THE FORUM FOR COLLABORATIVE RESEARCH

OCULAR DISEASES FORUM 2

Ocular Diseases Forum 2

Saturday, September 28, 2024
Washington, D.C.

1608 Rhode Island Avenue NW
Washington, DC 20036
www.forumresearch.org

THE FORUM
For Collaborative Research℠

Berkeley Public Health

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SESSION I: INTRODUCTIONS AND PROJECT OVERVIEW

Welcome and Introductions

Speakers: Veronica Miller, Forum for Collaborative Research; José-Alain Sahel, UPMC; Jim Wang, Regeneron
Recording: Introduction Interview Recording

In an introductory interview, ODF co-chairs Dr. José-Alain Sahel and Dr. Jim Wang discussed the Forum's aims for its second meeting. Dr. Sahel spoke about the need for translational approaches to address the needs of patients with retinal degeneration. Dr. Wang described how his experience overseeing earlier gene therapies now informs his work in regulatory affairs and ocular disease.

Dr. Sahel noted that Luxturna's 2017 approval remained a standalone achievement rather than the first in a wave of approvals. He stressed the importance of patient access to innovative therapies and of understanding disease evolution to improve treatment, citing preclinical model limitations and manufacturing challenges as ongoing obstacles. He also highlighted the FDA's openness to gene therapy and the importance of developing new research questions during clinical trials without introducing bias.

Dr. Wang described his experience engaging with global health authorities to bring gene therapies to patients, and how the ODF strengthens collaboration among regulators, clinicians, patient advocates, and industry. As a neutral platform, the ODF facilitates information exchange and problem-solving across the field. He identified the development of novel clinical endpoints that can measure meaningful effects within a reasonable time frame as the biggest challenge in gene therapy for retinal disease, particularly for rare disorders where traditional endpoints fall short. He noted that too much time has passed since Luxturna's 2017 approval, and that the ODF offers a valuable opportunity for multi-stakeholder impact.

Dr. Miller described the ODF's value in bringing all stakeholders, including patients, to the same table with equal voices. This structure ensures that everyone receives the same information and fosters a shared understanding to advance the field collaboratively.

Governance and Forum Process

Speakers: Alessi Ayvaz & Sehyr Khan, Forum for Collaborative Research

A review of the Forum's processes and a discussion regarding goals for the meeting was shared and discussed in this section. Read about the Forum's operating principles and working process here.

The ODF is sponsored by Adverum, Boehringer Ingelheim, Fortrea, iCare, and PYC Therapeutics.

Objectives for Ocular Diseases Forum 2 (ODF2)

Speakers: Claire Gelfman, Forum for Collaborative Research & Jim Wang, Regeneron

Dr. Claire Gelfman, a founding member and now consultant to the ODF, described the shared goal of helping patients. She explained that the ODF's mission centers on bringing all stakeholders — patient advocates, FDA and EMA representatives, physicians, and scientists — to the table, sharing insights openly rather than reinventing the wheel with each new project.

Dr. Gelfman expressed hope that the meeting would foster collaboration to refine and optimize clinical trial processes, with the goal of streamlining drug development and bringing treatments to patients faster.

Dr. Wang echoed Dr. Gelfman's commitment to advancing therapies for patients as quickly and efficiently as possible.

Regulatory Perspective: Call for Collaboration

Speakers: Heidi Becker & Lola Fashoyin-Aje, Center for Biologics Evaluation and Research, FDA
Slides: Regulatory Perspective: Call for Collaboration

Dr. Heidi Becker and Dr. Lola Fashoyin-Aje of the FDA's Center for Biologics Evaluation and Research (CBER) reviewed the FDA's commitment to advancing therapeutic options for rare and serious diseases with unmet needs, outlining the agency's mission to accelerate the availability of safe, effective medical products.

