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International Classification System for Ocular Complications of Anti-VEGF Agents in Clinical Trials

Marko M. Popovic, MD, MPH,[1] Michael Balas, MD,[1] SriniVas R. Sadda, MD,[2] David Sarraf, MD,[3] Ryan Huang, MD(C),[1] Sophie J. Bakri, MD,[4] Audina Berrocal, MD,[5] Andrew Chang, MBBS, PhD,[6] Chui Ming Gemmy Cheung, MBBS,[7] Sunir Garg, MD,[8] Roxane J. Hillier, FRCOphth,[9] Frank G. Holz, MD,[10] Mark W. Johnson, MD,[11] Peter K. Kaiser, MD,[12] Peter J. Kertes, MD,[1] Timothy Y.Y. Lai, MD,[13] Jason Noble, MD,[1] Susanna S. Park, MD, PhD,[14] Yannis M. Paulus, MD,[11] Giuseppe Querques, MD, PhD,[15] Aleksandra Rachitskaya, MD,[12] Paisan Ruamviboonsuk, MD,[16] Shohista Saidkasimova, MD,[17] Maria Teresa Sandinha, MD,[18] David H. Steel, MD,[19] Hiroko Terasaki, MD, PhD,[20] Christina Y. Weng, MD, MBA,[21] Basil K. Williams, Jr., MD,[22] Lihteh Wu, MD,[23] Rajeev H. Muni, MD, MSc[1]

Purpose: Complications associated with intravitreal anti-VEGF therapies are reported inconsistently in the literature, thus limiting an accurate evaluation and comparison of safety between studies. This study aimed to develop a standardized classification system for anti-VEGF ocular complications using the Delphi consensus process.

Design: Systematic review and Delphi consensus process.

Participants: Twenty-five international retinal specialists participated in the Delphi consensus survey.

Methods: A systematic literature search was conducted to identify complications of intravitreal anti-VEGF agent administration based on randomized controlled trials (RCTs) of anti-VEGF therapy. A comprehensive list of complications was derived from these studies, and this list was subjected to iterative Delphi consensus surveys involving international retinal specialists who voted on inclusion, exclusion, rephrasing, and addition of complications. Furthermore, surveys determined specifiers for the selected complications. This iterative process helped to refine the final classification system.

Main Outcome Measures: The proportion of retinal specialists who choose to include or exclude complications associated with anti-VEGF administration.

Results: After screening 18 229 articles, 130 complications were categorized from 145 included RCTs. Participant consensus via the Delphi method resulted in the inclusion of 91 complications (70%) after 3 rounds. After incorporating further modifications made based on participant suggestions, such as rewording certain phrases and combining similar terms, 24 redundant complications were removed, leaving a total of 67 complications (52%) in the final list. A total of 14 complications (11%) met exclusion thresholds and were eliminated by participants across both rounds. All other remaining complications not meeting inclusion or exclusion thresholds also were excluded from the final classification system after the Delphi process terminated. In addition, 47 of 75 proposed complication specifiers (63%) were included based on participant agreement.

Conclusions: Using the Delphi consensus process, a comprehensive, standardized classification system consisting of 67 ocular complications and 47 unique specifiers was established for intravitreal anti-VEGF agents in clinical trials. The adoption of this system in future trials could improve consistency and quality of adverse event reporting, potentially facilitating more accurate risk-benefit analyses.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology 2024;131:1457-1467*

Supplemental material available at www.aaojournal.org.

Aberrant neovascularization and vascular permeability in retinal vascular and choroidal diseases are major causes of vision loss, and the increased expression of VEGF is an important pathologic mediator of these conditions.[1] The development of anti-VEGF agents has revolutionized the treatment of neovascular age-related macular degeneration, diabetic macular edema, macular edema secondary to retinal vein occlusion, and other retinal vascular diseases.[2–5] Moreover, the indications for anti-VEGF agents continue to expand, with promising results reported for other

https://doi.org/10.1016/j.ophtha.2024.06.011
ISSN 0161-6420/24

conditions, such as neovascular glaucoma and retinopathy of prematurity.[6–9] With the advent of newer anti-VEGF agents such as brolucizumab and faricimab, as well as the introduction of biosimilar agents and the novel ranibizumab port delivery system, the need for standardized safety reporting associated with intravitreal anti-VEGF therapy is paramount to assure optimal patient outcomes.[10–12] Despite their proven success, intravitreal injections of anti-VEGF therapies still pose a risk of rare and severe complications.[5]

To compare different intravitreal anti-VEGF agents properly based on their relative safety profiles, they must be assessed in a standardized and systematic manner. Although measuring intervention effectiveness is fairly consistent across clinical trials, with clear criteria used for reporting best-corrected visual acuity and retinal thickness, the reporting of complications often is less robust and lacks consistency, especially in ophthalmic randomized controlled trials (RCTs).[13–16] It is imperative to establish a standardized adverse event reporting system to compare the safety profiles critically of both novel and traditional anti-VEGF agents.

The need for standardized adverse event reporting is underscored by experiences with agents such as abicipar pegol, for which positive phase III data were overshadowed by events of intraocular inflammation and retinal vasculitis. In the case of brolucizumab, clinical trials reported events of intraocular inflammation using the Medical Dictionary for Regulatory Activities (MedDRA) terms. Given the multiple overlapping and redundant terms without adequate structure in the MedDRA database, initially it was difficult to determine whether any intraocular inflammation events had associated retinal vasculitis.[17] Indeed, it was only learned that severe retinal vascular events had occurred in the trials on an independent postmarketing reanalysis of clinical trial data.[17–23] These complications, most importantly, have caused permanent loss of vision in some patients but have also led to a decline of confidence in the product and substantial financial losses to the associated company. Discrepancies in reported complications of clinical trials, in which broad terms like *uveitis* could signify anything from rare anterior chamber cells to extensive sight-threatening retinal vasculitis, likely contributed to the delayed detection and underestimation of these issues in clinical trials. This is exemplified in the HAWK and HARRIER trials, where it was noted that more generalized terms such as *intraocular inflammation* were used for certain cases of retinal vasculitis, complicating the discovery of retinal vasculitis cases.[17] Given that clinical trials conducted in the United States use MedDRA terms for adverse event reporting, the multiple overlapping or redundant terms within the MedDRA database hindered the ability to identify and report retinal vasculitis events uniformly across a broad spectrum of clinical trials, thereby impacting the overall recognition and management of this adverse effect.[18–21]

These factual examples highlight the major pitfalls of not having a uniform and detailed reporting system for complications associated with intravitreal anti-VEGF drugs in clinical trials. A significant gap exists in adverse event reporting in the literature, hindering clinicians' abilities to compare the safety profiles of different agents across studies accurately. Furthermore, it limits the ability of systematic reviews and meta-analyses to compare the safety of different agents and to provide clear evidence-based recommendations.[24]

To address this paucity in the literature, we conducted a Delphi consensus study involving a representative group of global retinal specialists. The Delphi method is an iterative process used to reach consensus within a group of experts.[25,26] The aim of our study was to establish a standardized, universally applicable classification system for the reporting of ocular complications associated with intravitreal anti-VEGF agents in clinical trials. We anticipate that the results of this study will guide future adverse event reporting in clinical trials, improve the comparability of safety data reporting across trials, and ultimately, enable more informed decision-making by clinicians and patients alike.

