean sensitivity was viewed as a more stable and informative parameter than individual pointwise change.

Structural measures are valuable complements to functional endpoints for patient selection and efficacy evaluation, participants said, due to their objectivity, reproducibility, and correlation with visual function. The EZ area is notably promising for enrollment strategies and longitudinal monitoring.

Endpoints must incorporate patient experience and perception of disease progression, according to patient advocates. Trial designs will be stronger when they account for the qualitative experience of vision loss, especially nonlinear progression.

SESSION III: FULL-FIELD STIMULUS TESTING (FST) FOR CONSIDERATION AS AN ENDPOINT

Reviewing the mission and activity of the Endpoints Working group, the development and application of FST, and the acceptability of FST as a primary endpoint for specific IRDs.

Overview: Endpoints Working Group

Speaker: Sehyr Khan, Forum

Slides: Overview: Endpoints Working Group

The mission of the Endpoints Working Group is to monitor the regulatory landscape and identify endpoints that capture meaningful change across disease stages and treatments.

Among other endpoints, the group is looking at FST, which measures the light sensitivity of the whole retina, for monitoring both natural-history progression and therapeutic response. FST is being evaluated across several ongoing studies and has demonstrated strong correlation with mobility-based measures such as the multi-luminance mobility test (MLMT). Since ODF2, the group has worked on defining patient populations best suited for FST, standardizing test protocols, and integrating FST into multi-endpoint frameworks.

The group has made progress on a white paper that will collect clinical data and propose FST for regulatory consideration. Collaboration and transparent data sharing remain central to the group's strategy for standardization, reproducibility, and eventual regulatory qualification of FST and related measures.

Overview of Full-field Stimulus Testing (FST)

Speaker: Artur Cideciyan, University of Pennsylvania
Slides: Overview of Full-field Stimulus Testing (FST)

Artur Cideciyan gave an overview of FST as a quantitative measure of whole-retina light sensitivity and as a functional endpoint for IRD trials. FST directly measures the lowest light intensity perceived across the entire visual field, capturing residual rod and cone function even in patients with advanced disease.

Dr. Cideciyan compared FST with other functional and structural modalities, such as perimetry, microperimetry, and pupillary light reflex. FST is unique in being able to measure global retinal sensitivity when localized testing is no longer feasible. Although FST is not localized on the retina, it provides clinically relevant data in eyes with low visual acuity (<20/50), where traditional measures are not reliable. The test's simplicity, short administration time, and minimal dependence on fixation make it especially valuable in pediatric and low-vision populations.

FST has been used as an efficacy endpoint in multiple gene-therapy trials. Based on the studies conducted so far, a clinically meaningful change is considered to be >1 log (>10 dB) for rods and >0.5 log (>5 dB) for cones.

FST provides a fast, objective, and reproducible method for quantifying photoreceptor sensitivity and should be considered a primary or co-primary endpoint for therapies targeting severe, diffuse vision loss.

FST Q&A

Key Takeaways

- Interpreting VA versus FST localization in advanced disease
- Defining clinical significance for FST responses
- Standardizing across testing sites
- Correlating FST with functional outcome measures and patient-reported outcome measures (PROMs)

After the FST overview, the discussion focused on the interpretation, applicability, and regulatory acceptance of FST. Participants looked at the relationship between VA and FST, particularly in gene therapy, where traditional foveal measurements are not sensitive enough.

The group discussed the challenge of interpreting VA in patients with severe retinal disease. People whose visual acuity is worse than 20/50 may have measured vision outside the fovea, especially in conditions like Leber congenital amaurosis (LCA). This limits the usefulness of VA as the only endpoint for treatment-related change. In contrast, FST measures the most light-sensitive photoreceptors across the retina. Consequently, meaningful improvements can be measured even when spatial mapping is impractical.

Participants debated the regulatory interpretation of FST and its potential as a primary endpoint. A key concern raised was that FST may record some responses from cells that do not contribute to functional vision, such as in areas anterior to the equator. Such responses should not be considered clinically meaningful. Researchers and clinicians responded that for people who have profound vision loss, any measurable retinal sensitivity can represent real-world quality of life, particularly in mobility and navigation. They emphasized that definitions of clinical relevance must include both visual field and the lived experience of patients.