They introduced two pilot programs supporting this goal: START (Support for clinical Trials Advancing Rare disease Therapeutics) and RDEA (Rare Disease Endpoint

Advancement). START offers a flexible, ad hoc communication framework for rapid collaboration on serious or life-threatening rare conditions within CBER or CDER, including diseases affecting individuals in their first decade of life. The scope of START meetings varies; early-stage trials with no enrolled patients, for example, may focus on animal studies to inform future human research.

RDEA focuses on drug development for rare diseases with an active IND or preIND, with natural history studies as one exception. The program emphasizes collaboration throughout endpoint development and seeks to promote endpoints with broad impact, especially where traditional endpoints are inadequate. The FDA plans up to three public workshops on endpoint development by 2027, and will allow novel endpoints developed through RDEA to be presented even before the associated drug is approved.

By promoting novel endpoints and keeping submission channels open, these programs aim to provide more efficient pathways for rare disease therapeutic development.

SESSION II: ENDPOINTS FOR IRDS: BUILDING CONSENSUS

Evaluating functional and structural endpoints for IRDs and building consensus on measures that capture clinically meaningful change.

Landscape for IRD Drug Development: Potential Endpoints in Clinical Trials

Speaker: Tomas Aleman, Scheie Eye Institute, University of Pennsylvania
Slides: Landscape for IRD Drug Development: Potential Endpoints in Clinical Trials

Dr. Tomas Aleman reviewed the use of Full-Field Stimulus Testing (FST) in clinical trials for inherited retinal diseases (IRDs), including Leber congenital amaurosis (LCA), bestrophinopathies such as Best disease, and Blue Cone Monochromacy (BCM). In these diseases, limitations in structural measures make more accurate functional measures necessary to assess vision outcomes.

In Dr. Aleman's early work with patients affected by RPE65-related LCA, some patients had structurally normal retinas on optical coherence tomography (OCT) but profound vision loss. Standard vision tests such as best-corrected visual acuity (BCVA) and electroretinography (ERG) failed to detect functional vision in these patients, revealing a disconnect between structural imaging and visual function and underscoring the need for alternative tools to measure photoreceptor sensitivity.

FST measures photoreceptor sensitivity across the retina, making it a useful tool for assessing residual vision in severe IRDs. FST offers several advantages over standard perimetry and other methods:

- Easy to administer,
- Identifies the most sensitive areas of the retina,
- Has a wide dynamic range (approximately 9 log units),
- Measures independently of fixation, making it suitable for patients with nystagmus or unstable fixation,
- Differentiates between rod- and cone-mediated vision using different color stimuli.

However, FST has some limitations:

- Cannot localize the extent of visual field loss.
- May not fully capture the visual defects in diseases affecting both photoreceptors and spatial resolution.

FST has been valuable in gene therapy trials for retinal degeneration, including choroideremia and RPGR mutations, where it tracked improvements in retinal sensitivity that were corroborated by other tests, including microperimetry.

Two decades of data show FST is reliable and reproducible, with inter-visit variability of approximately 2 dB, comparable to standard perimetry. FST is usable in pediatric populations, with children as young as six able to complete the test. In RDH12 retinopathy trials, video game-like interfaces and vibration feedback have been used to engage young children, including those with dual sensory impairment, as in Usher syndrome.

Dr. Aleman noted that FST should be assessed alongside other objective vision tests, such as pupillometry and virtual reality tasks. Data showed a strong correlation between FST results and pupillary light responses, further validating FST's ability to measure rod-mediated function, which is particularly relevant in rod-dominant diseases like LCA and congenital stationary night blindness.

FST correlates with real-world outcomes, including improvements in patient mobility and navigation. Studies using the multi-luminance mobility test (MLMT) and virtual reality tasks showed that increased FST sensitivity translated into better functional outcomes, such as improved obstacle navigation and object detection. In gene therapy trials for CEP290 mutations (LCA10), FST detected significant improvements in both rod and cone sensitivity after treatment.