Methods

Survey Creation

In this cross-sectional, survey-based study, we first performed a systematic literature search of RCTs investigating intravitreal anti-VEGF agents for any retinal disease with the aim of generating a comprehensive list of possible ocular complications. A literature search was performed on OVID MEDLINE (2005−November 2023), EMBASE (2005−November 2023), and Cochrane CENTRAL (2005−November 2023) using keywords and subject headings to identify relevant published articles (Table S1, available at www.aaojournal.org). Studies were included if they were RCTs reporting ocular adverse events of common anti-VEGF agents. An RCT was defined as a study explicitly described by the authors as "randomized," involving the randomized allocation of participants either to an intervention group or a control group. We manually screened and confirmed the randomized nature of each study, and although our primary focus was on phase III trials, we did not exclusively limit our search to phase III trials. Non-English or nonoriginal articles, abstracts, case reports, correspondence, letters, editorials, and reviews were excluded. Two reviewers (M.B., R.S.H.) independently screened all studies according to the selection criteria in a 2-phase process: (1) title and abstract screening, followed by (2) full-text screening of the remaining eligible articles. An independent third reviewer (M.M.P) was available to offer recommendations in the event that consensus was not reached.

A list of ocular complications was obtained by identifying all ocular complications in eligible studies from the literature search. The steering committee of the study (S.R.S., D.S., and R.H.M.) provided amendments to this list via additions, deletions, and rephrasing of the extracted complications. These complications then were organized by anatomic region, operationalized into a pilot list, and formatted into a survey. For each proposed complication in the list, a binary-choice question queried whether the complication should be included, with possible options of yes or no. If participants opted to exclude a complication, they were required to provide justification. At the end of every section of the survey, participants also had the opportunity to provide additional complications that were not represented and to share their comments or concerns on any proposed complications. Google Forms was used to build and distribute the survey to retinal specialists.

Delphi Consensus Methodology

The Delphi method is a process used to achieve consensus by surveying a panel of experts for several rounds of iterative scoring until the classification system is developed.[27] Based on Delphi

methodology, responses were aggregated and shared with participants after each round, such that they could choose to adjust their answer based on the results observed for the question across all participants in the previous survey round. After each round, the range of responses typically decrease, until the group converges toward a consensus response, at which point the process stops. The Delphi approach is a well-established method that has demonstrated robustness and reproducibility in several studies.[27–29]

We invited an internationally representative group of retinal specialists to take part in our Delphi consensus survey. Retinal specialists were recruited via direct correspondence with representatives of internationally focused retinal societies, namely, the American Society of Retina Specialists, the Asia Pacific Vitreo-retina Society, the British and Eire Association of Vitreoretinal Surgeons, the Canadian Retina Society, the European Society of Retina Specialists, the Macula Society, and the Retina Society. In correspondence with board members from each society, they were asked to participate directly or to nominate several active members of their society who were regarded as experts or thought leaders in the field, particularly those with experience in serving on data and safety monitoring boards for clinical trials. As soon as these potential participants were identified, correspondence with each identified participant was performed via e-mail. This study did not involve human subjects so institutional board review and informed consent were not required. This study adhered to the Declaration of Helsinki.

Consensus Definition

Consensus was defined as a ≥70% agreement for ≥90% of items, both of which are commonly used thresholds for similar Delphi studies in the literature.[30–33] For each item, the item was either rephrased or excluded if <30% of participants chose to include it.[30] Otherwise, the complication remained in subsequent rounds to be included or excluded until the cycle was complete. After each survey round, the data were reaggregated, and the survey cycle was repeated until consensus on >90% of complications was achieved.[26,27]

Complication Specifiers

After finalizing the list of complications via the Delphi process, we developed a second survey to determine which complication specifiers should be included in an adverse event classification system. A complication specifier was defined as a descriptor that may modify the meaning, severity, or implication of the complication. For example, uveitis is a complication, whereas bilateral uveitis or acute uveitis are different specifiers of the same complication term. Complication specifiers initially were derived based on the recommendations of the steering committee (S.R.S., D.S., and R.H.M.). For each proposed complication specifier, participants were asked whether it should be included in the complication system. In an optional free-text input, participants were asked whether additional complication specifiers should be included. Because specifiers are an optional addition to a listed complication, a more conservative threshold was used to determine consensus. For this survey, we used an inclusion threshold of ≥70% agreement for inclusion and distributed the survey once, with exclusion of specifiers that had <70% agreement.

Results

Literature Search

The literature search identified 18 229 articles (Fig 1). After excluding duplicates and screening titles and abstracts, 187 RCTs were selected. Full-text screening excluded another 42 articles, leaving a total of 145 studies that identified 244 unique ocular complications of intravitreal anti-VEGF agent administration.

From this list of 244 ocular complications, redundancies were removed, and similar complications were grouped together and organized by anatomic region and disease type to form an initial pilot list of 127 complications (Table S2, available at www.aaojournal.org). This list then was deployed in the first survey. Complications were stratified by anatomic site into the following groups for the first survey: eyelid, lacrimal system, and orbit (n = 10 complications); conjunctiva (n = 9); cornea (n = 10); sclera (n = 2); anterior chamber (n = 4); uveal tract (n = 13); lens (n = 3); intraocular pressure and glaucoma (n = 5); vitreous (n = 7); retina (n = 26); macula (n = 10); choroid (n = 4); procedural (n = 6); and others (n = 18).

