Review Article

A novel tool to assess the quality of RWE to guide the management of retinal disease

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ABSTRACT.

Despite the growing importance of real-world evidence (RWE) for guiding clinical decisions in retinal disease, there is currently no widely used guidance available for assessing the quality and relevance of RWE studies in ophthalmology. This paper summarizes the development of a user-friendly tool that facilitates assessment of the quality of available RWE for neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DME) and retinal vein occlusion (RVO). A literature search was conducted to identify tools developed to assess the quality of RWE, in order to identify the most appropriate framework on which to base this tool. The Good Research for Comparative Effectiveness (GRACE) guidelines was chosen for this purpose as it is designed to assess the quality of observational studies and has been extensively validated, including demonstration of strong sensitivity and specificity. The GRACE guidelines were adapted to develop a straightforward tabular tool that allows simple assessment and comparison of the quality of published evidence in retinal disease for researchers and physicians alike, and includes guidance on treatment details, outcome measures, study population, and controlling for bias. The newly developed tool provides a simple method to support assessment of the strength of evidence and certainty of conclusions drawn from RWE in retinal disease, to ensure clinical decision-making is influenced by the highest quality evidence.

INTRODUCTION

RWE is becoming increasingly important to complement data from randomized clinical trials (RCTs) and to provide insights that are outside their remit (de Lusignan et al. 2015; Talks et al. 2019). Additionally, RWE is increasingly considered and recognized by healthcare authorities as meaningful information to inform regulatory decisions, develop guidelines and demonstrate value (ABPI 2011; US Food & Drug Administration 2020). Sources of RWE include registries, records, claims databases, observational or longitudinal cohort studies and health surveys (de Lusignan et al. 2015; Mehta et al. 2018; Talks et al. 2019). These sources reflect routine clinical practice, so can confirm and complement results from RCTs by assessing their applicability in a more general population (Mehta et al. 2018; Talks et al. 2019).

Specifically, sources of real-world data (RWD) used to generate RWE include wider, more heterogeneous patient groups, including those with co-morbidities, those receiving concomitant therapies and those with baseline factors known to impact

treatment outcomes, who might not be included in RCTs due to rigorous selection criteria (de Lusignan et al. 2015; Talks et al. 2019). RWE can reflect variations in adherence or treatment access due to resource constraints, detect less common and later-onset adverse effects by examining treatment effectiveness over the longer term, and can include a broader range of endpoints more pertinent to routine clinical practice than RCTs (de Lusignan et al. 2015; Hoque et al. 2016; Mehta et al. 2018; Talks et al. 2019). Primary outcomes in RWE studies may include clinical effectiveness and safety, patterns of treatment use, resource utilization, cost, adherence and persistence, patient burden or patient-reported outcomes (e.g. quality of life [QoL]) and treatment satisfaction) (de Lusignan et al. 2015; Talks et al. 2019).

In the context of retinal disease, there is a growing wealth of RWE that has investigated the use of anti-vascular endothelial growth factor agents (anti-VEGFs) in clinical practice, following their development as a major therapeutic advance (Talks et al. 2019). In the context of nAMD, RWE has uncovered issues regarding the implementation of various treatment strategies in practice. This has led to research into optimizing anti-VEGF dosing regimens, with the aim of balancing clinical outcomes and treatment burden to achieve optimal long-term outcomes for patients (Daien et al. 2020 [in preparation]). Specifically, RWE supports proactive treat-and-extend (T&E) dosing of anti-VEGFs to optimize visual outcomes, while minimizing injection frequency (Hanemoto et al. 2017). However, RWE has also revealed that delay in the diagnosis and treatment of retinal disease is common, which often leads to suboptimal visual outcomes (Arias et al. 2009; Cavan et al. 2017).

The growing importance of RWE in retinal disease means that clinicians, payers and other stakeholders should consider implementing relevant findings into clinical practice (Talks et al. 2019). However, there are inherent limitations to data collection in real-world clinical practice, and as a result, RWE may vary in quality. In particular, outside the stringently controlled environment of an RCT, specific biases can occur, which necessitate appropriate study design and statistical analysis (de Lusignan et al. 2015; Dreyer et al. 2016; Talks et al. 2019). Without appropriate evaluation of study quality, clinical decisions may be taken based on evidence that is not sufficiently robust (Garrison et al. 2007).

