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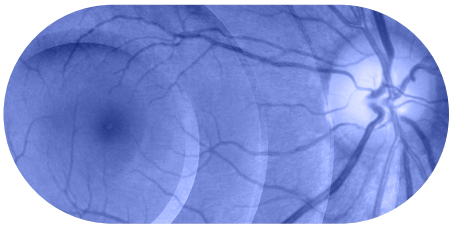
WHITE PAPER

Rewriting the rules of glaucoma trials

Cutting-edge endpoints enabling neuroprotection and neuroenhancement

Gustavo De Moraes, MD, PhD, MPH



Executive summary

Glaucoma remains one of the leading causes of irreversible blindness worldwide. Despite decades of research, all FDA-approved treatments still address only one mechanism: lowering intraocular pressure (IOP). Yet **up to 20–27% of patients still progress to blindness in at least one eye despite IOP reduction**, underscoring a critical unmet need for therapies that directly protect or restore the visual pathway[1,2].

For years, the possibility of neuroprotection—or even neuroenhancement—in glaucoma was constrained not by lack of scientific promise, but by the impracticality of clinical trial designs. Traditional endpoints, especially event-based visual field loss, require large sample sizes and follow-up periods of four or more years, rendering studies prohibitively expensive and slow.

Recent scientific and methodological advances, paired with open dialogue with regulatory authorities, are transforming this landscape. New approaches to patient selection, visual field-testing strategies, and endpoint modeling now enable **neuroprotective and neuroenhancement trials as short as 12–24 months, with far fewer patients and dramatically reduced variability.** For the first time, glaucoma researchers and industry partners can realistically evaluate intraocular pressure-independent therapies in humans.

This white paper examines the scientific rationale, regulatory evolution, and practical frameworks underlying this paradigm shift, led in part by novel analyses from Columbia University and Ora's clinical research teams.

The limitations of IOP-based glaucoma therapy

For decades, the assumption in glaucoma care has been simple: lowering IOP slows disease progression. While true for many, it fails for a substantial subset of patients.

1

No currently approved therapy claims to treat glaucoma itself; all lower IOP.

2

Even when IOP is well controlled, progression can continue.

3

Blindness rates in treated populations remain unacceptably high.

IOP remains the "lowest hanging fruit" in clinical trial design because it is easily measured and highly responsive to intervention. However, **glaucoma progression is fundamentally a neurodegenerative process**, and visual outcomes—not IOP—define patient quality of life.

The next generation of glaucoma therapies must address mechanisms beyond pressure.

Why measuring visual field progression is hard

Measuring visual field (VF) progression—the gold-standard indicator of glaucoma worsening—is inherently challenging because VF outcomes are highly variable. Results can differ from one test to the next, even within minutes, and this variability increases in eyes with substantial baseline damage, making it harder to detect true change. Traditional event-based endpoints further complicate matters by requiring long periods of observation before meaningful progression can be confirmed. This inherent noise contributed significantly to the failure of earlier neuroprotection trials, most notably the large and well-designed Memantine Trial, which did not meet its endpoints despite strong biological rationale. Two major issues were the high variability introduced by enrolling participants with severe initial VF loss and the large proportion of stable, well-controlled patients, which left little room to observe treatment effects. These lessons ultimately informed and enabled the development of improved trial designs.

Distinguishing neuroprotection from neuroenhancement

A critical conceptual shift in glaucoma research is the clearer distinction between:

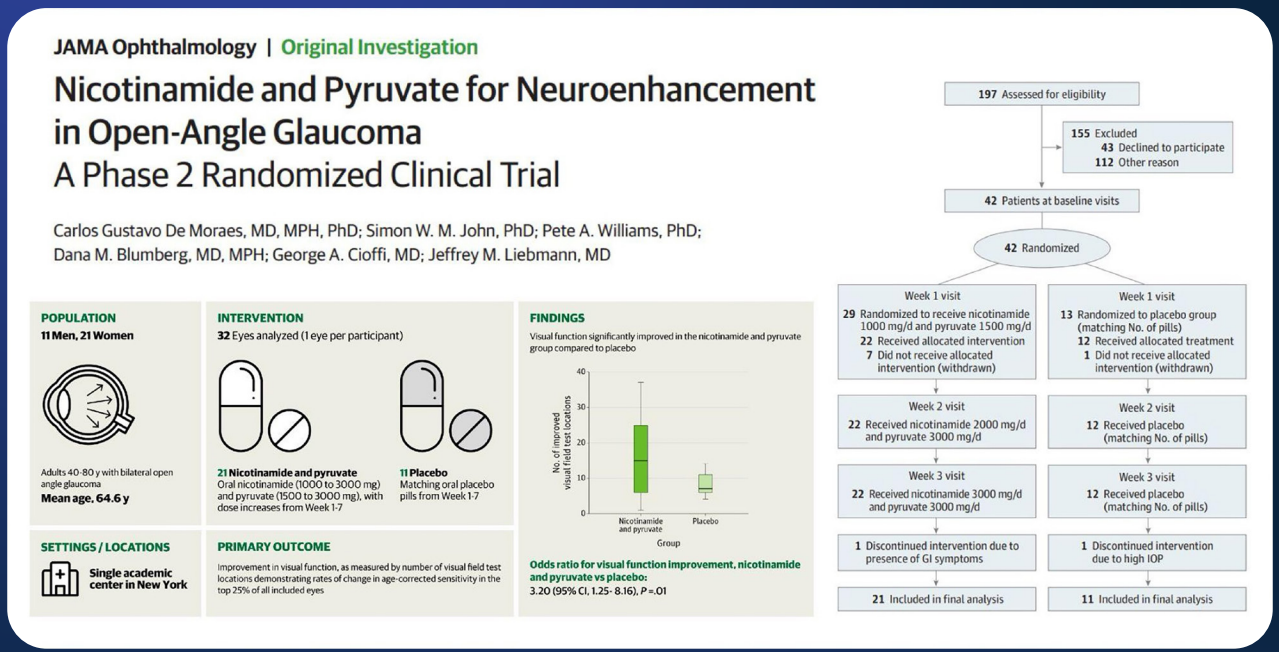
Neuroprotection

- **Goal:** preserve existing retinal ganglion cells.
- **Mechanisms:** pressure-independent pathways (e.g., ocular perfusion, mitochondrial resilience).
- **Endpoints:** demonstrating **reduced rate of progression** vs natural history.

Neuroenhancement

- **Goal:** improve or rescuing function of surviving but dysfunctional neurons.
- Historically thought impossible in glaucoma.
- Now supported by research in animals and humans.

A recent Phase II trial conducted collaboratively between Columbia University and Ora provided one of the first demonstrations of neuroenhancement in humans, showing **measurable visual field improvement** over just two months using nicotinamide + pyruvate supplements. While modest clinically, this proof-of-concept opened a new therapeutic frontier.



JAMA Ophthalmol, 2022

The path forward: alternative endpoints and FDA engagement

Recognizing the substantial barriers created by traditional glaucoma trial endpoints—particularly their long duration, high variability, and limited sensitivity to early neuroprotective effects—medical societies and research groups began working collaboratively with the FDA to identify more efficient pathways for evaluating emerging therapies. Through a series of scientific exchanges, workshops, and formal submissions, these groups highlighted the unmet need for endpoints capable of capturing meaningful biological change long before conventional visual field or structural loss becomes detectable. In response, **the FDA clarified that alternative, or novel endpoints may be considered acceptable when they are supported by strong evidence demonstrating their ability to reliably predict established, clinically meaningful outcomes.** This guidance not only validated the pursuit of more sensitive functional and structural biomarkers but also encouraged innovators to explore new imaging modalities, analytic frameworks, and modeling approaches that could accelerate drug development without compromising patient safety. The resulting shift opened the door for a new generation of trial methodologies—an area where Ora has played a leading role by developing, validating, and operationalizing cutting-edge endpoint strategies that are now shaping the future of neuroprotection and neuroenhancement research.