Participants

Our Delphi consensus survey was disseminated to 34 retinal specialists globally. The overall response rate was 74%, yielding a total of 25 expert retinal specialists contributing to this international classification system. The participant pool was distributed broadly, with 2 participants (8%) from Canada, 4 participants (16%) from the United Kingdom, 11 participants (44%) from the United States, and 1 participant (4%) from each of the following countries: Australia, Costa Rica, Germany, Hong Kong, Italy, Japan, Singapore, and Thailand. The distribution of retinal specialists was as follows: 5 specialists (20%) were nominated by Asia Pacific Vitreo-retina Society, 6 specialists (24%) were nominated by American Society of Retina Specialists, 4 specialists (16%) were nominated by British and Eire Association of Vitreoretinal Surgeons, 2 specialists (8%) were nominated by Canadian Retina Society, 2 specialists (8%) were nominated by European Society of Retina Specialists, 3 specialists (12%) were nominated by the Macula Society, and 3 specialists (12%) were nominated by the Retina Society.

Anti-VEGF Complications

Initially, a total of 127 complications were included in the first survey list. After the first round of the Delphi survey (n = 25 participants), participants achieved consensus on 68.5% of the complications. Overall, participants voted to include 79 complications (62.2%) and to exclude 8 complications (6.3%), whereas the remaining 40 complications (31.5%) did not reach agreement (Table S3, available at www.aaojournal.org). Participants suggested rewording and combining certain terms, which were revised and incorporated into the list for evaluation in the second round. For example, some suggested combining "eye irritation" with "foreign body sensation" or "eye pain" with "procedural pain" to minimize redundancy. After further refining these terms and including 4 new terms recommended by the participants, a total of 26 complications remained for adjudication in the second round of the Delphi process.

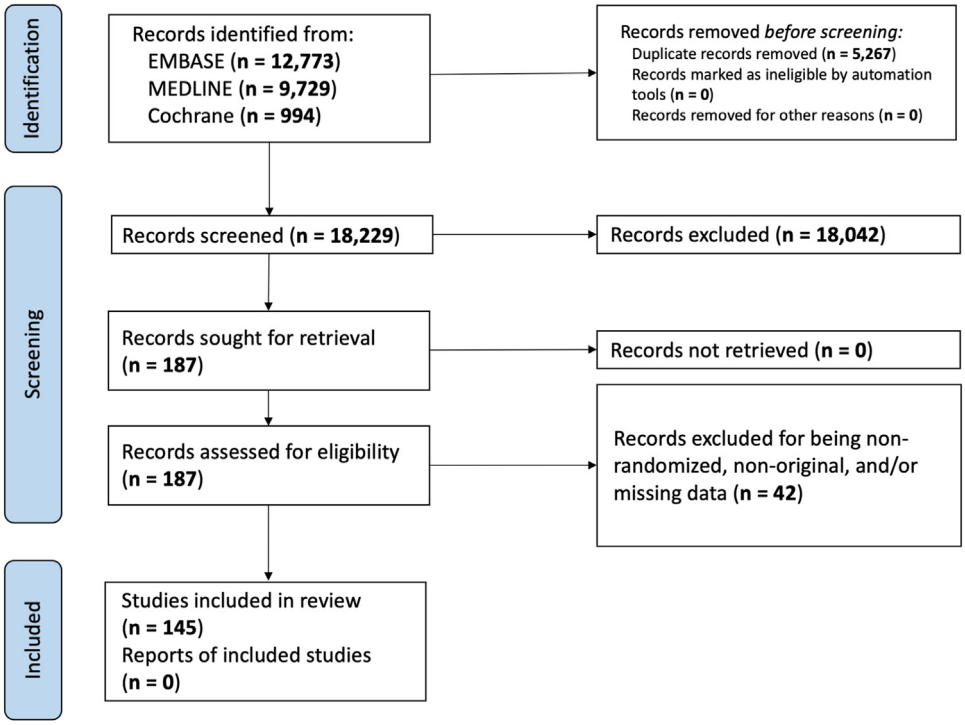


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart.

In the second round, participants (n = 24) opted to include 11 of the remaining 26 complications (42.3%; Table S4, available at www.aaojournal.org) and to exclude 3 complications (11.5%). The 12 complications that did not reach consensus included the following: conjunctival retraction (58% of participants elected to include), iris atrophy (58% of participants elected to include), retinal degeneration (46% of participants elected to include), retinal depigmentation (33% of participants elected to include), retinal pigment epitheliopathy (46% of participants elected to include), macular edema (50% of participants elected to include), macular scar (50% of participants elected to include), cystoid macular edema (50% of participants elected to include), choroidal neovascularization (42% of participants elected to include), asthenopia (46% of participants elected to include), refraction disorder (38% of participants elected to include), and chromatopsia (63% of participants elected to include). Given that consensus was not achieved for these items after 2 rounds, these complications were not included in the classification system.

In the third Delphi round (n = 20 participants), the literature search was updated to capture recent literature up until November 2023, and additional unique terms were identified (Table S5, available at www.aaojournal.org). These were operationalized into a list that was reviewed by the Delphi participants to determine inclusion. Of these 3 terms, xerophthalmia (20%) and orbital fracture (5%) were excluded by participants, whereas dry eye syndrome (65%) did not meet consensus. Panuveitis (95%) also was proposed to Delphi participants and achieved consensus for inclusion. After this round, consensus was reached for >90% of all items, thus terminating the Delphi process.

In summary, the Delphi consensus process occurred over 3 rounds, yielding a total of 91 complications reaching consensus for inclusion, 14 complications reaching consensus for exclusion, and 13 complications (9.6%) that failed to achieve consensus and subsequently were excluded. Throughout the iterative process of our Delphi study, adjustments were made to refine this list, and certain complications were either reclassified as specifier terms or were merged to reduce redundancies, resulting in a final standardized list comprising a total of 67 distinct complications related to intravitreal anti-VEGF agents (Table 6).

Complication Specifiers

After the establishment of the 67-item anti-VEGF complication list, 2 subsequent surveys were distributed to determine the necessary complication specifiers to include in our proposed classification system. Twenty-one of 25 participants (84%) from the first Delphi process completed the first complication specifier survey. A total of 64 specifiers were reviewed by the participants in a survey. Participants agreed to include 43 of all 64 specifiers (67.2%). The remaining 21 complication specifiers (32.8%) that did not reach the 70% inclusion threshold were excluded. In December 2023, after external peer review, an additional 11 specifiers were disseminated to Delphi participants (n = 20). Of these, 8 specifiers (73%) met inclusion thresholds, 4 of which replaced old specifiers from the original survey. Consensus was not achieved on 3 specifiers (27%), resulting in a total of 47 complication specifiers. The final list of complication specifiers along with their agreement scores are shown in Table 7.