Regulatory Endpoints and Trial Design for IRDs [REDI] Working Group – RUSH2A Key Findings

Speaker: Jacque Duncan, UCSF Department of Ophthalmology*
Slides: Regulatory Endpoints and Trial Design for IRDs [REDI] Working Group – RUSH2A Key Findings

Dr. Jacque Duncan summarized the RUSH2A natural history study and key findings from the Regulatory Endpoints and Trial Design for IRDs (REDI) Working Group, whose goal is to accelerate treatment development for IRDs by identifying the most sensitive, clinically meaningful endpoints. Drawing on longitudinal data from 48 international sites,

Dr. Duncan described how RUSH2A has become a cornerstone for evaluating functional and structural measures of disease progression in patients with biallelic USH2A variants.

The four-year dataset showed that conventional measures such as visual acuity and ellipsoid zone (EZ) area have limited sensitivity to change over time. Mean visual acuity change was minimal, with only 12% of eyes exceeding the coefficient of repeatability after four years, while EZ area showed a significant floor effect in two-thirds of participants. These limitations point to the need for alternative outcome measures that can detect meaningful functional change within a trial's timeframe.

Dr. Duncan presented comparative analyses across static perimetry, microperimetry, and full-field stimulus threshold testing. Static perimetry and microperimetry both correlated with disease duration and showed consistent rates of progression, but FST emerged as the most sensitive and reproducible functional endpoint, with the largest standardized rate of change, low test-retest variability, and the highest proportion of eyes exceeding the threshold for real change — 30% at two years and 47% at four years. FST's minimal floor effect and its ability to detect both rod- and cone-mediated function support its use across disease severities.

The REDI group used these findings to model sample size and trial design implications. Continuous outcomes such as FST or microperimetry mean sensitivity could substantially reduce required sample sizes compared to traditional endpoints like best-corrected visual acuity. FST's performance as a binary outcome, being the proportion of eyes exceeding repeatability limits, also suggests feasibility for shorter or smaller trials. These data support FST as a promising functional endpoint with strong psychometric properties and direct relevance to patient experience, warranting further engagement with regulators on its use in interventional trials.

FFB Clinical Consortium FST Data Review

Speaker: David Birch, Retina Foundation of the Southwest
Slides: FFB Clinical Consortium FST Data Review

Dr. David Birch expanded on the RUSH2A findings, presenting the REDI Working Group's review of full-field stimulus threshold data across multiple IRDs. FST evaluates the dimmest flash of light perceived by a dark-adapted patient, quantifying generalized retinal sensitivity and capturing the function of the most intact photoreceptors.

Dr. Birch showed that FST has a minimal floor effect and a wide dynamic range, allowing detection of both deterioration and improvement over time. Its short duration and automated analysis give it high reproducibility and low patient burden, comparable to standard visual acuity testing. The annual rate of decline was consistent across white, blue, and red stimuli, at approximately 20–25% sensitivity loss per year.

FST correlated significantly with disease duration, ellipsoid zone area, and patient-reported outcomes. Lower FST sensitivity aligned with greater disease duration, smaller EZ area, and worse patient-reported scotopic and mesopic vision, indicating that FST reflects how patients see and function in low light, an aspect other endpoints often miss. FST also distinguished between rod- and cone-mediated function, capturing disease transitions over time.

Dr. Birch concluded that FST meets multiple criteria for a clinical endpoint: low variability, high sensitivity to change, and a direct link to visual function and quality of life. With nearly half of eyes exceeding repeatability limits after four years, FST is among the most promising measures for interventional IRD trials. Ongoing REDI efforts aim to formalize these findings in a published data review and build a harmonized evidence dossier for regulators.