A systematic review found that there was no consensus on a preferred instrument for assessing RWE (Briere et al. 2018), although some resources to support evaluation of the quality of ophthalmology-specific RWE exist. For example, the International Consortium for Health Outcomes Measurement (ICHOM) has defined a minimum set of standardized and patient-oriented outcome measures that should be collected and reported as RWD associated with macular degeneration (Rodrigues et al. 2016). The lack of consensus on how to define quality in this setting can make RWE interpretation difficult for ophthalmology clinicians, and a framework to facilitate systematic assessment of RWE quality and relevance – specifically concerning intravitreal anti-VEGFs – would be valuable. Inclusion of retinal disease-specific considerations when collecting RWD would help ophthalmologists to more accurately assess the RWE quality relating to the use of anti-VEGF therapies.

This paper summarizes the development of a user-friendly framework that facilitates assessment of the quality of available RWE for nAMD, DME and RVO. The framework will allow ophthalmologists to independently draw relevant and reliable conclusions from RWE in retinal disease.

METHODS

Literature review

A literature search was conducted on 1 December 2018, to identify tools developed to assess the quality of RWE, irrespective of clinical indication or setting, using the following search terms: (Checklist OR tool OR assess* [tiab] OR apprais*[tiab] OR score[tiab] OR 'Checklist'[Majr]) AND (('real-world data' OR 'real-world evidence' OR 'real-world outcomes' OR 'Observational Studies as Topic'[Majr] OR 'Epidemiologic Studies'[Majr]) NOT 'Randomized Controlled Trial' [Publication Type]). PubMed was used for automated searching of the indexed literature in MEDLINE, which was limited to English language publications within the last 5 years. Abstracts were scanned for appropriateness using preagreed inclusion and exclusion criteria, and full-text copies of articles that were accepted after the initial screening were reviewed and assessed for eligibility. Following full-text review, articles deemed eligible for inclusion were accepted. In addition, a search was performed on Google and of ISPOR abstracts to supplement the indexed literature search.

Collaboration with panel of experts

The authors of this article comprise a steering committee of experts in the field of RWE and ophthalmology. Having discussed the results of the literature review during a series of meetings and online surveys, the most appropriate tool to be used as a framework for assessing RWE for retinal disease was decided on. Once the framework was established, considerations specific to assessing the quality of RWE in retinal disease were discussed and added alongside the existing tool framework, to support recommendations on how the tool should be used when assessing RWE in retinal disease. These recommendations comprise the observations, guidance, and clinical and research experience of the authors, who have generated and published RWE in retinal disease extensively.

RESULTS

Literature review

The literature review identified 39 articles, describing 13 tools for evaluating quality of RWD used to generate RWE (Downs & Black 1998; Berger et al. 2014; Dreyer et al. 2014; Roche et al. 2014; BMJ Clinical Evidence Blog 2015; Malmivaara 2015; Downes et al. 2016; Dreyer et al. 2016; Malmivaara 2016; Rao et al. 2016; Briere et al. 2018; Camm et al. 2018; CASP UK 2018; Miksad & Abernethy 2018; Schaumberg et al. 2018; CASP UK 2018; Scottish Intercollegiate Guidelines Network 2019; Ottawa Hospital Research Institute 2020); 11 tools for reporting RWD collection and study design (Stroup et al. 2000; von Elm et al. 2007; Berger et al. 2009; Loring & Bowden 2014; Vandenbroucke et al. 2014; Benchimol et al. 2015; Bennett

et al. 2015; Fitchett et al. 2016; Lachat et al. 2016; Langan et al. 2016; Morton et al. 2016; Agha et al. 2017; Horby et al. 2017; Hornell et al. 2017; Sharp et al. 2017; Yang et al. 2017; European Network of Centres for Pharmacoepidemiology & Pharmacovigilance 2018; Pandey et al. 2018; Patient-Centred Outcomes Research Institute 2019); and two tools to aid statistical analysis (Sauerbrei et al. 2014; VanderWeele & Ding 2017). Therapy area-specific tools and guidelines for reporting RWD and study design were generally extensions of STROBE. None were identified as being ophthalmology-specific.