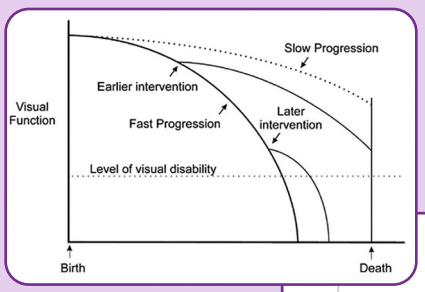
The rise of trend (rate)-based endpoints

Instead of asking **"Did a visual field event occur?"**, rate-based endpoints ask:

"How fast is the patient losing vision?"

This simple shift offers major advantages:

- Rate of progression (slope of Mean Deviation decline) is **more predictive** of long-term outcomes.
- Detectable in **shorter timeframes** than event-based analyses.
- Requires smaller sample sizes when paired with optimized testing frequency.



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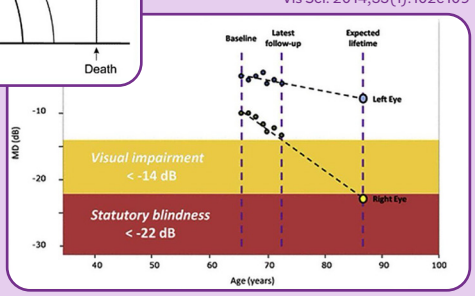

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Nature scientific reports

>90% of patients reached FDA-accepted endpoint in 5 years

A 2-year clinical trial is possible as long as:

- Sample enriched with fast progressors
- Clustering of visual fields
- Comparison of MD slopes between groups

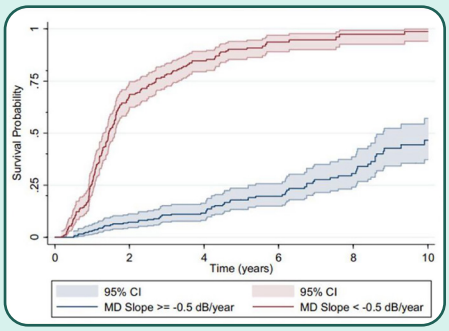


Figure adapted from De Moraes et al., Scientific Reports (2023)[3]

Patients who progress quickly at baseline provide the most statistical power. For example:

- Selecting patients with baseline slopes worse than –0.5 dB/year significantly increases the likelihood of detecting drug effects.
- In large real-world datasets analyzed by Ora and Columbia, **approximately 90% of such patients reached an FDA-accepted endpoint** during observation when rate-based modeling was applied.

This provided the FDA with strong evidence supporting rate of change as a valid primary endpoint.

