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Development and standardization of “time-in-range” measurement for clinical endpoints in retinal diseases

Based on the Vision Academy publication by Frizziero L *et al*. *Eye* 2025; Epub ahead of print. https://doi.org/10.1038/s41433-025-04112-6 This presentation is based on material developed by the Vision Academy members and does not necessarily reflect the views of Bayer. Medical writing and editorial support was provided by Caudex, an IPG Health company, and funded by Bayer.
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The Vision Academy is a group of over 80 international experts who, through their collective expertise, provide consensus guidance for managing clinically challenging situations, especially in areas of controversy or with insufficient conclusive evidence.

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This presentation is based on the Vision Academy publication by Frizziero L *et al*. *Eye* 2025; Epub ahead of print. https://doi.org/10.1038/s41433-025-04112-6 and is intended for healthcare professionals. The opinions expressed, and guidance laid out, by the Vision Academy are developed independently by the members and do not necessarily reflect the opinions of Bayer.

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Contents

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TIR, time-in-range.

Objectives

To identify a possible reliable TIR endpoint of clinical outcomes in ophthalmology, with a focus on exudative diseases involving the posterior pole of the eye

To propose possible future applications of this new TIR endpoint

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QUESTION

How can we apply the concept of TIR in ophthalmology to improve understanding of disease course and treatment response over time?

TIR, time-in-range.

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Background

Endpoints: clinical, surrogate, and biomarker

Endpoints are specific measures of outcomes of an intervention or its absence[1]

Clinical endpoints capture how a person **feels, functions, or survives**, and directly reflect their wellbeing and quality of life

- Reported by clinicians, patients, or observers, or assessed via performance measures[1,2]

Non-clinical endpoints are indicators of **biological or pathogenic processes**, objectively measured for diagnosis, prognosis, or monitoring (e.g., imaging results)[1]

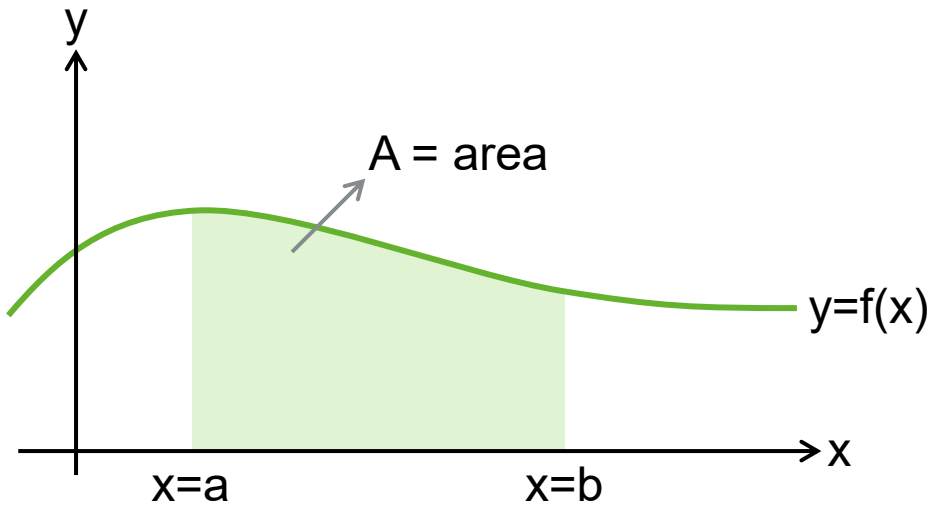
Surrogate endpoints directly measure **causal intermediaries** of clinically meaningful outcomes, and are reliable **substitutes of clinical endpoints** due to association[1]

- May include morphological biomarkers that correlate with visual benefit or loss[2]

1. McLeod C *et al*. *Contemp Clin Trials Commun* 2019; 16: 100486; 2. Schmetterer L *et al*. *Prog Retin Eye Res* 2023; 97: 101160.

Main clinical endpoints currently accepted in ophthalmology

- **BCVA** is the most widespread primary endpoint for ocular diseases in clinical practice and clinical trials, providing a single measurement of a patient's visual function[1]
- **Main current limit:** No consistent detection of the effect of intervention across all stages of disease[2,3]
- **Possible alternative:** Area under the curve (**AUC**)[4]



AUC provides an averaged measure over a period but **without giving an idea of the fluctuations** or of the **time spent within the certain value** of a metric presumed to be a "safe range"[4]

BCVA, best corrected visual acuity.