Panelists agreed that regulatory acceptance of FST will depend on rigorous standardization. Ongoing work aims to harmonize key testing parameters.

Participants identified ways to strengthen the evidence for FST as a primary endpoint:

- Demonstrating functional benefit: Linking FST improvements to PROs, multi-luminance mobility test (MLMT) performance, or National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) scores.
- Supporting with natural-history data: Establishing correlations between FST change and disease trajectory across genotypes.
- Ensuring reporting consistency: Disclosing device specifications, test–retest variability, and site-level quality control.
- Defining thresholds of meaningful change: Providing rationale for photoreceptor-type–specific cutoffs (>10 dB for rods, >5 dB for cones).
- Enhancing spatial interpretability: Exploring the use of large-spot stimulation paradigms to derive limited topographical insight in low-vision cohorts.

Clinical Trial Presentation #1: Spark

Speaker: Daniel Chung, SparingVision (as of May 2025)

Dr. Dan Chung reintroduced Luxturna as the first FDA- and EMA-approved gene therapy for an IRD. He linked the Luxturna development program to the day's discussions of functional endpoints.

Dr. Chung reviewed the regulatory history of Luxturna and the MLMT, which measures a patient's ability to navigate a course at multiple luminance levels, to assess real-world visual performance. He described how improvements in MLMT scores corresponded with gains in FST sensitivity (correlation) and other objective measures of retinal function. These endpoints complement each other: FST quantifies light sensitivity, and MLMT shows how changes translate to functional vision.

Full-field Stimulus Testing (FST) as a Clinical Endpoint in a Phase 1/2 Study of ATSN-101

Speaker: Laura Pardon, Atsena Therapeutics
Slides: Full-field Stimulus Testing (FST) as a Clinical Endpoint in a Phase 1/2 Study of ATSN-101

This presentation reviewed the efficacy of the FST as a clinical endpoint in a Phase 1/2 study of ATSN-101, targeting Leber Congenital Amaurosis type 1 (LCA1).

ATSN-101 was injected subretinally to deliver *GUCY2D* proteins to the photoreceptors to improve recovery after light stimulation in the phototransduction pathway. The trial tested the safety of dose escalation and expansion and evaluated visual function with a variety of measures, including FST. FST can assess the full-field visual sensitivity of patients with low vision and nystagmus, despite many patients retaining relatively normal retinal structure. FST had a test–retest variability of approximately ±3 dB in people with retinal degeneration as well as healthy individuals.

Trial participants who received high doses of *GUCY2D* sustained improvements in their FST scores for at least 36 months after treatment, compared to people whose eyes were not treated.

These gains in FST were consistent with performance on the MLMT. FST also correlated well with PROs, indicating real-world benefits in patients' vision-related quality of life. Overall, the data support FST as a clinically meaningful endpoint for evaluating gene therapies for LCA1.

Recovery of Cone-Mediated Vision in a Severe Ciliopathy after Gene Augmentation: One Year Results of a Phase Ib/IIa Trial for LCA5-LCA

Speaker: Tomas Aleman, University of Pennsylvania
Slides: Recovery of Cone-Mediated Vision in a Severe Ciliopathy after Gene Augmentation: Use of Complementary Readouts in a Phase Ib/IIa Trial for *LCA5*-LCA

This presentation examined a Phase Ib/IIa clinical trial of OPGx-LCA5, a gene therapy for *LCA5*-LCA. Like other LCA types, *LCA5*-LC causes early blindness; the *LCA5* type

involves ciliopathy. The study demonstrated the potential for vision in the most severely affected patients for the first time.
Several complementary readouts showed the biological efficacy of OPGx-LCA5. Treated eyes showed gains in visual acuity when compared to their baseline measurements and to untreated eyes. The trial also documented the restoration of the fovea. Patients had observable sensitivity gains and more stable fixation at the foveal center. FST was used to detect improvements in photoreceptor sensitivity across the retina. FST is considered most appropriate for detecting improvements from retina-wide vision loss.