FST in Clinical Trials: Phase I/II Data

Speaker: Laura Pardon, Atsena Therapeutics
Slides: FST in Clinical Trials: Phase I/II Data

Dr. Laura Pardon presented clinical data from Atsena Therapeutics' Phase I/II gene therapy trial in Leber congenital amaurosis type 1 (LCA1) caused by GUCY2D mutations, showing how FST can serve as a clinically meaningful endpoint. ATSN-101, a subretinal AAV5-based vector delivering the GUCY2D gene, was evaluated across dose-escalation and expansion cohorts in adult and pediatric participants with severe congenital vision loss but preserved retinal structure.

Across high-dose cohorts, FST showed substantial improvements in dark-adapted retinal sensitivity, averaging approximately 20 dB (a 100-fold increase), with some patients gaining more than 40 dB (10,000-fold). These improvements were consistent across white, blue, and red stimuli and were maintained over 12 to 24 months post-treatment, with significant differences between treated and untreated eyes ($p < 0.01$ for all stimuli).

FST results correlated strongly with improvements on the multi-luminance mobility test, showing that FST captures functionally meaningful change. Patients with FST gains also showed better navigation under low light, paralleling the endpoint validated for voretigene neparvovec. Dr. Pardon noted that FST's sensitivity far exceeds test-retest variability, supporting its potential as a primary or co-primary endpoint in Phase 3 trials.

She noted FST's logistical advantages — commercial availability, ease of standardization, and minimal site burden — compared with the resource-intensive setup of real-world mobility mazes, positioning it as a scalable measure for bridging early- and late-phase gene therapy development.

Panel Discussion

Moderator: Bart Leroy, Ghent University
Panelists: David Birch, Retina Foundation of the Southwest**;** Jacque Duncan, UCSF Department of Ophthalmology***;** Ash Jayagopal, Ocuphire Pharma***;** Laura Pardon, Atsena Therapeutics

Key Takeaways

- Contextualizing FST's global retinal response against focal treatment effects
- Early, precompetitive engagement with regulators
- Anchoring FST to patient-reported and mobility outcomes
- Defining clinically meaningful change in FST scores

Dr. Bart Leroy led a regulatory and scientific panel discussion on the acceptability of FST as a clinical endpoint for IRDs, with academic investigators, industry representatives, and regulators from the FDA and EMA. The discussion centered on whether FST can serve as a primary efficacy measure and how it should be validated against established functional and patient-reported outcomes.

Participants agreed that FST shows several features of a credible functional endpoint: objectivity, reproducibility, and strong correlation with patient experience. Regulators from the FDA and EMA acknowledged its technical robustness but emphasized the need to define what constitutes a clinically meaningful change in FST scores, and to correlate FST with patient-reported outcomes, activities of daily living, and validated mobility measures.

Regulatory scientists encouraged early engagement and precompetitive collaboration to formalize validation pathways. FDA representatives noted that uncertainty around novel endpoints can be mitigated through early data sharing and consistent methodology across trials, and suggested that FST may need anchoring to quality-of-life or vision-related function data before use in pivotal trials.

Panelists also discussed variability in disease severity and treatment localization, and the need to contextualize FST's global retinal response relative to focal therapeutic effects. Despite these limitations, the group agreed that FST represents a major step toward harmonizing objective functional endpoints for IRDs, and that ongoing REDI and Forum collaborations could build the regulatory evidence base needed to advance its acceptance.

Questionably/Definitely/Decreased AutoFluorescence (QDAF, DDAF, DAF) on Short Wavelength-AutoFluorescence: Current Understanding and Rationale

Speaker: Bart Leroy, Ghent University
Slides: Questionably/Definitely/Decreased AutoFluorescence (QDAF, DDAF, DAF) on Short Wavelength-AutoFluorescence: Current Understanding and Rationale

Dr. Bart Leroy presented an overview of quantitative and definite decreased autofluorescence (QDAF and DDAF) as structural endpoints for IRDs, drawing parallels to endpoints already accepted for geographic atrophy (GA) in AMD. Blue-light autofluorescence imaging enables precise delineation of outer retinal atrophy by quantifying loss of retinal pigment epithelium and photoreceptor integrity, which correlates closely with functional vision loss.