1. Schmetterer L *et al*. *Prog Retin Eye Res* 2023; 97: 101160; 2. Grewal MK *et al*. *Eye* 2022; 36 (2): 398–406;
3. Cheung CMG *et al*. *Ophthalmologica* 2021; 244 (5): 451–464; 4. Kozak I *et al*. *Eye* 2023; 37 (16): 3367–3375.

The “time-in-range” (TIR) concept

TIR measures the **proportion of time** spent **within a certain range**, offering a more complete reflection of a disease than single time points or averages[1-3]

TIR is well accepted in **diabetology**, originating from **continuous glucose monitoring**[1,2]

- Defined as the percentage of time spent within a **specific glucose range**[2]
- TIR is associated with diabetes **complications**, all-cause **mortality**, and prevalence of **diabetic retinopathy**, and is proposed as a clinical endpoint in clinical trials[2,4,5] and recommended as part of daily diabetes management[6]

?

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

Reliable endpoints that provide information on retinal disease course in a continuous manner are lacking and the application of a TIR concept should be explored

RECOMMENDATION

1. Timmons JG *et al. Diabetes Spectr* 2021; 34 (2): 133–138; 2. Lu J *et al. Diabetes Care* 2018; 41 (11): 2370–2376; 3. Kozak I *et al. Eye* 2023; 37 (16): 3367–3375; 4. Beck RW *et al. Diabetes Care* 2019; 42 (3): 400–405; 5. Lu J *et al. Diabetes Care* 2021; 44 (2): 549–555; 6. Al Sifri S *et al. Int J Clin Med* 2021; 12 (8): 316–327.

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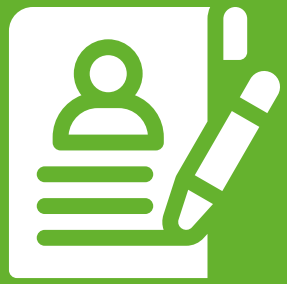
Clinical challenges

Clinical challenges requiring guidance

Clinical endpoints and application of the TIR concept

What is the best clinical endpoint to apply to the TIR concept in retinal diseases?



Practical recommendations

How can we use this knowledge to produce recommendations for the assessment of retinal diseases?

Click on a section

TIR, time-in-range.

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Clinical endpoints in ophthalmology

Visual function endpoints

Endpoint	Test	Indications	Advantages	Disadvantages
BCVA	BCVA score; mean change in BCVA[1]; percentage of VA gain (>0, >5, >10, >15 letters); percentage with VA >20/40[2]	All ocular diseases	Widespread; inexpensive, rapid, intuitive; possibly self-administered; correlates with QoL	Limited value in early disease and tracking small changes; does not consider changes during study period
LLVA	LLVA score[3]; mean change in LLVA[4]	AMD, DME, DR, CSCR, IRD	Simple, inexpensive, rapid; possibly self-administered	Selected information (foveal function); related to time point assessed
Contrast sensitivity	Contrast sensitivity level; change in contrast sensitivity[3,4]	AMD, DME, DR, refractive surgery, CSCR, IRD	Rapid; correlates with QoL	Difficult to set up accurately; limited sensitivity; not well standardized, not widespread; related to time point assessed
Perimetry	Mean sensitivity and mean deviation[5]	Glaucoma, neurological conditions, retinal diseases	Comprehensive measure of visual function	Needs adequate instruments and time; influenced by execution conditions and patient learning curve
Microperimetry	Scotopic / mesopic sensitivity[3,4]	AMD, DME, vitreoretinal disorders, retinotoxicity disorders, macular dystrophies, IRD	Better understanding of morphology, function; used to determine fixation in advanced AMD	Not widespread; long testing duration; related to time point assessed; learning curve
Dark adaptometry	Change in visual performance[1,3,4]	AMD, DME, DR; differentiate AMD from genetic variants, diagnosis of early progression	Assesses photoreceptor dynamic response	Needs adequate instruments and time; lack of standardization; related to time point assessed
Reading speed	Mean change in reading speed[3,4]	AMD, DME, vitreoretinal disorders, refractive surgery	Linked to vision-related QoL	Lack of standardization and agreement on methodology; depends on patient literacy; related to time point assessed

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CSCR, central serous chorioretinopathy; DME, diabetic macular edema; DR, diabetic retinopathy; IRD, inherited retinal diseases; LLVA, low-luminance visual acuity; QoL, quality of life; VA, visual acuity.