When interpreting FST results, it is important to understand which photoreceptor type (rods or cones) primarily mediates the response. Different photoreceptor types may respond differently to therapeutic interventions, and what constitutes a "meaningful change" in FST varies based on the predominant photoreceptor response. For instance, a meaningful change for rods might be greater than 1 log (or 10 dB), while for cones, it could be greater than 0.5 log (or 5 dB).

Dr. Aleman addressed the common criticism that FST does not localize to specific retinal areas, noting that global measures like visual acuity (especially below 20/50) also lack precise retinal localization. This suggests that for conditions causing widespread vision loss, a full-field measurement can still provide valuable insights into overall retinal function.

Patients showed improved orientation and mobility as early as the first assessment after treatment. These improvements continued for up to 12 months after treatment. The findings represent an advance in the treatment of *LCA5*-LCA.

FST Minimal Clinically Important Difference

Speaker: Lee McDaniel, Jaeb Center for Health Research

Dr. Lee McDaniel delved into the Jaeb Center’s research on establishing the MCID for the FST endpoint in IRD trials, with a particular focus on LCA-related trials. This research responds to the FDA requirement that clinical trials use patient experience to define how much change in a measurement, such as FST, is truly meaningful. The FDA advocates anchor-based methods to determine the MCID, emphasizing that raw correlations or test-retest variability alone are insufficient, as they do not directly incorporate the patient's lived experience.

To achieve this, Jaeb Center researchers adopted a rigorous three-step approach: first, selecting "anchors" — external, clinically proven and meaningful variables that reflect patient experience; second, performing regression analyses to ascertain if changes in FST were indeed associated with changes in these anchors; and finally, using ROC analysis to pinpoint the specific FST change (the cut point) that corresponds to a meaningful change in the anchor.

This investigation used two anchors. The MLMT with a 2-light level change is considered clinically significant. Using data from the Luxturna trial with 29 participants, the analysis showed that an FST change of at least 13.2 dB correlated with MLMT improvements.

The second anchor was the NEI VFQ-25. The FDA values this patient-reported outcome measure for its direct capture of the patient's voice. A 10-point change in VFQ subscales or composite scores was considered a meaningful improvement, based on evidence in other retinal conditions. Analyzing data from the ATSN-101 trial (of 15 participants), the estimated FST MCID for the VFQ Composite scale was 6.67 dB. Similarly, various other VFQ subscales yielded different MCID estimates, ranging from 4.1 dB for Role Difficulties to 11.5 dB for Dependency.

The data largely support a 10 dB change in FST as a meaningful improvement for patients with LCA. While this may not represent minimal meaningful change, it provides a patient-centric benchmark for assessing treatment efficacy in future IRD clinical trials.

Open Discussion

Key Takeaways

- Standardizing FST reporting
- Limitations of VFQ-25 and the need for better PROMs
- The potential of the PGI-S/PGI-C for PROM development
- Task-based PROMs and functional tests
- Challenges and solutions for PROM development
- Regulatory flexibility and early interaction

Participants focused on the need for more appropriate and validated outcome measures in clinical trials. Discussion returned repeatedly to the limitations of assessment tools and the need for new ways to capture meaningful change.

Clinicians said that FST results should be reported in log candela per second per meter squared, not decibels. This allows direct comparison across studies and proper interpretation, as the zero point in decibel scales is often undefined.

After presentations from the sponsors, stakeholders discussed the limitations of the Visual Function Questionnaire-25 (VFQ-25), including broadness and variability, and the merits of other patient-reported outcome measures, including the Michigan Retinal Degeneration Questionnaire (MRDQ). Participants noted that the Patient Global Impression of Severity/Change (PGI-S/C) might help with PROM development, as it can synthesize one weighted response from complex patient experiences, although this may not work for all trials.

Clinician participants shared that they would like standardized task-based tests that reflect patients' activities of daily living, such as assessing daily activities under different light levels. These would have less subjective bias and better reflect real-world conditions.

Developing and validating patient-reported measures is a time-consuming and expensive process that can take years. Two major challenges in development are the heterogeneity of inherited retinal diseases and the variability of patients' experiences. The variability of IRDs could be addressed with a "toolbox" of validated PROM questions and functional tasks from which researchers could choose a set for their specific trial design.