Dr. Leroy showed how QDAF represents transitional zones of decreased autofluorescence, while DDAF corresponds to regions of complete atrophy. Drawing from the multicenter ProgStar studies, he noted that DDAF incidence and progression rates are quantifiable and reproducible. Approximately 50% of eyes without DDAF at baseline developed new lesions within five years, with expansion rates correlating with baseline lesion size, mirroring metrics used in GA trials.

Dr. Leroy compared Stargardt disease and AMD, noting that measurement approaches such as lesion area growth on fundus autofluorescence have already been validated as primary endpoints in AMD trials, including pegcetacoplan and avacincaptad pegol. These parallels suggest similar atrophy-based metrics could be applied to IRDs, particularly conditions with central photoreceptor loss.

He concluded that structural endpoints like QDAF and DDAF offer objectivity, high repeatability, and compatibility with widely available imaging modalities, but that broader acceptance will require linking these measures to clinically meaningful functional outcomes and demonstrating consistency across IRD genotypes.

Open Discussion

Moderator: Ash Jayagopal, Ocuphire Pharma*

Key Takeaways

- Patient-reported outcomes to support structural measures
- Cross-agency alignment between CBER and CDER
- FDA and EMA views on anatomic endpoints for photoreceptor loss
- Integrating structural (QDAF/DDAF) and functional (FST) endpoints

Dr. Ash Jayagopal facilitated an open discussion on how structural endpoints such as QDAF/DDAF and functional measures like FST can be integrated into a coherent regulatory framework, building on prior presentations and lessons from AMD.

Participants from academia, regulators, and industry reflected on the FDA's acceptance of structural endpoints in recent GA approvals and discussed how these principles might translate to rare, early-onset retinal disease. FDA representatives said the agency is willing to consider anatomic endpoints reflecting photoreceptor loss, provided they correlate with measurable functional or patient-centered outcomes, and emphasized quantifying rate of change at multiple timepoints with reproducibility across graders and imaging systems.

An EMA representative echoed similar criteria, noting that structural endpoints in IRDs could be acceptable if supported by robust natural history data and anchored to meaningful visual function. Participants also discussed the need for alignment between FDA's CBER and CDER divisions on structural endpoints across gene and small-molecule therapies.

Speakers compared patient populations in AMD and IRDs, noting that IRD patients, who are often younger and highly engaged, may find structural preservation meaningful even without immediate functional improvement. The group agreed that patient-reported outcomes, microperimetry, and quality-of-life instruments should support anatomic measures in submissions.

The discussion reflected a shared interest among regulators, clinicians, and sponsors in establishing a unified evidentiary pathway for structural and functional endpoint validation, with the Forum positioned as a neutral convener for these conversations.

SESSION III: PATIENT PERSPECTIVES IN IRDS AND AMD: CALL FOR CLINICAL TRIALS AND A PATH FORWARD

The role of the patient perspective in IRD and AMD clinical trials, and how it can be better incorporated.

Living with Retinal Disease: A Patient (Parent) Perspective

Speaker: Marylee Dilling, Blue Cone Monochromacy Families Foundation
Slides: Living with Retinal Disease: A Patient (Parent) Perspective

Dr. Marylee Dilling, representing the Blue Cone Monochromacy Families Foundation, shared her experience as a parent of a child with Blue Cone Monochromacy (BCM), an ultra-rare inherited retinal disorder affecting approximately 1 in 100,000 people, including 3,000 in the United States. She described BCM as an X-linked recessive disorder primarily affecting males, and its functional impact on those living with it.

BCM symptoms include severe nearsightedness, low vision (about 5% of normal), extreme light sensitivity, nystagmus, and poor color discrimination due to non-functional red and green cones; many individuals are legally blind (20/200 vision). The BCM Families Foundation, formed in 2014 by parents of affected children, funds biomedical and scientific research aimed at eradicating BCM, and has supported preclinical and clinical studies, a patient registry, and free DNA testing for families.