1. Csaky KG *et al*. *Invest Ophthalmol Vis Sci* 2008; 49 (2): 479–489; 2. Diabetic Retinopathy Clinical Research Network *et al*. *N Engl J Med* 2015; 372 (13): 1193–1203;
3. The Vision Academy. 2023. Additional Measures of Macular Function Beyond Visual Acuity. Available at: https://www.visionacademy.org/media/3026/download;
4. Cheung CMG *et al*. *Ophthalmologica* 2021; 244 (5): 451–464; 5. Schmetterer L *et al*. *Prog Retin Eye Res* 2023; 97: 101160.

Morphological metrics

Endpoint	Test	Indications	Advantages	Disadvantages
GA area	GA area; GA area enlargement[1]	AMD	Accurate, rapid	Influenced by image quality; related to time point assessed; for atrophic diseases only
Ellipsoid zone and / or external limiting membrane defects	Percentage of defect; rate of change in defect as measured by OCT[2]	Macular diseases	Well related to visual function	Influenced by image quality; related to time point assessed; provides information on photoreceptor status only
CST	Mean thickness; change in thickness on OCT[1]	Macular diseases	Rapid, standardized, widespread	Weakly correlated with VA; limited area of evaluation (fovea, perifovea); related to time point assessed
Macular volume	Mean volume; change in volume on OCT[1]	Macular diseases	Rapid, standardized, widespread; greater area of evaluation than CST	Not highly correlated with VA; related to time point assessed
Foveal avascular zone size	Change in area and / or perimeter on OCT-A[2]	DME, DR, retinal vascular diseases	Rapid, precise	Related to device used and image quality; absence of shared normal reference values
Vessel density / perfusion	Change in capillary perfusion / density on OCT-A[2]	DME, DR, retinal vascular diseases	Precise	Related to device used and image quality; absence of shared normal reference values

AMD, age-related macular degeneration; CST, central subfield thickness; DME, diabetic macular edema; DR, diabetic retinopathy; GA, geographic atrophy; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; VA, visual acuity.

1. Schmetterer L *et al*. *Prog Retin Eye Res* 2023; 97: 101160; 2. Cheung CMG *et al*. *Ophthalmologica* 2021; 244 (5): 451–464.

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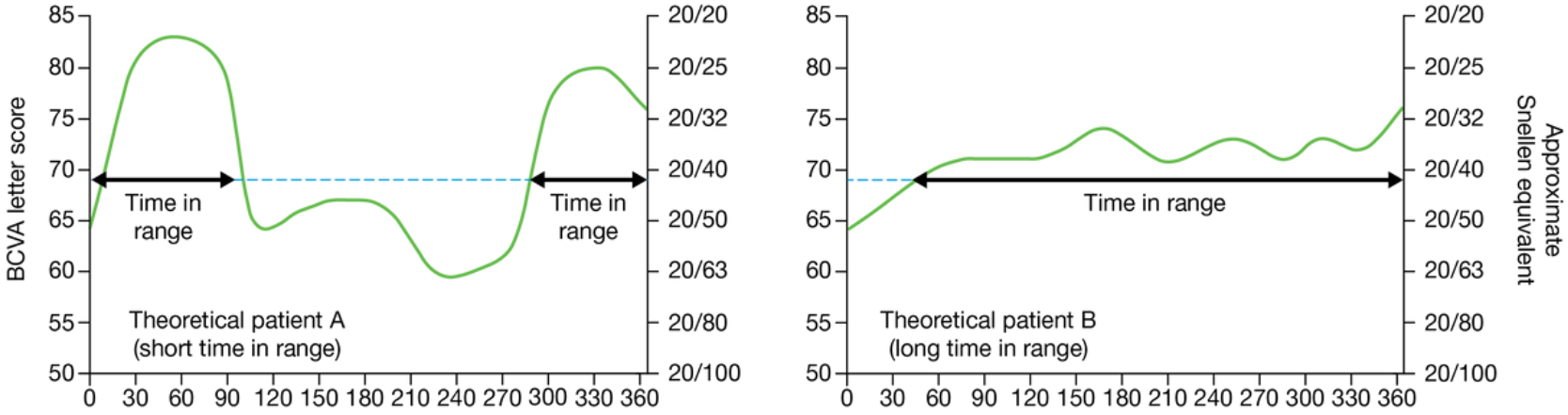
Application of the TIR concept in retinal diseases

TIR, time-in-range.