To accommodate individual patient experiences, it is important to reduce researcher bias. One way to do this would be to have someone other than the primary investigator conduct structured interviews with patients, and record their experiences and feelings in their own words. Using language processing with patient descriptions may provide insights. With patients such as young children and older adults, caregivers may provide more reliable reports of a patient's abilities than the patient themselves.

Clinical and industry participants asked for more flexibility from regulators on outcome measures, particularly in rare diseases where patient numbers are small and heterogeneity is high. Developing acceptable outcome measures will require early and continuous interaction between researchers and/or developers and regulators. Looking at multiple secondary endpoints, even if a primary endpoint fails, could be a pragmatic approach for complex rare disease trials.

SESSION IV: ENDPOINTS WORKING GROUP: DEFINING THE PATIENT POPULATION FOR FST

Exploring how patient selection, disease stage, and outcome-measure choice influence the design of IRD clinical trials.

Considerations for Clinical Trial Population for FST

Speaker: Rachel Huckfeldt, Massachusetts Eye and Ear
Slides: Considerations for Clinical Trial Population for FST

Dr. Rachel Huckfeldt discussed factors that go into choosing FST as an endpoint in a clinical trial, including specific retinal dystrophies and disease severity. She described the attributes of an ideal outcome measure, including accuracy, reproducibility, range without major floor or ceiling effects, objectivity, and clinical relevance. Feasibility, cost, and patient burden are equally important factors when selecting endpoints for IRD trials. Endpoints should align with both the expected effect of the therapy and the disease stage being studied.

Using examples from recent studies, Dr. Huckfeldt illustrated how FST performs across different IRDs. In a CEP290-associated retinal-dystrophy cohort, FST values for red, blue, and white stimuli correlated with disease duration and baseline EZ area, confirming that FST captures meaningful progression even in patients with severe vision loss. In four-year longitudinal data, nearly half of all eyes exceeded the repeatability threshold by year 4, showing FST's sensitivity as a progression marker.

Dr. Huckfeldt also highlighted FST's ability to delineate rod- and cone-mediated responses. Over time, people in the RUSH2A natural-history study experienced shifts from rod- to mixed- or cone-mediated function, consistent with the expected course of their disease. FST outcomes also correlated with multiple patient-reported measures. Similar correlations were observed in preliminary Pro-EYS data, where FST showed the strongest associations across several quality-of-life domains.

FST is an attractive endpoint for many reasons: low burden on patients, reproducibility, minimal subjectivity, and alignment with both anatomical and patient-reported measures. More investigation is needed to learn whether FST is generalizable across genotypes and disease severities, but these are being studied. Trial designers should account for trial phase, mechanism of action, and expected therapeutic effect when proposing FST as an endpoint. This will promote efficient, interpretable IRD studies and help advance FST toward regulatory qualification.

Panel Discussion: How does FST impact clinical trial inclusion criteria?

Moderator: Claire Gelfman, Forum
Panelists: David Bingaman, MERIT CRO; David Hoelscher, Fortrea; Tanya Richardson, Fortrea; David Tanzer, Lexitas

Key Takeaways

- Reducing patient and site burden
- Standardization and quality of data
- FST in clinical trials
- Morphologic endpoints

The panel of representatives from three ophthalmic clinical/contract research organizations discussed challenges in the clinical trial ecosystem, as well as views on developing standard endpoints.

Significant challenges faced by most clinical trials include the need for dedicated space and trained staff, expensive and resource-intensive facilities (such as the lab space and instruments required for MLMT), and the physical toll from extensive testing on patients. Streamlining procedures and limiting assessments to the "must-haves" can reduce these burdens.

In addition, trials must use consistent and accurate instrumentation and protocols to ensure reliable data, especially in rare diseases with small patient numbers.

Specific endpoints such as FST may provide the needed data. FST is already being used for participant screening *and* as a secondary outcome in trials. Using FST as a patient-selection tool ensures that trial participants have viable photoreceptors before undergoing intensive treatment, demonstrating the endpoint's diverse value.