Table 6. Consensus-Driven Complications of Intravitreal Anti-VEGF Agents

Category	Complication	Agreement (%)
Eyelid, lacrimal system, and orbit	Discharge	84
	Ptosis	88
	Periorbital hematoma	72
	Skin abrasion	76
Conjunctiva	Subconjunctival hemorrhage	92
	Conjunctivitis	92
	Conjunctival erosion	80
	Conjunctival granuloma	84
	Conjunctival edema	88
Cornea	Corneal abrasion	92
	Punctate keratitis	96
	Corneal edema	84
	Corneal ulcer	88
Sclera	Episcleritis	88
	Scleritis	84
Anterior chamber	Hypopyon	100
	Hyphema	100
	Pupillary disorder	80
	Toxic anterior segment syndrome	92
Uveitis	Anterior uveitis	100
	Intermediate uveitis	100
	Posterior uveitis	100
	Panuveitis	95
Lens	Cataract or lens penetration	100
	Posterior capsule rupture	96
Intraocular pressure and glaucoma	**Increased intraocular pressure**	100
	Glaucoma progression	100
	Angle closure glaucoma	92
	Hypotony	88
	Conjunctival filtering bleb	75
Vitreous	Vitreous hemorrhage	100
	Posterior vitreous detachment	88
	Vitreous opacities	88
Retina	Retinal hemorrhage	92
	Retinal tear	100
	Retinal pigment epithelial tear	96
	Retinal detachment	100
	Retinal pigment epithelial detachment	72
	Retinal artery occlusion	100
	Retinal vein occlusion	96
	Retinal edema	84
	Epiretinal membrane	80
	Cotton wool spots	72
	Retinal ischemia	84
Macula	Macular hole	88
	Paracentral acute middle maculopathy	80
Choroid	Choroidal hemorrhage	84
	Chorioretinal atrophy	76
	Choroidal effusion	88
Other	Reduced visual acuity	96
	Foreign body sensation	96
	Photopsia	92
	Photophobia	88
	Pruritus	92
	Diplopia	72
	Infectious endophthalmitis	100
	Sterile endophthalmitis	100
	Amaurosis fugax	80
	Blindness	88
	Visual field defect	92
	Optic atrophy	88
	Ischemic optic neuropathy	88

(*Continued*)

Table 6. (Continued.)

Category	Complication	Agreement (%)
Procedural	Drug hypersensitivity	96
	Procedural pain	95
	Iodine allergy	80
	Medication error	96
	Wound leak	92
Investigator-reported*	Free-text space to record complications not encompassed in this list	

Boldface terms currently are not included in the Medical Dictionary for Regulatory Activities system.
*For clinical trial investigators reporting complications that are not included in this classification system.

Overall, this Delphi consensus study culminated in a standardized classification system consisting of 67 complications with 47 unique complication specifiers. Each complication has at least 1 corresponding specifier, with 2.3 specifiers per complication on average. We also provided a system to apply our classification system intuitively using either Microsoft Excel (Appendix 1, available at www.aaojournal.org) or Google Sheets (available at: https://docs.google.com/spreadsheets/d/1rMQZBQtttZwTotewgPNc4wb5W6ydgPv76rhteiCzGnI/edit?usp=sharing).

Discussion

Intravitreal anti-VEGF agents have revolutionized the management of various retinal conditions.[1,2] However, their administration is not without risk of complications, some of which can be severe and vision threatening. This study establishes a comprehensive, methodologically rigorous classification system for the reporting of ocular complications associated with intravitreal anti-VEGF agents based on international consensus. Our Delphi approach underscores the commitment of a diverse global team of retinal specialists to refine and enhance the standardization of adverse events reporting in future clinical trials.

Despite the widespread use of intravitreal anti-VEGF therapies, the clinical literature shows a significant lack of standardized reporting regarding the associated complications. This discrepancy is notably problematic given the recent emergence of safety concerns with newly developed intravitreal anti-VEGF agents such as abicipar pegol[20] or brolucizumab.[17–21] These instances underscore how, despite rigorous testing in phase II and III clinical trials, concerning adverse events in some cases were evident only after approval. The variation in terminologies and definitions used to report these complications leads to ambiguity and inconsistency, hindering the accurate assessment of safety profiles and comparison between studies.[13,14]

The integration of this system into future clinical trials will involve collaborative efforts with regulatory bodies, clinical trial networks, and professional societies. Educational initiatives will be key to familiarizing the ophthalmology community with the benefits and application of this system, ensuring its widespread use. We also advocate for the incorporation of this system into the protocol design of future clinical trials. To support the adoption of this tool, we are providing an accessible copy via Microsoft Excel (Appendix 1) or Google Sheets (available at: https://docs.google.com/spreadsheets/d/1rMQZBQtttZwTotewgPNc4wb5W6ydgPv76rhteiCzGnI/edit?usp=sharing), designed for easy tracking and recording of adverse events. Continuous feedback and updates will ensure that the classification system remains relevant and robust, reflecting the evolving landscape of intravitreal anti-VEGF therapies and enhancing our understanding of their safety profiles.

Various well-known classification systems exist for medical and surgical complications, such as the Clavien–Dindo system for surgical complications, along with others like the Accordion and Memorial Sloan Kettering Cancer Center classifications for cancer surgery.[34–37] In clinical trials, the MedDRA system has been recognized as the gold standard for adverse event reporting; however, its application in the field of ophthalmology has revealed significant inconsistencies, particularly in the specificity and granularity of terms used to describe ocular adverse events.[38] Despite its widespread use, variations in terminology selection by local principal investigators and differential requirements by regulatory bodies across countries have led to discrepancies that obscure the true incidence of certain adverse events. Recent publications of grading systems developed using the Delphi method to classify the complications of glaucoma surgery and rhegmatogenous retinal detachment surgery signal a promising change.[26,39] These studies aimed to standardize harm reporting and to quantify the severity of surgical complications, thus highlighting the vital role of standardization for accurate complication reporting across diverse trials and ocular conditions. Our current study further extends this methodology, introducing a comprehensive classification system tailored for the reporting of complications associated with intravitreal anti-VEGF therapies in clinical trials. For instance, all complications related to uveitis have been harmonized with the Standardization of Uveitis Nomenclature criteria to ensure enhanced precision and consistency in medical reporting. It not only complements, but also enriches, the MedDRA framework by offering a comprehensive classification system of intravitreal anti-VEGF therapy complications, thereby facilitating a more detailed and harmonized reporting system across studies in this setting.