Rationale for using the GRACE checklist as the basis of the retina-specific RWE quality tool

The steering committee identified a published RWE quality checklist from the literature review (the GRACE guidelines) (Dreyer et al. 2016) for adaptation and inclusion of retinal disease-specific considerations. The steering committee agreed that GRACE was the most appropriate framework for the retina-specific tool as it is designed to assess the quality of observational studies and has been extensively validated, including demonstration of strong sensitivity and specificity. Other checklists identified by the literature review were typically restricted to the assessment of evidence generated from certain designs of real-world study. The STROBE checklist, and its extensions, were discounted as a framework as they are tools to guide the reporting of RWD, aimed at authors preparing a manuscript for publication, rather than assessing published data.

Guidance on RWE quality

The original GRACE checklist (Dreyer et al. 2016) was adapted to ensure relevance to the ophthalmological community. In doing so, some questions were combined or omitted and some minor modifications made to wording.

Specifically, 'Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment?' was combined with 'Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?', and 'Were important covariates that may be known

confounders or effect modifiers available and recorded?' was combined with 'Were important confounding and effect-modifying variables taken into account in the design and/or analysis?' This was done in an effort to bring similar concepts together as single questions, thereby increasing the simplicity of the tool.

'Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?' was adapted significantly to ''Was the study population relevant to the research question and clinical practice?' This was driven by the fact that many patients with retinal disease are previously treated or currently on a course of treatment at the start of observation in real-world studies – as such, this does not necessarily preclude high-quality research in this therapy area.

Finally, 'Is the classification of exposed and unexposed person-time free of 'immortal time bias'?', a concept that can be challenging to assess without a thorough methodological review, was omitted.

The resulting tool to aid assessment of the quality of RWE in retinal disease is outlined in Table 1. To provide context and background information relevant to the checklist questions, detailed guidance on retinal disease-specific criteria to consider when assessing the quality of RWE has been included.

Treatment details
It is important that information on the various treatments administered in the studies is defined in detail, as regimens are often interpreted and applied differently between clinics, and this may influence outcomes.

Outcome measures
It is important to consider if the reported outcomes of a RWE study are appropriate to answer the research question and relevant to clinical practice. The primary endpoint should also be captured appropriately and accurately, with the likelihood of missing outcome values from the RWD source considered.

The study design should incorporate a duration of follow-up adequate to measure the outcome of interest. nAMD, DME and macula oedema secondary to RVO are chronic diseases

(Schmidt-Erfurth et al. 2019), so sufficient time should be allowed to assess long-term effects of treatment. For example, a study with a follow-up of 6 months may be useful to assess the early effectiveness of anti-VEGF loading doses on vision outcomes, but conclusions on the long-term impact of continued anti-VEGF dosing on maintenance of vision should not be drawn from these data. At least 1 year of follow-up should be available to assess the effectiveness of a treatment and dosing regimen, and longer follow-up is required to draw valid conclusions when comparing different treatment regimens (e.g. T&E vs PRN).

Outcomes should be measured using standardized and validated methods, and/or undergo independent validation or systematic adjudication. A clinical outcome can be considered objectively measured if it is assessed using a standardized test; it is not objectively measured if it is based on a physician's opinion or observation.

Outcomes should be measured in an equivalent manner, using the same method and measurement, across comparison groups to provide uniformity and allow for a like-for-like assessment of outcomes, wherever possible. If the study design necessitates the use of different methods or measurements, the method used to transform the data to ensure comparability should be fully described and any limitations acknowledged.

Study population
The study population should represent the typical range of patients seen in clinical practice. In addition, it is important to consider the setting/environment of the population to ensure applicability to other cohorts of patients. For example, healthcare systems can differ significantly between regions, and public and private systems, which may introduce differences in treatment patterns that potentially affect outcomes. Data from a single centre may be less generalizable, whereas a multi-national, multi-centre study could provide data from several settings and may be more widely applicable.