Panelists discussed the development of improved morphologic endpoints derived from high-resolution retinal imaging (e.g., SD-OCT). While such measures may offer sensitive detection of structural change, their utility in clinical trials depends on establishing a clear and clinically meaningful association with functional outcomes.

SESSION V: ENDPOINTS WORKING GROUP: LOOKING TOWARDS THE FUTURE

The role of patient-reported outcomes in clinical-trial design.

Patient Perspective: Fireside Chat

Moderator: Claire Gelfman, Forum
Panelists: Matthew Baier; Ned Reade and Barbara Wade Sergent, BCM Families Foundation

Key Takeaways

- Limited access to IRD specialists and expertise
- Greater need for proactive low-vision support and referral
- Empowering patient advocacy and self-education
- Continued hope through gene-therapy advancement

The panelists shared personal experiences as patients and caregivers. Their stories illustrated why patient perspectives are important, and why clinical research professionals need to ensure that their work respects and reflects patients' lived realities.

Matthew Baier described being diagnosed with retinitis pigmentosa (RP) in 2021 at age 48 and being told very little, except that he would eventually lose his sight. Determined to find answers, he relentlessly pursued genetic testing, which reclassified his PRPF21 variant to likely pathogenic. This made him eligible to join clinical trials.

Barbara Wade Sergent spoke as the mother of Jack, a 19-year-old living with blue cone monochromacy (BCM). He was diagnosed at four months old due to his mother's chance connection with a genetic-testing lab. For years, she was told there was "no treatment or cure," until she discovered the BCM Families Foundation and a broader patient community. She noted that Jack often feels "too sighted for the blind and not sighted enough for the sighted." Despite academic success, he faces misunderstanding about his legal blindness, light sensitivity, nystagmus, and color discrimination. She emphasized that researchers and clinicians must focus on outcomes that are truly meaningful to patients and their families.

Ned Reade, also living with BCM, shared a multigenerational perspective, as five generations of his family has experienced the condition. He has never had normal vision and has ongoing social and functional challenges, such as difficulty reading signs and

being unable to drive. Some people with BCM struggle to cope, sometimes experiencing mental-health or substance-use challenges. Yet, he also said he was optimistic that progress in gene therapy and other technologies can improve the quality of life of future generations.

Common themes emerged: The panelists agreed that access to IRD specialists remains inconsistent, and many patients receive incomplete or delayed information about their condition. Patients also need proactive low-vision rehabilitation and psychosocial support. Ms. Sergent noted that her son's early interventions were possible only because she had experience navigating the healthcare system. Most patients are not as fortunate, Mr. Baier said. The panelists encouraged ophthalmologists to routinely refer patients to low-vision resources and to help them develop self-advocacy skills early in life.

The panel closed on a note of gratitude and hope. The accelerating progress in gene-therapy research offers tangible optimism for improving visual function and reducing the social and practical burdens of living in what one participant described as a "20/20-centric world." All patients need equitable access to specialists, genetic testing, and education, so they can understand their condition and benefit from advances in treatment.

Outcome Measures in IRDs: Focus on PBTs

Speaker: José-Alain Sahel, UPMC Vision Institute

Dr. José-Alain Sahel presented an overview of performance-based testing (PBT) for quantifying patient experiences. Traditional assessments such as visual acuity, visual field, and FST measure visual function, but they do not always capture the ability to perform tasks in everyday life. His work at the StreetLab measures how vision loss and therapeutic interventions affect patients' real-world activities.

Dr. Sahel described the continuum of therapies for retinal degenerations — from gene therapy and gene editing aimed at curing disease, to neuroprotection that preserves remaining vision, to restoration approaches such as optogenetics, prosthetics, and stem-cell therapy. With all of these approaches, the major challenge is showing benefit in terms that matter to patients. One benefit of Luxturna's development was the validation of a new outcome measure: the MLMT. But the MLMT is not a universal standard: endpoints must reflect disease-specific mechanisms and functional impact. StreetLab was designed to quantify mobility and spatial-navigation ability under controlled conditions. In its early iteration, patients with different patterns of vision loss

performed real-world tasks such as obstacle avoidance and doorway navigation. Researchers tracked their gaze, gait, and head motion during the tests. This testing showed reproducible correlations between trajectory and visual-field size, confirming that behavioral data can serve as reliable functional measures. New physical and virtual-reality (VR) paradigms also allowed for maze navigation across six lighting levels, and has now been adopted by the FFB for the RUSH2A follow-up studies.