The use of the Delphi consensus process facilitated the integration of the experiences and perspectives of a wide

Table 7. Consensus-Driven Complication Specifiers of Intravitreal Anti-VEGF Agents

Complication(s)	Specifier	Agreement (%)
Corneal ulcer	Visually significant or insignificant	81
Anterior, intermediate, or posterior uveitis or panuveitis	**Unilateral** or **bilateral**	91
Anterior, intermediate, or posterior uveitis or panuveitis	Acute, **recurrent**, or **chronic** course	95
Anterior, intermediate, or posterior uveitis or panuveitis	Visually significant or insignificant	85
Posterior uveitis or panuveitis	**Specify the suspected etiology**	85
Posterior uveitis or panuveitis	Retinitis, choroiditis, retinochoroiditis, or chorioretinitis	90
Posterior uveitis or panuveitis	With or without retinal vasculitis	90
Posterior uveitis or panuveitis	With or without retinal vascular occlusion	80
Posterior uveitis or panuveitis	**Diagnosed on clinical examination, IVFA, or both**	80
Cataract or lens penetration	Visually significant or insignificant	86
Posterior capsule rupture	Visually significant or insignificant	76
Posterior capsule rupture	With or without **retained lens products**	71
Posterior capsule rupture	**With or without need for surgical intervention**	81
Glaucoma or elevated IOP	**With or without need for surgical intervention**	95
Hypotony	**With or without need for surgical intervention**	86
Increased intraocular pressure	**Specify the maximum IOP**	86
Vitreous hemorrhage	Visually significant or insignificant	95
Vitreous hemorrhage	**With or without need for surgical intervention**	91
Vitreous opacities	Visually significant or insignificant	86
Retinal hemorrhage	Intraretinal or subretinal	91
Retinal hemorrhage	Macular or **extramacular**	91
Retinal hemorrhage	Visually significant or insignificant	81
Retinal detachment	Exudative, rhegmatogenous, or tractional	100
Retinal detachment	Macula-on or macula-off	86
Retinal pigment epithelial tear	Visually significant or insignificant	91
Retinal artery occlusion	**Macular** or **extramacular**	76
Retinal artery occlusion	With or without retinal artery embolism	85
Retinal vein occlusion	**Macular** or **extramacular**	81
Retinal edema	Visually significant or insignificant	76
Epiretinal membrane	Visually significant or insignificant	81
Chorioretinal atrophy	**Macular** or **extramacular**	86
Choroidal hemorrhage	Visually significant or insignificant	71
Choroidal hemorrhage	**With or without need for surgical intervention**	81
Choroidal effusion	Visually significant or insignificant	71
Infectious endophthalmitis	**With or without intravitreal therapy**	71
Infectious endophthalmitis	**With or without pars plana vitrectomy**	76
Infectious endophthalmitis	With or without BCVA 20/200 or better	81
Sterile endophthalmitis	**With or without intravitreal therapy**	90
Sterile endophthalmitis	**With or without pars plana vitrectomy**	71
Visual field defect	**Specify the suspected diagnosis**	86
Blindness	**Specify the suspected diagnosis**	91
Reduced visual acuity	**Specify the suspected diagnosis**	95
Reduced visual acuity	**Mild (<1 line loss), moderate (1−3 lines loss), or severe (>3 lines loss)**	95
Reduced visual acuity	**Acquired or present before study**	74
All "other" terms	Visually significant or insignificant	81
All "other" terms	**Specify the suspected diagnosis**	86
All terms	**Likely or unlikely to be related to the injection**	100

BCVA = best-corrected visual acuity; IOP = intraocular pressure; IVFA = intravenous fluorescein angiography.
Boldface terms are not currently included in the Medical Dictionary for Regulatory Activities system.

geographic range of retinal specialists. The final list of complications and complication specifiers was developed in accordance with the iterative nature of the Delphi methodology, which provides an environment for refining the precision and applicability of the items in question.[25,27] In light of the broad international consensus achieved on specific adverse events, a compelling argument emerges for the potential inclusion of these terms and their specifiers in an updated version of the MedDRA system. Our comparison with the most recent version of MedDRA (version 27.0, updated March 2024) revealed that, aside from *increased intraocular pressure*, our classification system's terms largely are represented within MedDRA's framework. However, the introduction of several unique specifiers pertaining to aspects such as unilateral versus bilateral disease manifestation, recurrence or chronicity of uveitis, or the anatomic localization of generally described ocular events underscores the need for enhancements to MedDRA. This would ensure that the standardized terminology reflects the collective expertise and contemporary practices of retinal specialists worldwide. Beyond these gaps, the degree of complexity and redundancy within the MedDRA system can lead to inconsistent reporting of adverse events specific to anti-

VEGF therapy, because investigators may select different terms for the same complication based on their initial encounter in the MedDRA hierarchy. This underlines the importance of our classification system in providing clear guidance for the consistent application of terms, thereby enhancing the accuracy and comparability of safety data across clinical trials and ensuring a more precise communication of risk to patients and clinicians.

Although patient-reported outcome measures and consumer involvement may provide valuable insights into patient experiences of treatment outcomes, they were not part of the standard methodology for similar Delphi studies in ophthalmology.[26,39–41] Consequently, they were not incorporated because of the nature of the ocular complications being classified, which require a specialized understanding of the underlying clinical assessment and multimodal imaging interpretation that can be offered only by retinal specialists.

Other intravitreal agents, with mechanisms other than anti-VEGF inhibition, have been associated with sight-threatening complications. For example, rare episodes of intraocular inflammation and retinal vasculitis can be associated with intravitreal pegcetacoplan, a complement inhibitor shown to slow the rate of geographic atrophy progression in eyes with nonexudative age-related macular degeneration.[42] These associations were reported after Food and Drug Administration approval. Our international classification system was developed for clinical trials of intravitreal anti-VEGF agents and may not be applied optimally to other medications that may have a slightly different profile of complications. For example, intravitreal complement inhibitors can be complicated by exudative age-related macular degeneration. Similar classification systems should be designed for other intravitreal agents.

It is important to acknowledge several limitations of our study. First, although our survey achieved a high response rate, the participant pool was still relatively small and skewed toward regions in the developed world, potentially limiting the generalizability of our results. It is also possible that not all potential complications were included in the initial list generated from our literature review, particularly those that are extremely rare or have been reported only in languages other than English. To address this, our final classification system includes an additional investigator-reported category, thus providing an avenue to record complications that are not included in our list. Notably, the spectrum of potential complications arising from novel alternative methods of anti-VEGF delivery (e.g., sustained-release port delivery platforms) were not specifically considered in this study and may differ compared with traditional intravitreal injection delivery. Furthermore, although the Delphi consensus method is an effective tool for reaching expert consensus, it inherently relies on the opinions of participants, which can introduce subjectivity into the process.[43] Also, the possibility remains that complications that did not achieve consensus could be clinically important in certain situations, and thus, the exclusion of these may limit the comprehensive aim of our classification system. Finally, the usefulness and effectiveness of our classification system will depend on its adoption in future clinical trials. This requires that researchers and clinicians recognize its value and apply it consistently when reporting their findings. As such, ongoing efforts will be necessary to promote its use and periodically to evaluate its impact on the quality of reporting in clinical trials.