Application of a BCVA threshold to the TIR concept

- A **BCVA threshold** may be the **best metric to apply to the TIR concept** as a clinical endpoint
- **69 Early Treatment Diabetic Retinopathy Study letters** is a **common threshold score** for good visual acuity in clinical trials and a target for holding a driving license in the USA[1-3]
- This threshold appears adequate to delineate the area of **patient autonomy**[3]

Theoretical visualization of AUC, TIR, and mean change in BCVA when evaluating vision outcomes in a theoretical patient[4]



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.)	AUC of the change from baseline in BCVA letter score	+8 (approx.)
<170 days or <50%	TIR (threshold BCVA letter score ≥69, approx. Snellen equivalent 20/40 or better)	>300 days or >85%

Figure adapted from Kozak I *et al*. *Eye* 2023; 37 (16): 3367–3375.[4]
AUC, area under the curve; BCVA, best corrected visual acuity; TIR, time-in-range.
1. Baker CW *et al*. *JAMA* 2019; 321 (19): 1880–1894; 2. Diabetic Retinopathy Clinical Research Network *et al*. *N Engl J Med* 2015; 372 (13): 1193–1203;
3. Steinkuller PG. *Virtual Mentor* 2010; 12 (12): 938–940; 4. Kozak I *et al*. *Eye* 2023; 37 (16): 3367–3375.

Other potential applications of the TIR concept in retinal diseases

TIR can be applied to functional endpoints such as **LLVA, contrast sensitivity, and microperimetry**, to help address knowledge gaps concerning **retinal disease course**[1,2]

TIR may also be applied to **morphological biomarkers** such as **CST, macular volume, or fluid volume**, to track **structural changes** over time and their correlation with VA[3]

Applying TIR to **retinal disease monitoring** could help to evaluate the effectiveness of therapy, improve understanding of disease progression, personalize healthcare, and detect treatment failure earlier[4,5]

Before implementing TIR metrics in routine ophthalmology practice, prospective studies are needed to validate feasibility, patient relevance, and correlation with long-term outcomes

CST, central subfield thickness; LLVA, low-luminance visual acuity; TIR, time-in-range; VA, visual acuity.

1. Nixon DR, Flinn NA. *Clin Ophthalmol* 2018; 12: 191–197; 2. The Vision Academy. 2023. Additional Measures of Macular Function Beyond Visual Acuity. Available at: https://www.visionacademy.org/media/3026/download; 3. Terheyden JH *et al*. *Ophthalmologica* 2021; 244 (5): 387–395; 4. Kozak I *et al*. *Eye* 2023; 37 (16): 3367–3375; 5. Timmons JG *et al*. *Diabetes Spectr* 2021; 34 (2): 133–138.

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Vision Academy recommendations

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

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

BCVA, best corrected visual acuity; TIR, time-in-range.

TIR may be applied to morphological parameters as additional metrics to the functional ones

TIR, time-in-range.

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Summary

Vision Academy recommendations

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

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

TIR may be applied to morphological parameters as additional metrics to the functional ones

BCVA, best corrected visual acuity; TIR, time-in-range.

Further considerations

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

Applying TIR in **clinical practice** may improve our understanding of **individual disease behavior**, enabling more **targeted and informed treatment decisions**

The **utility of TIR** is likely to increase with the trend towards **extended treatment intervals** and integration of **home monitoring and telemedicine**

While potentially increasing upfront costs due to frequent assessments, TIR offers long-term economic benefits by enabling **earlier detection of treatment failure**, **personalized therapy**, and **reduced societal costs** of vision loss

The current **lack of prospective studies** designed to assess TIR as a primary endpoint in retinal diseases **limits the full understanding** of its potential

BCVA, best corrected visual acuity; TIR, time-in-range.