After StreetLab moved to the University of Pittsburgh's UPMC Vision Institute in 2024, its testing capability expanded to working with patients whose central vision loss limits their ability to perform other tasks. This led to the development of new standardized, scalable test methods, including virtual reality–based tests.

More vision-testing tools are being developed at StreetLab: VR-VISA, to assess object localization and grasping for people with moderate vision loss; and PROMA, for ultra-low-vision patients in optogenetic or prosthetic-vision trials.

Patient-Reported Outcome Measures in IRDs: Informing a Consensus Statement

Speaker: Todd Durham, Foundation Fighting Blindness
Slides: Patient-Reported Outcome Measures in IRDs: Informing a Consensus Statement

Dr. Todd Durham discussed the role of patient-reported outcome measures (PROs) in IRD clinical-trial design and efforts to establish a consensus on validated instruments. PROs can document treatment benefits and disease effects that clinical tests do not directly measure. Citing the FDA's 2022 guidance, Dr. Durham described the strengths and limitations of PROs: They provide insight into how patients perceive their vision and quality of life. But they must be standardized and offer robust content validity and psychometric rigor.

Dr. Durham reviewed several PRO tools used in IRD studies. The NEI-VFQ has limited sensitivity to IRD-specific visual impairments. In contrast, the Michigan Retinal Degeneration Questionnaire (MRDQ) was designed specifically for IRDs. The MRDQ has shown strong correlations with visual-function parameters.

The ViSIO-PRO is a newer tool for use with people who have RP or LCA that shows excellent reliability and strong content validity. Questions cover visual symptoms, daily activities, mobility, and health-related quality of life.

Dr. Durham concluded with a look at when to create a new PRO and when to adapt an existing tool. When existing tools do not capture key aspects of a disease or are not validated for specific age groups, a new tool may be needed. Modifying an existing tool may be adequate if the test only needs adaptation for language, culture, or context. If a new PRO will be submitted for regulatory approval, it must show clear content validity, measurement reliability, and interpretability.

To develop a consensus on PROs, the field must consider how to:

- Define a core set of tools that can work for a variety of mechanisms of action
- Create reporting standards that promote ongoing learning for the field
- "Future-proof" PROs

Open Discussion

Key Takeaways

- Adaptation to condition can affect how long-term patients respond to PRO questions
- PROs are appropriate primary endpoints only in limited circumstances
- PROs have been accepted as primary endpoints in other therapeutic areas
- Other rare diseases offer examples of PRO endpoints
- Looking at PROs alongside PBTs provides a more complete picture of treatment benefit

Participants discussed the role of PROs and PBTs, focusing on their validity, interpretability, and potential as primary endpoints.

Participants observed that older patients scored lower than younger ones on the ViSIO-PRO questionnaire. Long-term patients often adapt to their visual limitations, which can affect their responses and scores. This raised questions about how PROs can reflect patient experience when coping strategies evolve over time.

Participants also looked at whether PROs can serve as primary endpoints in IRD trials. Several participants suggested that this would only be appropriate if a therapy directly targets a symptom or domain best captured by patient experience. Otherwise, PROs are better suited to anchoring or contextualizing objective measures. Clinicians expressed concern about the inherent variability in self-reported data and emphasized the importance of objective confirmation through measurable performance-based assessments.

A participant from the regulatory side of the field noted that PROs have been accepted as primary endpoints in other therapeutic areas. Although PROs may not always be as "convincing" as objective findings, they hold strong regulatory potential if validated and linked to meaningful aspects of patient experience.