We present a comprehensive and standardized classification system for the reporting of ocular complications associated with intravitreal anti-VEGF agents in clinical trials. We anticipate that this classification system will be instrumental in improving the consistency and quality of adverse events reporting in future trials investigating intravitreal anti-VEGF agents, thereby allowing for more accurate and reliable risk–benefit analyses. We encourage researchers and clinical trialists to adopt this classification system in their studies and to invite others to provide feedback on its implementation and role in research and practice.

Acknowledgments

The authors thank the board members of each of the following retina societies for encouraging and nominating their members to participate in our Delphi survey: the American Society of Retina Specialists, the Asia Pacific Vitreo-retina Society, the British and Eire Association of Vitreoretinal Surgeons, the Canadian Retinal Society, the European Society of Retina Specialists, the Macula Society, and the Retina Society.

Footnotes and Disclosures

Originally received: September 16, 2023.
Final revision: April 10, 2024.
Accepted: June 6, 2024.
Available online: June 13, 2024. Manuscript no. OPHTHA-D-23-01718.

[1] Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada.

[2] Doheny Eye Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California.

[3] Stein Eye Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California.

[4] Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota.

[5] Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Leonard M. Miller School of Medicine, Miami, Florida.

[6] Sydney Retina Clinic, Sydney Eye Hospital, University of New South Wales, Sydney, Australia.

[7] Department of Ophthalmology, National University of Singapore, Singapore, Republic of Singapore.

[8] Mid Atlantic Retina, The Retina Service of Wills Eye Hospital, Wills Eye Hospital, Philadelphia, Pennsylvania.

[9] Newcastle Eye Centre, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom.

[10] Department of Ophthalmology, University of Bonn, Bonn, Germany.

[11] Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan.

[12] Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

[13] Department of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong, Kowloon, Hong Kong, China.

[14] Department of Ophthalmology & Vision Science, University of California Davis Eye Center, Sacramento, California.

[15] Department of Ophthalmology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy.

[16] Department of Ophthalmology, College of Medicine, Rangsit University, Rajavithi Hospital, Bangkok, Thailand.

[17] Tennent Institute of Ophthalmology, Glasgow, Scotland, United Kingdom.

[18] Department of Eye and Visual Science, University of Liverpool, Merseyside, United Kingdom.

[19] Sunderland Eye Infirmary, Sunderland, United Kingdom.

[20] Nagoya University Hospital, Nagoya, Japan.

[21] Cullen Eye Institute, Baylor College of Medicine, Houston, Texas.

[22] Cincinnati Eye Institute, Department of Ophthalmology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

[23] Department of Ophthalmology, Asociados de Mácula Vitreo y Retina de Costa Rica, San José, Costa Rica.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

M.M.P.: Financial support – PSI Foundation, Fighting Blindness Canada

M.B.: Financial support – Glaucoma Research Society of Canada; Consultant – Ontario Medical Association

S.R.S.: Consultant – AbbVie/Allergan, Astellas/IvericBio, Apellis, Novartis, Oxurion, Roche/Genentech, Centervue, Heidelberg Engineering, Optos, Notal, Biogen, Samsung Bioepis, Boehringer Ingelheim, Nanoscope, RayTx, 4dMT, Alexion; Financial support – Carl Zeiss Meditec; Nonfinancial support – Optos, Carl Zeiss Meditec, Nidek, Centervue, Heidelberg Engineering

D.S.: Consultant – Amgen, Boehringer, Genentech, Visionix/Optovue, Bayer, Novartis; Financial support – Amgen, Boehringer Ingelheim, Genentech, Regeneron, Visionix/Optovue

S.J.B.: Consultant – AbbVie, Adverum, Allergan, Amgen, Annexon, Apellis, Aviceda, Cholgene, Eyepoint, Ilumen, Iveric bio, Kala, Genentech, Neurotech, Novartis, Ocular Therapeutix, Outlook, Pixium, Regenxbio, Regeneron, Rejuvitas, Revana, Roche, VoxelCloud, Zeiss

A.C.: Advisory board – Bayer, Roche (Asia-Pacific region), Novartis, Alcon, Apellis, Zeiss

C.M.G.C.: Financial support – Bayer, Boehringer Ingelheim, Novartis, Topcon; Consultant – Novartis, Roche; Lecturer – Allergan, Bayer, Novartis, Roche, Topcon, Zeiss

S.G.: Consultant – Allergan, Apellis, Bausch and Lomb, Boehringer Ingelheim, Johnson and Johnson, Kanaph; Financial support – American Academy of Ophthalmology, Apellis, Boehringer Ingelheim, NGM Bio, Regeneron

R.J.H.: Financial support, Lecturer, and Advisory Board – Roche

F.G.H.: Financial support – Heidelberg Engineering, Optos, Zeiss, Novartis, Bayer Healthcare, Genentech, Acucela, Boehringer Ingelheim, Alcon, Allergan

M.W.J.: Data and Safety Monitoring Board – Syneos Health, Amgen, Pfizer, Aura Biosciences

P.K.K.: Consultant – AAVAntgarde Bio, Allergan, Bayer, Bausch and Lomb, Biogen Idec, Boehringer Ingelheim, Carl Zeiss Meditec, Coherus, Genentech/Roche, Innovent, Kanghong, Novartis, Ocular Therapeutix, Oculis, Regeneron, RegenxBio, Samsung Bioepis, 4D Molecular Therapeutics

P.J.K.: Lecturer – Novartis, Bayer, Roche, Boehringer Ingelheim, RegenxBio, Apellis; Advisory board – Novartis, Bayer, Roche, Novelty Nobility, Viatris, Biogen; Financial support – Roche, Novartis, Bayer, RegenxBio, Janssen, Ora Gene

T.Y.Y.L.: Financial support – Bayer, Chengdu Kanghong Biotech, Novartis; Consultant – Bayer, Boehringer Ingelheim, Iveric Bio, Novartis, Oculis, Roche; Lecturer – Alcon, Bayer, Chengdu Kanghong Biotech, Novartis, Roche

