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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.

Navigating Real-World Evidence in Ophthalmology

Background

Randomized controlled trials (RCTs) address clinical questions using strict criteria and specific methods, meaning they may not fully represent patient populations and treatment outcomes in routine clinical practice.[1,2]

Real-world data (RWD) are generated from studies that more closely reflect routine clinical practice,[1] and when collected and analyzed appropriately, the resulting real-world evidence (RWE) can positively guide the treatment of retinal disease. For example, identifying variation in treatment practices with anti-vascular endothelial growth factor (anti-VEGF) agents in neovascular age-related macular degeneration has resulted in treatment improvements, an understanding of the need for proactive treatment, and the establishment of new treatment regimens such as treat-and-extend.[3]

RWD-related study design limitations highlight the importance of carefully assessing the quality of RWE, ensuring reliable conclusions can be drawn that are applicable to clinical practice.[1,4-6]

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Viewpoint

RWD can provide valuable information, but it is important to be aware of and correct for potential biases, in addition to being aware of the strengths and weaknesses of different data sources. This awareness permits assessment of the applicability of RWE to clinical practice and the translation of findings into clinical practice for optimized patient care. RWD collection is associated with study design and data source limitations, so critical evaluation of the method of RWD collection, the subsequent analysis and reporting, and the conclusions drawn are important to enable effective interpretation of the validity of published RWE.

Consider and control for biases

Specific biases can influence the quality of RWE due to data generation outside of stringently controlled RCT environments.

Selection bias	Arises when non-comparable groups are studied, for example when exposed and non-exposed groups differ in some respect other than the exposure
Information bias	Results from incorrect determination of exposure, outcome, or both. This can occur if information is gathered in a different way for one group than for another
Recall bias	Differing recollection of exposures or symptoms among cases compared with controls
Ascertainment bias	Systematic deviations from an expected result which can be attributable to the sampling processes used to find and measure an outcome. Incompleteness of data capture may lead to ascertainment bias
Confounders	A mixing or blurring of effects, for example when it is attempted to relate an exposure to an outcome, but it actually measures the effect of a third factor (the confounding variable)

Types of bias that can impact the quality of RWD[3,7,8]

Statistical analyses are required to control for the presence of biases so that robust and clinically relevant conclusions can be made.

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References

1. Garrison LP, Jr., Neumann PJ, Erickson P *et al.* Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health* 2007; 10 (5): 326–335.
2. Mehta H, Tufail A, Daien V *et al.* Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. *Prog Retin Eye Res* 2018; 65: 127–146.
3. Talks J, Daien V, Finger RP *et al.* Utility of real-world evidence for evaluating anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration. *Surv Ophthalmol* 2019; 64 (5): 707–719.
4. Berger M, Daniel G, Frank K *et al.* A framework for regulatory use of real-world evidence. Available at: https://healthpolicy.duke.edu/publications/framework-regulatory-use-real-world-evidence. Accessed November 2, 2020.
5. Parke DW II, Lum F and Rich WL. The IRIS® Registry: purpose and perspectives. *Ophthalmologe* 2017; 114 (Suppl 1): 1–6.
6. RWE Navigator. Healthcare databases: focus on electronic health records. Available at: https://rwe-navigator.eu/use-real-world-evidence/sources-of-real-world-data/healthcare-databases-with-a-focus-on-electronic-health-records/. Accessed November 2, 2020.
7. Grimes DA and Schulz KF. Bias and causal associations in observational research. *Lancet* 2002; 359 (9302): 248–252.
8. SNP FAQ Archive [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005. Ascertainment Bias. Available at: https://www.ncbi.nlm.nih.gov/books/NBK9792/. Accessed November 19, 2020.
9. Lewallen S and Courtright P. Epidemiology in practice: case-control studies. *Community Eye Health* 1998; 11 (28): 57–58.
10. Dreyer NA, Velentgas P, Westrich K *et al.* The GRACE checklist for rating the quality of observational studies of comparative effectiveness: a tale of hope and caution. *J Manag Care Pharm* 2014; 20 (3): 301–308.

Different sources from which RWD are obtained also have various strengths and weaknesses that can contribute to the quality of the published RWE.

The main sources of RWD in retinal disease

Source of RWD	Strengths and weaknesses
Non-interventional studies	Can be prospective or retrospective and can follow different study designs
Cohort studies	Most widely used study design in ophthalmology. A prospective design allows for standardized patient inclusion criteria and calculation of incidence rates, relative risk, and attributable risks within a set time period
Case-control studies	Usually retrospective, therefore cost-effective and quick to establish; susceptible to recall bias and poor record-keeping[3,9]
Case studies/series	May focus on key elements of disease history and treatment such as adverse events. Low patient numbers risk selection bias that can lead to overestimation or misinterpretation of outcomes
Patient registries	Data typically prospectively collected. Can be used to collect post-marketing safety data, understand the natural history of a condition, or assess qualities of care experienced by patients[6]
Electronic health records	Can be simply used to retrospectively compare outcomes between patients treated using different approaches; dependent on completeness of record-keeping
Reimbursement claims databases	Large, diverse patient populations lacking selection bias allow insight into rare events. Limitations include incomplete, inaccurate, or missing data and an inability to evaluate appropriateness of care
Patient surveys and questionnaires	Can be conducted in person or remotely to collect data on adherence, preferences, functional status, and quality of care. Limitations include introduction of subjectivity on outcome reporting, potential of wording to influence answers, and recall bias[3]

Resources to aid ophthalmologists in evaluating the quality of RWE are available, such as the Good ReseArch for Comparative Effectiveness (GRACE) principles, which can support the evaluation of observational comparative effectiveness studies.

GRACE checklist to support ophthalmologists in the evaluation of RWE[10]

Data	Methods
☑ Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	☑ Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?
☑ Were the primary outcomes adequately recorded for the study purpose?	☑ If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?
☑ Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment?	☑ Were important confounding and effect-modifying variables taken into account in the design and/or analysis?
☑ Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	☑ Is the classification of exposed and unexposed person-time free of "immortal time bias"?
☑ Was the primary outcome(s) measured or identified in an equivalent manner between the treatment/intervention group and the comparison group?	☑ Were any meaningful analyses conducted to test key assumptions on which primary results are based?
☑ Were important covariates that may be known confounders or effect modifiers available and recorded?	

Table adapted from Dreyer NA *et al. J Manage Care Pharm* 2014; 20 (3): 301–308 (Table 1). While used with permission of the publisher, the publisher disclaims all endorsement of any organization, product or technique as a matter of policy.

Further considerations

Evidence for intravitreal anti-VEGF therapy has specific considerations and needs, so a framework to facilitate the systematic assessment of the quality and relevance of RWE specifically for this therapeutic class would be valuable. The framework should include retinal disease-specific considerations, such as method of administration and injection clinic set-up, to help ophthalmologists more easily and accurately assess the quality of the RWE related to the use of anti-VEGFs.

Vision Academy Viewpoints are intended to raise awareness of a clinical challenge within ophthalmology and provide an expert opinion to engage in further discussion.
They can be downloaded from https://www.visionacademy.org/resource-zone/resources/all
The Vision Academy is sponsored by Bayer. This document was prepared by the Real-World Evidence Steering Committee, all of whom are members of the Vision Academy.
Always refer to local treatment guidelines and relevant prescribing information.
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