Patient numbers can affect the statistical weight and applicability of any RWE findings. Larger patient numbers increase the reliability of the data set; however, the exact number of patients required to ensure reliability of

Table 1. Retinal disease-specific tool to evaluate the quality of RWE

	Quality assessment question	Retinal disease-specific considerations	Checklist
Treatment details	Were important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	Treatment details should include: • Name of treatment and dose • Treatment strategy/regimen (e.g. T&E, fixed dose, pro re nata [PRN], including length of treatment intervals, criteria for decision-making, and frequency of monitoring, if applicable) • Duration of treatment	☐Yes ☐No
Outcome measures	Were the primary outcomes adequately recorded for the study purpose (can the primary outcome adequately address the research question)?	Examples of appropriate use of outcomes include: • Change in visual acuity from baseline to assess effectiveness of therapy • Claims data reporting on the cost of treatment to assess economic burdenAn example of an inappropriate use of outcomes includes: • Injection number to assess the overall cost of treatment, without accompanying system-wide cost analysisIn retinal disease, it is also important to distinguish if differences in outcomes are statistically and/or clinically significant • The proportion of patients reaching a visual acuity that allows them to read or drive is often considered as the most clinically relevant endpoint. In addition, a change in visual acuity of 10–15 ETDRS letters is generally accepted as clinically significant	Yes No
	Was the primary outcome measured objectively, and adjudicated/validated where required?	Examples of objective methods to measure outcomes in retinal disease include: • ETDRS letters, Snellen equivalent or LogMAR to measure visual acuity • National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) to measure quality of life • Independent adjudication of OCT images by a reading centre, to confirm diagnoses or the presence of retinal fluid	Yes No
	Were outcomes measured or identified in an equivalent manner between treatment groups?	Where possible, outcomes should be measured using the same method • For example, visual acuity scores should be measured using either ETDRS or LogMAR, and uniformly with or without correctionExamples of when the use of different methods may be necessary include: • If equipment used for OCT varies across sites in a multi-centre study • If disease activity is defined differently between clinics or physicians, e.g. varying amounts of retinal fluid observed on OCT being tolerated and classified as 'inactive' disease	☐Yes ☐No
Study population	Was the study population relevant to the research question and clinical practice?	The population in the study should closely reflect the patients seen in clinical practice to ensure translatability of conclusions Whether patients are treatment-naïve or treatment-experienced can affect outcomes. However, it is common for patients with retinal disease to switch treatments or treatment regimens, and it is therefore appropriate for a study to include patients who are treatment-naïve or treatment-experienced • For treatment-experienced patients, the duration of prior therapy, as well as response and injection frequency, should be stated	☐Yes ☐No
	If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison group(s)?	Treatment approaches and the standard of care for retinal disease used in clinical practice have differed significantly over time; therefore, the era in which the study was conducted should be taken note of • The use of historical comparators in retinal disease is often not justified, and without a concurrent comparator, the impact of any data is reduced significantly	☐Yes ☐No
Controlling for bias	Were important covariates, confounding, and effect-modifying variables taken into account in the design and/or analysis?	If confounding variables that may affect outcomes between treatment groups are present (e.g. differences in baseline visual acuity between groups), these should be appropriately adjusted for using statistical analyses to minimize the risk of bias Variables that might affect outcomes in retinal disease include: Age, gender, smoking status, concomitant conditions and treatments, baseline visual acuity, and bilateral involvement	☐Yes ☐No

Table 1 (Continued)

Quality assessment question	Retinal disease-specific considerations	Checklist
	Specifically in DME, variables that might affect outcomes include: Diabetes disease characteristics (glycemic control, duration of diabetes), blood pressure and characteristics of macular oedema (macular thickness, extension of oedema and presence of hard exudates) Specifically in nAMD, variables that might affect outcomes include: Presence of PCV and duration of visual symptoms Specifically in RVO, a variable that might affect outcomes includes duration of macular oedema and subsequent photoreceptor damage	
Were any meaningful analyses conducted to test key assumptions on which primary results are based?	Sensitivity, subgroup and stratified analyses may be used to further test the robustness of primary research findings	☐Yes ☐No

DME = diabetic macular oedema; ETDRS = Early Treatment Diabetic Retinopathy Study; nAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography; PCV = polypoidal choroidal vasculopathy; PRN = pro re nata; RVO = retinal vein occlusion; T&E = treat-and-extend.

conclusions depends on the research question being assessed. The statistical power of the data set used should be described and associated power calculations reported.

The standard epidemiological approach is to restrict a study population to new initiators of treatment when comparing outcomes between treatment groups. However, since patients with retinal disease commonly switch treatments (e.g. from ranibizumab to aflibercept, or vice versa) or treatment regimens (e.g. from PRN to T&E) in real life, it is appropriate for a study to include patients who switch from one therapy to another, if appropriately accounted for in both the study design and analysis.