J.N.: Advisory Board – Novartis, Bayer; Lecturer – Novartis

S.S.P.: Financial support – Ophthea Ltd., Novartis

Y.M.P.: Consultant – Hedgefog Research, Inc., Iridex; Patents – University of Michigan, PhotoSonoX LLC; Equity owner – PhotoSonoX LLC

G.Q.: Consultant – Alimera, Allergan, Bayer, Lumithera, KBH, Novartis, Roche, Sandoz, Sifi, Zeiss, Topcon, Thea, Heidelberg, Fidia-Sooft, Bausch & Lomb

A.R.: Lecturer – Alcon, Novartis, Zeiss, Allergan

P.R.: Financial support – Roche; Consultant, Lecturer – Roche, Bayer, Novartis, Iveric Bio

David H. Steel: Financial support – Alcon, Bayer, DORC; Consultant – Roche, Gyroscope

H.T.: Lecturer – Rohto Pharmaceutical, Takeda Pharmaceutical, Mitsubishi Tanabe, AbbVie, Daiichi Sankyo, Chuo Sangio, Sanofi, Nihon Tenganyaku, Alcon Pharma, Bayer, Graybug Vision; Financial support – Nidek, Otsuka, Pfizer, Santen, Alcon, Novartis, Senju, Kowa, Wakamoto, HOYA, Allergan Japan, Carl Zeiss Meditec; Nonfinancial support – Carl Zeiss Meditec

C.Y.W.: Consultant – Allergan/AbbVie, Novartis, Alcon, Alimera Sciences, Genentech, DORC, Regeneron, Regenxbio, Apellis, IvericBio, EyePoint

B.K.W.: Consultant – Alcon, Allergan/AbbVie, Alimera Sciences, Astellas/IvericBio, Castle Biosciences, Eyepoint Pharmaceuticals, Genentech/Roche, Regeneron; Equity owner – Lumata Health

L.W.: Consultant – Bayer, Quantel Medical; Lecturer – Bayer, Roche, Quantel Medical

R.H.M.: Advisory board and Consultant – AbbVie, Alcon, Bausch + Lomb, Bayer, Novartis, Roche; Financial support – AbbVie, Bayer, Novartis, Roche

Supported by Silber TARGET Fund.

Dr. SriniVas R. Sadda, MD, an editorial board member of this journal, was recused from the peer-review process of this article and had no access to information regarding its peer-review.

HUMAN SUBJECTS: No human subjects were included in this study. Institutional Review Board approval and the requirement for informed consent were waived because of the retrospective nature of the study. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Popovic, Balas, Sadda, Sarraf, Muni

Analysis and interpretation: Popovic, Balas, Sadda, Sarraf, Muni

Data collection: Popovic, Balas, Sadda, Sarraf, Huang, Bakri, Berrocal, Chang, Cheung, Garg, Hillier, Holz, Johnson, Kaiser, Kertes, Lai, Noble, Park, Paulus, Querques, Rachitskaya, Ruamviboonsuk, Saidkasimova, Sandinha, Steel, Terasaki, Weng, Williams, Wu, Muni

Obtained funding: Silber TARGET Fund

Overall responsibility: Popovic, Balas, Sadda, Sarraf, Huang, Bakri, Berrocal, Chang, Cheung, Garg, Hillier, Holz, Johnson, Kaiser, Kertes, Lai, Noble, Park, Paulus, Querques, Rachitskaya, Ruamviboonsuk, Saidkasimova, Sandinha, Steel, Terasaki, Weng, Williams, Wu, Muni

Abbreviations and Acronyms:
MedDRA = Medical Dictionary for Regulatory Activities; **RCT** = randomized controlled trial.

Keywords:
Adverse event reporting, Delphi consensus process, Intravitreal anti-VEGF, Ocular complications, Randomized controlled trials.

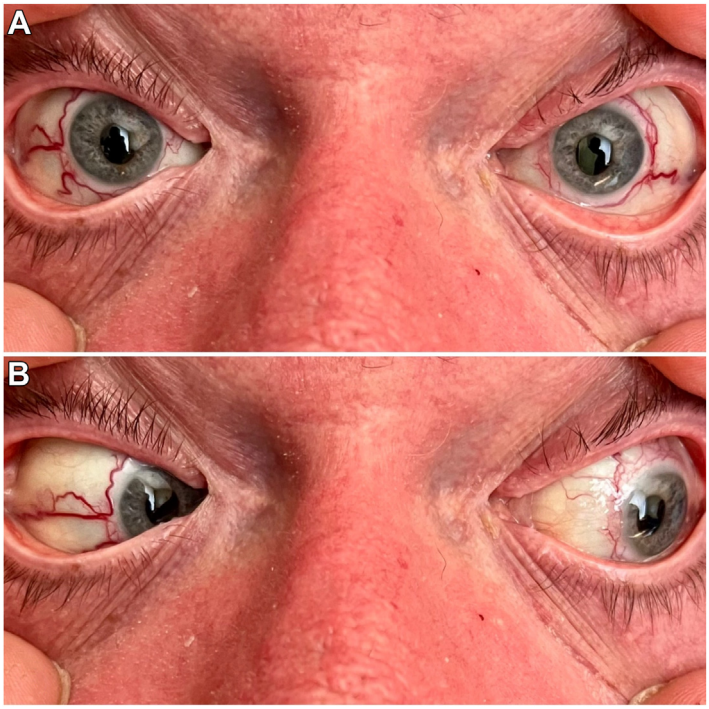
Correspondence:
Rajeev H. Muni, MD, MSc, Department of Ophthalmology, St. Michael's Hospital/Unity Health Toronto, 30 Bond Street, Donnelly Wing, 8th Floor, Toronto, Ontario, Canada M5B 1W8. E-mail: rajeev.muni@utoronto.ca.