Using her son's experience as an example, Dr. Dilling described the real-life difficulties of living with a rare ocular disease, in the classroom, at home (needing high-contrast furniture or soft corners), socially, and in sports, including orientation and mobility.

Dr. Dilling emphasized the need for clinical trials with functional endpoints specific to BCM, such as visual acuity, light sensitivity, and color discrimination, or non-standard outcome measures. She argued that even incremental improvements in these areas would meaningfully improve quality of life for those with BCM, and stressed the urgency of early gene therapy intervention, since progressive cone loss limits the window for successful treatment and visual cortex development.

Patient Engagement Strategies in Clinical Trials

Speaker: Julia Carpenter-Conlin, Alkeus Pharmaceuticals
Slides: Patient Engagement in Clinical Trials

Julia Carpenter-Conlin of Alkeus Pharmaceuticals reviewed the role of patient advocacy in the pharmaceutical industry. Advocacy operates at the disease level, integrating the patient perspective into drug development; advocacy teams should collaborate across departments to align corporate goals with patient needs, ensuring patient and caregiver insight informs trial design and program development.

Key roles of advocacy include managing expectations with patient organizations, providing transparent communication about the development process, and building trust through empathy and collaboration. Carpenter-Conlin noted that advocacy can enhance an organization's reputation, improve trial retention, and lead to solutions that better meet patient needs.

Effective patient engagement can impact multiple phases of clinical development, from protocol design and study initiation to trial operations and post-approval communications. Understanding patient experience and expectations helps companies make more patient-centric decisions that improve trial outcomes.

Carpenter-Conlin reviewed milestones for patient engagement at the FDA, from PDUFA's establishment in 1992 to the 21st Century Cures Act in 2016, and the points at which patient input can be leveraged, from clinical studies through pre-market review.

Panel Discussion

Moderator: Jim Wang, Regeneron

Panelists: Julia Carpenter-Conlin, Alkeus**;** Marylee Dilling, Blue Cone Monochromacy Families Foundation**;** Todd Durham, Foundation Fighting Blindness

Key Takeaways

- Broad demographic representation in future treatments
- Limitations of VFQ-25 and LLQ; potential of MRDQ and ViSIO-PRO
- Fair, transparent engagement practices, including compensation
- Soliciting patient input early and after trial completion

The panel discussion centered on integrating the patient voice throughout drug development, ensuring patient perspectives directly inform trial design and evaluation. Panelists emphasized that patient input should be solicited early, before study initiation

and after trial completion, to help identify endpoints that meaningfully reflect real-world functional outcomes.

The discussion highlighted fair and transparent engagement practices, including appropriate compensation for patient contributions and clear communication about study design, milestones, and post-trial expectations. Panelists noted that patient advisory boards can enhance the relevance of trial endpoints by capturing aspects of disease progression and quality of life that matter most to patients.

A recurring theme was the need for better alignment between traditional clinical endpoints and patient-reported experience. Speakers noted that instruments such as the VFQ-25 and LLQ may omit aspects of functional vision important to daily life, and pointed to newer tools such as the MRDQ and ViSIO-PRO, designed specifically for IRDs, as better suited to represent patient perspectives across age groups, disease severities, and visual functions.

The panel discussed how regulatory and academic frameworks can support early, structured dialogue between patients and developers to guide endpoint validation and minimize burdensome procedures. Broad demographic representation was emphasized as key to ensuring future treatments serve diverse populations equitably.

SESSION IV: ENDPOINTS FOR AMD: OPPORTUNITIES AND CHALLENGES

Exploring how learnings from AMD can inform endpoint development, regulatory alignment, and translational strategies, with a focus on harmonizing endpoints across disease areas, identifying parallels between GA and IRD progression, and outlining next steps toward qualification of objective, patient-relevant outcome measures.