The rapid evolution of available therapies and dosing regimens for the treatment of retinal disease means the management landscape has changed markedly over the past decade, which could influence outcomes and subsequent conclusions if comparing treatment during different time periods. Ideally, data relating to all comparison groups should be captured concurrently in the same observation period, and historical comparisons should be avoided; if a study undertakes a historical comparison, it should be justified and resulting limitations acknowledged. Studies incorporating historical comparators, such as those comparing outcomes in the same patients who switch from one treatment or regimen to another or examining the impact of revised treatment

guidelines on patient outcomes, should note whether the patients or eyes followed in the first and subsequent treatment periods are the same and, if not, should state if baseline characteristics are similar between the populations being compared. In addition, the limitations of the historical approach should be appropriately considered and include reference to any change in the standard of care for patient monitoring or postinjection aftercare, which could affect treatment outcomes.

Controlling for bias
Confounding refers to an association between an exposure and an outcome being distorted by the presence of another variable (Talks et al. 2019). The confounding variable may exert a measurable effect, which could either be recorded as an association between an exposure and an outcome where none exists, or diminish a true association (Norgaard et al. 2017). All variables that could affect outcomes should be accurately recorded as part of reporting RWE and, if confounding variables are present, adjustments should be made using appropriate statistical analyses to minimize the risk of bias.

It is important that patients are followed appropriately to record the course of their disease, and how it changes over time and with treatment. How patients were followed over the course of study, and how patient loss to follow-up was addressed should be clearly stated. Drop-out rates should be taken into account when

interpreting study results and be discussed in the conclusions, if appropriate. Insight into reasons for patient drop-out is also valuable and should be collected and reported where possible.

Analyses to assess the potential for a biased evaluation of exposure or outcome should be performed. Sensitivity analyses and stratified or subgroup analyses can be performed to test key assumptions on which study results are based. In retinal disease, these may take into account, for example, differences in baseline patient characteristics such as visual acuity, patient age or prior treatment at study start. Subgroup analyses according to postbaseline factors, such as number of injections received, should be interpreted with caution since it is difficult to control for inherent bias in such factors.

Discussion and conclusions

Intravitreal anti-VEGFs are the standard of care for nAMD, DME, RVO (Schmidt-Erfurth et al. 2014; Schmidt-Erfurth et al. 2017; Schmidt-Erfurth et al. 2019). While data from RCTs provide valuable insights into disease management, the controlled treatment protocols and selective patient populations may not reflect real-world clinical practice (de Lusignan et al. 2015; Mehta et al. 2018; Mulder et al. 2018; Talks et al. 2019). RWE has already contributed to the optimization of anti-VEGF therapy for retinal disease in the

real world and has the potential to address other important clinical questions. Therefore, RWE is of increasing importance in the field of ophthalmology (Talks et al. 2019). Here, we report the development of a tool to support evaluation of the quality of RWE studies, to ensure only reliable conclusions from robust, good-quality evidence are translated to everyday clinical practice.

Rather than create a new tool, the published GRACE checklist (Dreyer et al. 2016) has been used as a framework, with permission of the GRACE authors, and with adaptations to incorporate details specific to the quality of RWE in retinal disease, based on opinion of this group of leading experts in the field of opthalmology. While this retinal disease-specific tool is closely based on the GRACE checklist, which has been extensively validated and is robustly sensitive and specific, ideally the adaptation should be further validated through a Delphi consensus or similar robust method. This would further increase its utility to identify high-quality observational comparative RWE in the field of retinal disease that is applicable for decision support.

In nAMD, DME and RVO, a global consensus on the requirements to classify RWE as high quality would facilitate balanced comparison of published results (Mehta et al. 2018). The ICHOM has previously defined a minimum set of standardized and patient-oriented outcome measures that should be collected and reported as RWD on macular degeneration (Rodrigues et al. 2016), which is valuable to guide outcome collection for those generating RWD in the field. However, the tool reported here goes further to outline guidance to aid the assessment of the standard for RWD collection and analysis in retinal disease, covering the full range of aspects that should be considered, including study design and controlling for bias. The straightforward tabular format allows simple assessment and comparison of the quality of published evidence for researchers and physicians alike. In particular, this tool provides practising physicians with a simple method to support assessment of the strength of evidence and certainty of conclusions drawn from RWE in retinal disease to ensure clinical decision-making is influenced by the highest quality evidence.

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