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VISION ACADEMY VIEWPOINT

The Vision Academy is a partnership between Bayer and ophthalmic specialists, established with the aim of addressing key clinical challenges in the field of retinal diseases: www.visionacademy.org.

Development and Standardization of "Time-in-Range" Measurement for Clinical Endpoints in Retinal Diseases

Background

Endpoints are specific measures of outcomes resulting from an intervention or the absence of an intervention.[1] Measurable endpoints are essential for assessing disease progression and treatment effectiveness in both clinical trials and clinical practice.[1] A range of functional and morphological endpoints has been used in ophthalmology, but while comparisons versus baseline at various time points are commonly recommended to evaluate statistical and clinically relevant differences, few metrics capture the disease course continuously over time, and some may overlook fluctuations that occur during treatment.[2] An approach to address this limitation is the concept of "time in range" (TIR), originating from continuous glucose monitoring in diabetology and recently introduced in ophthalmology.[3] TIR describes the proportion of time spent within a certain range, offering a more complete reflection of a disease than isolated measurements.[4] Measuring the time spent within a certain range may help to determine what degree or duration of effect represents a clinically meaningful outcome.[1]

A review of the literature and available evidence[5] was conducted to:

- Identify a possible reliable TIR endpoint of clinical outcomes in ophthalmology, with a particular focus on exudative diseases involving the posterior pole of the eye
- Propose potential future applications for this new endpoint

Endorsed by the Vision Academy in December 2025

Viewpoint

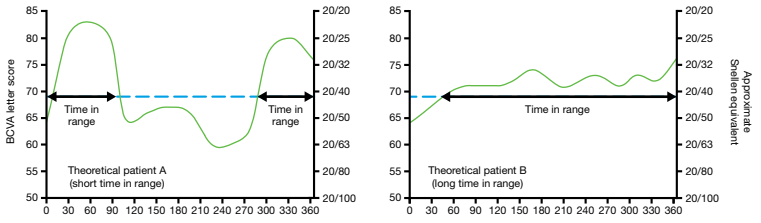
Clinical endpoints in ophthalmology

In retinal diseases such as age-related macular degeneration, diabetic retinopathy, and diabetic macular edema, the currently reported clinical endpoints include the functional metrics best corrected visual acuity (BCVA), low-luminance visual acuity (LLVA), contrast sensitivity, perimetry, microperimetry, dark adaptometry, and reading speed. In addition, geographic atrophy area, ellipsoid zone and/or external limiting membrane defects, central subfield thickness, macular volume, foveal avascular zone size, and vessel density/perfusion have been proposed as morphological endpoints, showing a high correlation with visual prognosis and disease progression, particularly in diabetic macular edema.[6] Some metrics have the advantage of easy repeatability, which is one of the key points to establishing robust, meaningful, and standard clinical endpoints for interventional clinical trials,[7] and all functional and morphological endpoints, as well as their indications, have advantages and disadvantages, as described by Frizziero et al.[5]

Application of the TIR concept in retinal diseases

BCVA is the most accepted and meaningful clinical marker for ocular disease.[8] While mean change in visual acuity considers both improvement and worsening, it reflects only a single time point. A score of 69 Early Treatment Diabetic Retinopathy Study letters (approximately 20/40 Snellen acuity) is a common threshold for good visual acuity in clinical trials[9,10] and a frequently recognized target to hold a driving license in the USA.[11] This threshold appears adequate to delineate the area of patient autonomy. A visual acuity threshold may be the best metric to apply to the TIR concept as a clinical endpoint.

Figure. Theoretical visualization of area under the curve, TIR, and mean change in BCVA when evaluating vision outcomes in a theoretical patient



Patient A	BCVA measure	Patient B
64	Baseline BCVA letter score	64
76	BCVA letter score at Week 52	76
+12	Change from baseline in BCVA letter score at Week 52	+12
+7.5 (approx.)	Area under the curve of the change from baseline in BCVA letter score	+8 (approx.)
<170 days or <50%	Time in range (thershold BCVA letter score ≥69, approximate Snellen equivalent 20/40 or better)	>300 days or >85%

Figure adapted from Kozak I *et al. Eye* 2023; 37: (16) 3367–3375. Reproduced under Creative Commons license BY 4.0: https://creativecommons.org/licenses/by/4.0/

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TIR can also be applied to other functional endpoints including LLVA, contrast sensitivity, and microperimetry, each with defined thresholds. TIR could help address knowledge gaps concerning retinal disease course; however, it does not address the existing limitations of each metric.[12,13] Given the increasing importance of morphological biomarkers in managing retinal diseases, driven by advances in imaging technologies, it would be logical to also apply TIR to the main standardized morphological biomarkers, such as central subfield thickness, macular volume, or fluid volume. These may provide information on structural changes over time and their correlation with visual acuity.[14]

Applying TIR to retinal disease monitoring in clinical practice could help evaluate the effectiveness of intravitreal therapy, improve understanding of disease progression and treatment response, personalize healthcare, and detect treatment failure earlier, aiming to reduce vision loss and improve patient outcomes.[3,5] However, before implementing TIR metrics in routine ophthalmology practice, prospective studies are needed to validate feasibility, patient relevance, and correlation with long-term outcomes.

Vision Academy recommendations

Upon evaluating the recent evidence on the TIR concept and clinical endpoints in retinal diseases, a Vision Academy workstream developed a set of recommendations which was subsequently reviewed, commented upon, and endorsed by a majority of the Vision Academy membership before publication. It should be noted that TIR is proposed not as a replacement for existing endpoints such as BCVA but as a complementary measure that adds temporal insight into disease control and treatment response.

Recommendation 1

When evaluating disease course and treatment response, the limitations of reporting a one-time endpoint should be recognized.

Recommendation 2

Future analyses should consider, among other metrics, the BCVA TIR (i.e., the percentage of time the patient had a BCVA above a certain threshold).

Recommendation 3

TIR may be applied to morphological parameters as an additional metric to the functional ones.

Further considerations

Potential impacts of the application of the TIR concept in clinical trials

Primary endpoints for clinical trials should ideally be based on functional metrics such as BCVA. These may be combined with morphological metrics from optical coherence tomography (OCT) and OCT angiography for insights into disease progression. Other endpoints, including LLVA, contrast sensitivity, and patient-reported outcomes, are gaining relevance but require further standardization and validation. BCVA TIR may provide crucial information on clinical trial outcomes and overall visual function, both at the end of treatment and as fluctuations occur over the disease course.

Potential impacts of the application of the TIR concept in clinical practice

The application of TIR can improve disease control by improving understanding of disease behavior in different patients, thus improving treatment compliance,[3,15,16] without requiring additional evaluations at visits. As more therapeutic options emerge, the use of TIR in *post hoc* analyses of clinical trials may provide a more specific measure of differences among drugs, enabling more targeted treatment and better understanding of treatment responses and the necessity of switching.[17]

The increasing use of drugs that allow progressive extension of treatment intervals may see a reduction in the frequency of measurements taken at visits. TIR might be particularly informative with the increasing availability and integration of home monitoring and telemedicine,[18] which would allow more measurements to be taken daily or multiple times per day, possibly increasing the sensitivity of the metric.

Applying TIR metrics may require more frequent assessments, potentially increasing upfront costs; however, these are offset by potential long-term economic benefits. Improved disease monitoring through TIR may enable earlier detection of treatment failure, better individualization of therapy, and reduced risk of vision loss, which is associated with societal and healthcare costs.

While this Viewpoint focuses on retinal diseases, particularly exudative diseases involving the posterior pole, the concept of TIR can be applied to other eye conditions.

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