Current Landscape for AMD Drug Development

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

Dr. Cheryl Rowe-Rendleman reviewed the evolving therapeutic landscape in age-related macular degeneration (AMD), drawing parallels to the Forum's work in IRDs. Since 2004, six major drugs and multiple biosimilars have been approved for neovascular AMD, one of the fastest periods of innovation in retinal disease. Therapeutic development for dry AMD and geographic atrophy (GA) remains more limited, though pegcetacoplan and avacincaptad pegol represent important recent breakthroughs.

Clinical trial registrations for neovascular AMD outnumber dry AMD by more than twofold, reflecting persistent challenges in endpoint selection for early and intermediate disease stages. Dr. Rowe-Rendleman noted that imaging technologies such as OCT and fundus autofluorescence (FAF) have enabled earlier detection and better characterization of “AMD suspects.”

Dr. Rowe-Rendleman reviewed the diversification of trial approaches, including photobiomodulation devices, repurposed oral therapies, and nutritional or behavioral interventions. Current pipelines for GA and early AMD explore complement inhibition, oxidative stress, mitochondrial protection, and cell replacement, with over 100 recruiting or planned interventional studies listed on ClinicalTrials.gov.

Dr. Rowe-Rendleman noted that despite this progress, the lack of validated endpoints for early AMD remains a key limitation, paralleling the challenge in IRDs. As imaging biomarkers such as lesion area growth and photoreceptor layer thickness become better correlated with function, lessons from AMD development can directly inform endpoint qualification for rare retinal diseases.

Case Study: GA Clinical Trials

Speaker: Peter Kaiser, Cole Eye Institute*
Slides: Case Study: GA Clinical Trials

Dr. Peter Kaiser reviewed the design and outcomes of recent GA trials and their relevance to structural endpoint development in other retinal conditions. He reviewed pivotal Phase 3 programs — OAKS and DERBY (pegcetacoplan) and GATHER1 and GATHER2 (avacincaptad pegol) — noting that all used reduction in GA lesion growth rate, quantified by fundus autofluorescence, as their primary endpoint.

Dr. Kaiser explained that while both agents significantly slowed lesion expansion, neither improved visual acuity directly, prompting ongoing discussion about the definition of "clinically meaningful benefit." He noted that regulatory acceptance of GA lesion area change as a surrogate endpoint reflects a broader shift toward anatomic measures supported by modeling, natural history, and patient-level data on preserved visual function.

Dr. Kaiser also reviewed emerging GA trials evaluating integrin inhibition, complement factor modulation, and mitochondrial protection. Dr. Kaiser emphasized harmonizing imaging methodologies and analytical frameworks across trials and disease areas, and the need for cross-disease learning between GA and IRDs in how structural endpoints are validated, standardized, and eventually recognized as reliable surrogates for functional vision preservation.

Panel Discussion

Moderator: Claire Gelfman, Forum for Collaborative Research
Panelists: Peter Kaiser, Cole Eye Institute*; Szilárd Kiss, Weill Cornell*; Kali Stasi, SalioGen Therapeutics; Jim Wang, Regeneron

Key Takeaways

- White papers and harmonized endpoint compendia as next Forum deliverables
- Early, aligned dialogue with the FDA and EMA
- Linking FST, microperimetry, and imaging metrics to patient benefit
- GA approvals as a precedent for structural endpoints in IRDs

The meeting concluded with a panel discussion moderated by Dr. Claire Gelfman, synthesizing themes across sessions and focusing on next steps for endpoint alignment. Panelists from academia, industry, and patient advocacy reflected on the

day's discussions of functional and structural endpoint validation, regulatory engagement, and the Forum's role as a convener.