The “wait-and-see” and clustering strategies

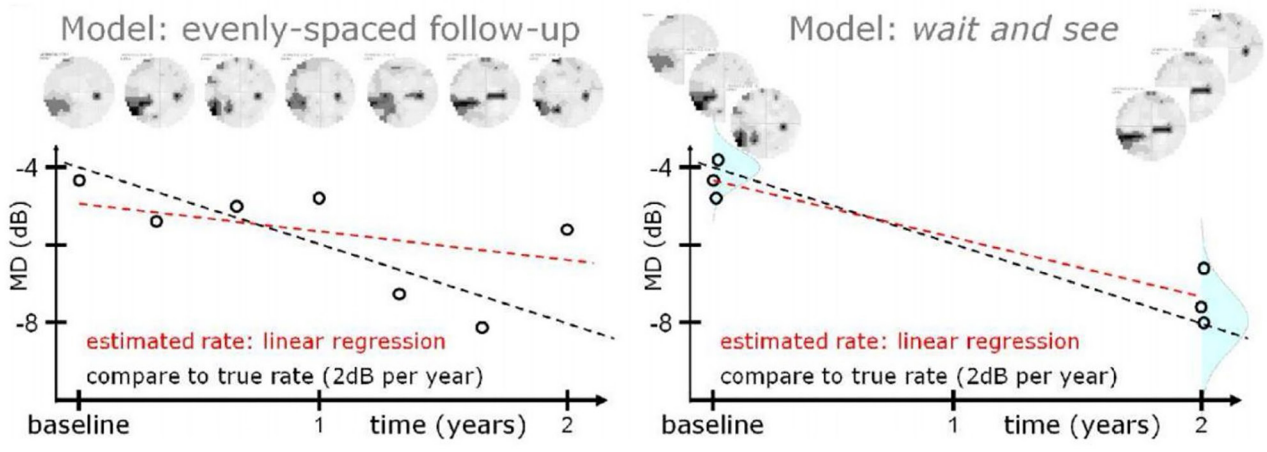
UK researchers introduced a pivotal methodological innovation that reshaped how VF progression can be measured in glaucoma trials: instead of spacing VF assessments evenly throughout the study, they concentrated multiple “clustered” tests at both the beginning and the end of the trial period. This approach substantially reduces measurement noise by averaging out short-term variability, thereby producing a far more accurate estimate of each participant’s true rate of VF change. The impact of this design has been striking. In UK clinical trials employing clustered testing, investigators were able to detect a clear separation between treatment groups within just 24 months—a significant improvement over the traditional expectation of 48 months or longer for VF-based endpoints. Even more compelling, secondary analyses demonstrated that statistically significant differences could be identified **as early as 12 months**, a milestone previously thought unattainable because VF endpoints were considered too noisy and slow to change over such short intervals. Recognizing the power of this strategy to increase sensitivity without inflating sample sizes, Ora incorporated clustered VF testing into modern neuroprotection trial designs, enabling shorter, more efficient studies while maintaining the statistical rigor required to support regulatory decision-making.

Power and sample size

Glaucoma

Intervals between Visual Field Tests When Monitoring the Glaucomatous Patient: Wait-and-See Approach

David P. Crabb[1] and David F. Garway-Heath[2]



Invest Ophthalmol Vis Sci. 2012;53960:2770-6

Designing a 12–18 month neuroprotection trial

Based on comprehensive reviews of real-world datasets, modeling, and regulatory guidance, short-duration neuroprotection trials are now feasible with:

12–18 months total duration

200–400 patients
(vs. >2,000 in prior attempts)

Rate-of-change endpoints,
not event-based

Targeted enrollment of
rapidly progressing patients

High-quality visual field acquisition
with clustered testing schedules

These advancements have reinvigorated industry interest, enabling novel assets to progress from preclinical stages to first-in-human evaluation

Next generation endpoints: toward even shorter trials

Ongoing research into next generation endpoints is driving the possibility of glaucoma trials that last six months or less. One major area of advancement is Regional Visual Field Analysis, which focuses on regions of interest—particularly the border zones between healthy and damaged tissue—and provides heightened sensitivity to early deterioration or treatment-related rescue, similar to how geographic atrophy progression is analyzed in retinal diseases.

Structural endpoints based on OCT imaging also contribute to shorter trials by offering objective, reproducible measurements of nerve fiber and ganglion cell layers; **OCT metrics are already FDA-accepted in some retina contexts**, and applying ROI-based OCT analysis could accelerate signal detection even further.

Another emerging technique involves mitochondrial activity imaging, a novel, noninvasive approach that visualizes retinal mitochondrial function and may detect cellular rescue within weeks, making it valuable for early-stage decision making even though it is not yet FDA-approved **as a primary endpoint**. Together, these innovations mark significant progress toward enabling rapid, efficient development of neuroprotective and neuroenhancement therapies.

Summary and outlook

For the first time in glaucoma research history:

- **Neuroprotection and neuroenhancement can be tested in feasible, affordable human trials.**
- **Regulators are open to innovative endpoints** backed by strong predictive modeling.
- **Visual field slope analysis**, optimized test clustering, and selective enrollment allow credible trials in **1–2 years**, not four or more.
- **Emerging imaging technologies** may shorten timelines even further.

This transformation requires deep expertise in trial design, patient selection, visual field methodology, and statistical modeling.Ora's work with Columbia University has helped establish a practical, regulatory-endorsed roadmap for next-generation glaucoma trials, renewing industry momentum and advancing groundbreaking innovation.

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