Participants also brought up cross-disease models of PRO endpoints. A recent Reagan-Udall Foundation workshop on primary mitochondrial disease was cited as a model for developing individualized or symptom-specific endpoints in rare, heterogeneous populations. The group also discussed the PRO validation path in a case study on pruritus from the FDA's Center for Drug Evaluation and Research (CDER) Accelerating Rare Disease Cures (ARC) program. In this case, the path runs from patient interviews and item development to endpoint definition and anchor analysis.

Getting a complete picture of patients' functional vision and quality of life requires both PBTs and PROs, participants said. To be useful and accepted, these tools must have thoughtful design and content validity. PROs must also demonstrate measurable correlation with functional measures. Learning from other rare-disease fields will speed progress toward regulatory acceptance of PROs in ophthalmology.

SESSION VI: ENDPOINTS WORKING GROUP: CONSIDERATIONS FOR AGE-RELATED MACULAR DEGENERATION

How insights from AMD and geographic atrophy research can inform endpoint development through parallels and opportunities for harmonization.

Current Landscape for iAMD Drug Development

Speaker: Cheryl Rowe-Rendleman, Omar Consultants
Slides: Current Landscape for iAMD Drug Development

Dr. Cheryl Rowe-Rendleman presented an overview of the drug-development landscape for intermediate age-related macular degeneration (iAMD), and the lessons it offers for IRD endpoint development.

There has been significant progress in treating neovascular AMD (nAMD) since 2004, but there are still more than twice as many nAMD trials as trials for dry AMD (dAMD), showing that challenges persist in defining and measuring disease progression in earlier stages.

Endpoints such as BCVA are not sensitive enough to capture early or intermediate disease change, and that defining iAMD categories, remains inconsistent across studies. New imaging and diagnostic advances allow earlier detection of “AMD suspects,” creating opportunities to intervene before irreversible atrophy occurs.

Dr. Rowe-Rendleman reviewed the evolution of AMD treatment, from the AREDS studies, where antioxidant supplementation reduced risk of advanced AMD, to the recent approvals of pegcetacoplan and avacincaptad pegol. These complement inhibitors slow the growth of geographic atrophy (GA) lesions without restoring vision. No therapy has yet been approved for intermediate dry AMD.

In the clinical-trial pipeline, there are 121 actively recruiting AMD trials as of April 2025, including 15 in iAMD and 26 in GA. Ongoing interventional studies target mechanisms including complement inhibition, photobiomodulation, integrin antagonism, and mitochondrial protection, as well as lifestyle interventions such as exercise and diet changes. These approaches reflect greater focus on prevention and early intervention rather than late-stage rescue.

Imaging and technology have growing roles in endpoint development. Promising biomarkers include ellipsoid-zone integrity, hypertransmission defects, and incomplete retinal pigment epithelium and outer-retinal atrophy (iRORA/cRORA). However, these have yet to be validated as endpoints. Fundus autofluorescence (FAF) is the standard for measuring GA progression, and optical coherence tomography (OCT) can help identify AMD early. The two are complementary for tracking iAMD progression and evaluating whether patients are responding to therapies.

The new iAMD Endpoints Working Group, co-led by Dr. Rowe-Rendleman and Dr. Szilárd Kiss, will work toward consensus definitions of iAMD, identify meaningful clinical endpoints, and propose feasible trial designs for early-stage AMD. These efforts are intended to accelerate regulatory dialogue and create a structured pathway for drug development in iAMD — and offer a model for standardization in IRDs.

Open Discussion

Moderators: Cheryl Rowe-Rendleman, Omar Consultants, and Maryam Mokhtarzadeh, Regenxbio

Key Takeaways

- Precisely define the iAMD population; plan for heterogeneity and asymptomatic patients
- Engage early with regulators; CDRH precedents don't automatically map to CDER/CBER
- GA precedent: approvals hinged on slowing rate of progression with curve separation over time
- Structural metrics (EZ/FAF, iRORA/cRORA, hypertransmission defects) need consistent use and validation
- Three-line BCVA prevention is often impractical in iAMD; enrichment and prognostic markers are priorities
- Preventive treatment in asymptomatic patients raises feasibility and adoption questions
- Accelerated approval via "reasonably likely" surrogates is possible but requires long confirmatory follow-up
- New iAMD Working Group (Rowe-Rendleman/Kiss) will drive definitions, endpoints, and trial-design proposals