Panelists agreed that the success of GA trials in securing approval based on structural endpoints offers an encouraging precedent for IRD programs, but emphasized the need to generate integrated evidence linking FST, microperimetry, and imaging metrics to patient-perceived benefit. Harmonizing datasets and ensuring access to well-annotated natural history cohorts were identified as key priorities.

The discussion also highlighted the importance of early dialogue with the FDA and EMA to clarify evidentiary standards for new endpoints and avoid divergent regulatory expectations. Industry representatives noted that alignment across agencies would improve efficiency and reduce development uncertainty, while patient advocates emphasized that preserving vision, even in small measurable ways, has a profound impact on independence and quality of life.

Dr. Gelfman closed by reaffirming the Forum's commitment to collaborative science through data sharing and precompetitive dialogue. Future Forum activities will focus on producing white papers and harmonized endpoint compendia to support formal qualification of FST, structural imaging biomarkers, and combined functional-structural measures across the IRD and AMD spectrum.

SESSION V: WRAP UP & NEXT STEPS

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

Closing Panel, Summary and Next Steps

Panelists: Claire Gelfman & Veronica Miller, Forum for Collaborative Research; Jim Wang, Regeneron

Key Takeaways

- The importance of the patient and family perspective in regulatory discussions
- Parallels between FST and potential AMD structural and functional endpoints
- Possible expansion of the endpoints working group to GA and AMD
- Regulators' openness to transparent, collaborative data review rather than outright rejection
- The Forum's progress in bringing regulators and stakeholders together on IRD and AMD endpoints

This closing session reflected on the day's discussions, synthesized insights, and outlined next steps, emphasizing the importance of sustained multi-stakeholder collaboration for IRDs and AMD.

Dr. Gelfman opened by noting that the meeting helped launch a deeper, expanded conversation among stakeholders, highlighting the Forum's progress in bringing together expertise, including from regulators, to advance discussions on endpoints for IRDs and AMD. Contributions from agencies like the FDA were particularly valuable in reinforcing the importance of working together toward concrete deliverables for patients.

Sehyr Khan suggested that the endpoints working group, currently focused on IRDs, should consider expanding to address endpoints for geographic atrophy (GA) and AMD, which could accelerate progress in both research and clinical application.

Dr. Miller shared her optimism about the openness of regulatory agencies, who as public health professionals aim to approve effective drugs. She noted that regulators are not rejecting proposals outright but are asking researchers to present data transparently to support discussion and decision-making. For IRDs, especially under the FDA's CBER, data packages need to include raw data rather than only final outcomes. She emphasized the importance of additional analysis to establish thresholds and clarify the

relationship between markers and clinical outcomes, noted discrepancies around sham controls in AMD trials as a topic for a future workshop, and stressed using existing data to clarify, for example, when lesion size indicates specific disease states or outcomes.

Dr. Wang echoed this optimism, describing the open dialogue with regulators as fostering a collaborative environment in which researchers and regulators sit together as equals.

Dr. Wickström emphasized the focus on FST, which correlates with improvements in vision and quality of life, noting the value of strong data on mean retinal sensitivity for regulatory interpretation. For GA, she noted that the Icelandic Medicines Agency does not always align with other agencies, requiring at least a trend in functional benefit. She advised selecting endpoints based on the patient population size required for a study, emphasizing benefit-risk assessments in smaller exploratory trials tailored to the target population.

Dr. Gelfman thanked Marylee Dilling for sharing her family's experience, underscoring the importance of including the patient and family perspective in regulatory and clinical discussions.

Dr. Ohnsman noted parallels between AMD and the day's FST discussions, suggesting that photoreceptor parameters, such as areas of tissue loss or thickness change, could be a promising direction for future AMD endpoints, even though they have not yet been used in approvals.

The session closed with appreciation for the day's presentations and engaged participation, and an emphasis on continued collaboration to shape the future of therapeutic development.

The next in-person meeting is scheduled for May 28, 2025, in Washington, D.C., with interim working group meetings focused on endpoints and FST in the meantime.

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