Participants examined how endpoint strategy for intermediate AMD differs from IRDs and what lessons from recent GA approvals may (or may not) be applicable. While rare-disease programs sometimes benefit from regulatory flexibility, a larger public-health

condition like AMD requires what was termed “regulatory creativity,” with early, frequent dialogue with regulatory agencies. Any endpoint plan must include a precise definition of who has intermediate AMD, and whether this should include patients with more severe disease, as well as recognize the heterogeneity of the condition. The recent Valeda Light Delivery System FDA clearance in iAMD was instructive, but speakers cautioned that approval pathways in the FDA’s Center for Devices and Radiological Health are not necessarily the same as for the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research.

Participants considered whether GA precedents, such as approvals based on slowing lesion-growth rate, could apply to other ocular diseases or to IRDs using structural markers (e.g., EZ or autofluorescence). FDA’s perspective was that slowing photoreceptor loss is inherently beneficial, provided the metric is used consistently and the effect is balanced against risk. The GA decisions hinged on rate of progression and progressive curve separation over time, not an absolute change at isolated time points, according to the FDA. Regional differences also surfaced: products cleared in the U.S. were not approved in Europe, reflecting divergent views on structural endpoints versus functional benefit.

The group revisited the long-standing “three-line BCVA loss” bar. For intermediate AMD, many patients may never lose three lines, making prevention-of-loss designs difficult. Participants considered ideas to enrich or redefine populations (such as risk of conversion to nAMD, imaging features such as iRORA/cRORA, and hypertransmission defects), and regulators said predictors must be validated and predict meaningful deterioration. Participants mentioned multi-stakeholder efforts as resources for identifying early “trigger” events and refining enrichment strategies. Low-luminance VA and high-contrast BCVA are treated essentially the same by the CDER.

Practical considerations in preventive treatment of asymptomatic patients were discussed, including how to justify intravitreal injections before any perceived vision loss.

Final discussion points included the need for robust natural-history datasets and “big-data” analyses to stratify risk and anchor earlier endpoints, and how a lack of international regulatory alignment affects patient access and development costs. The new iAMD Working Group will address these challenges and others, including refining disease definitions, evaluating candidate structural and functional measures, and proposing feasible trial designs that can withstand regulatory scrutiny across regions.

SESSION VII: WRAP UP AND NEXT STEPS

Reflections on the meeting's discussions and the next steps for the field.

Closing Panel, Summary and Next Steps

Speakers: Daniel Chung, SparingVision; Veronica Miller, Forum for Collaborative Research; José-Alain Sahel, UPMC

Key Takeaways

- FST is not ready for use as a primary endpoint, but it remains a valuable secondary, physiological endpoint
- For FST to be approved as a primary endpoint in IRDs, the following objectives must be achieved:
    - Standardization of testing and reporting across sites
    - Linkage to functional and patient-centered measures
- Ongoing collaboration is essential to harmonize data and accelerate qualification
- The Forum will convene working sessions to determine next steps and keep work going

The final session pulled together the day's themes, especially how to promote approval of FST as a primary endpoint for IRDs. To achieve this goal, the field should act collectively to establish reproducible, interpretable endpoints for IRD trials.

Participants considered several practical next steps, including more consistency in how FST data are collected, reported, and analyzed. To resolve differences in site calibration, baseline definitions, and reporting formats, research sites should follow existing standards, and use identical equipment and software, and train staff in a consistent way.

More analysis of the correlation between FST and existing endpoints is needed to show how changes in FST translate to meaningful clinical benefit. FST should be anchored to other measures of visual function, such as PROs or mobility-based tests to improve interpretability. Documentation of inclusion criteria, data handling, and site-level methodology should be standardized.

FST remains a valuable secondary endpoint. But to become a primary endpoint, FST changes must be linked more closely with functional vision. This will require collective effort, larger datasets, and harmonized analytic methods.

The Ocular Diseases Forum should continue to facilitate cross-sector collaboration in a precompetitive setting, including smaller, focused working sessions. This will help to refine FST methodology, align data standards, and clarify regulatory expectations.

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