References

1. Tah V, Orlans HO, Hyer J, et al. Anti-VEGF therapy and the retina: an update. *J Ophthalmol*. 2015:627674.
2. Wong TY, Liew G, Mitchell P. Clinical update: new treatments for age-related macular degeneration. *Lancet*. 2007;370(9583):204−206.
3. Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:915−930.
4. Wong TY, Scott IU. Retinal-vein occlusion. *N Engl J Med*. 2010;363(22):2135−2144.
5. Ghasemi Falavarjani K, Nguyen Q. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye*. 2013;27(7):787−794.
6. Falavarjani KG, Modarres M, Nazari H. Therapeutic effect of bevacizumab injected into the silicone oil in eyes with neovascular glaucoma after vitrectomy for advanced diabetic retinopathy. *Eye*. 2010;24(4):717−719.
7. Nazari H, Modarres M, Parvaresh MM, Ghasemi Falavarjani K. Intravitreal bevacizumab in combination with laser therapy for the treatment of severe retinopathy of prematurity (ROP) associated with vitreous or retinal hemorrhage. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:1713−1718.
8. Detorakis ET, Agorogiannis G, Drakonaki EE, et al. Successful management of choroidal metastasis with intravitreal ranibizumab injections. *Ophthalmic Surg Lasers Imaging Retina*. 2012;43(6):e47−e51.
9. Pożarowska D, Pożarowski P. The era of anti-vascular endothelial growth factor (VEGF) drugs in ophthalmology, VEGF and anti-VEGF therapy. *Cent Eur J Immunol*. 2016;41(3):311−316.
10. Kapur M, Nirula S, Naik MP. Future of anti-VEGF: biosimilars and biobetters. *Int J Retina Vitreous*. 2022;8(1):1−8.
11. Tadayoni R, Sararols L, Weissgerber G, et al. Brolucizumab: a newly developed anti-VEGF molecule for the treatment of neovascular age-related macular degeneration. *Ophthalmologica*. 2021;244(2):93−101.
12. Sharma A, Kumar N, Kuppermann BD, et al. Faricimab: expanding horizon beyond VEGF. *Eye*. 2020;34(5):802−804.
13. Penedones A, Mendes D, Alves C, Batel Marques F. Safety monitoring of ophthalmic biologics: a systematic review of pre-and postmarketing safety data. *J Ocul Pharmacol Ther*. 2014;30(9):729−751.
14. Van der Reis MI, La Heij EC, De Jong-Hesse Y, et al. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. *Retina*. 2011;31(8):1449−1469.
15. Ioannidis JP, Contopoulos-Ioannidis DG. Reporting of safety data from randomised trials. *Lancet*. 1998;352(9142):1752−1753.
16. Martin RC, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg*. 2002;235(6):803−813.
17. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion−related events with brolucizumab: post hoc review of HAWK and HARRIER. *Ophthalmology*. 2021;128(7):1050−1059.
18. Sharma A, Kumar N, Parachuri N, et al. Brolucizumab-related retinal vasculitis: emerging disconnect between clinical trials and real world. *Eye*. 2021;35(5):1292−1294.
19. Hussain RM, Weng CY, Wykoff CC, et al. Abicipar pegol for neovascular age-related macular degeneration. *Expert Opin Biol Ther*. 2020;20(9):999−1008.
20. Sharma A, Kumar N, Kuppermann BD, Bandello F. Abicipar pegol: the non-monoclonal antibody anti-VEGF. *Eye*. 2020;34(5):797−801.
21. Hutton D. ASRS reports six cases of occlusive retinal vasculitis linked to pegcetacoplan injection. *Ophthalmology Times*; 2023. Available from: https://www.ophthalmologytimes.com/view/asrs-reports-six-cases-of-occlusive-retinal-vasculitis-linked-to-pegcetacoplan-injection. Accessed November 15, 2023.
22. Apellis Pharmaceuticals Inc. SYFOVRE® (pegcetacoplan injection) continued to demonstrate increasing treatment effects over 30 months in patients with geographic atrophy. In: *(GA)*. Press Release; July 30, 2023.
23. American Society of Retina Specialists ReST Committee. *ReST Committee Update on intraocular inflammation (IOI)*; 2023. Available from: https://www.ophthalmologytimes.com/view/asrs-reports-six-cases-of-occlusive-retinal-vasculitis-linked-to-pegcetacoplan-injection. Accessed November 15, 2023.
24. Patil NS, Dhoot AS, Popovic MM, et al. Risk of intraocular inflammation after injection of antivascular endothelial growth factor agents: a meta-analysis. *Retina*. 2022;42(11):2134−2142.
25. Brown BB. *Delphi Process: A Methodology Used for the Elicitation of Opinions of Experts*. Santa Monica, CA: Rand Corporation; 1968.
26. Xu ZY, Azuara-Blanco A, Kadonosono K, et al. New classification for the reporting of complications in retinal detachment surgical trials. *JAMA Ophthalmol*. 2021;139(8):857−864.
27. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12(1):10.
28. Duffield C. The Delphi technique: a comparison of results obtained using two expert panels. *Int J Nurs Stud*. 1993;30(3):227−237.
29. Murphy M, Black N, Lamping D, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess*. 1998;2(3). i−88.
30. McDermott DS. The prebriefing concept: a Delphi study of CHSE experts. *Clin Simul Nurs*. 2016;12(6):219−227.
31. Bruinsma SM, Roobol MJ, Carroll PR, et al. Semantics in active surveillance for men with localized prostate cancer—results of a modified Delphi consensus procedure. *Nat Rev Urol*. 2017;14(5):312−322.
32. Muthu V, Agarwal R, Patel A, et al. Definition, diagnosis, and management of COVID-19-associated pulmonary mucormycosis: Delphi consensus statement from the Fungal Infection Study Forum and Academy of Pulmonary Sciences, India. *Lancet Infect Dis*. 2022;22(9):e240−e253.
33. Martin D, Mantziari S, Demartines N, Hübner M. Defining major surgery: a Delphi consensus among European Surgical Association (ESA) members. *World J Surg*. 2020;44:2211−2219.
34. Clavien PA, Barkun J, De Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187−196.
35. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a

cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205.
36. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. *Ann Surg*. 2009;250(2):177−186.
37. Strong VE, Selby LV, Sovel M, et al. Development and assessment of Memorial Sloan Kettering Cancer Center's surgical secondary events grading system. *Ann Surg Oncol*. 2015;22:1061−1067.
38. Brown EG. Using MedDRA: implications for risk management. *Drug Saf*. 2004;27(8):591−602.
39. Sii S, Barton K, Pasquale LR, et al. Reporting harm in glaucoma surgical trials: systematic review and a consensus-derived new classification system. *Am J Ophthalmol*. 2018;194:153−162.
40. Munk MR, Kashani AH, Tadayoni R, et al. Recommendations for OCT angiography reporting in retinal vascular disease: a Delphi approach by international experts. *Ophthalmol Retina*. 2022;6(9):753−761.
41. Kodjikian L, Baillif S, Couturier A, et al. Recommendations for the management of diabetic macular oedema with intravitreal dexamethasone implant: a national Delphi consensus study. *Eur J Ophthalmol*. 2022;32(5):2845−2856.
42. Cruz-Pimentel M, Wu L. Complement inhibitors for advanced dry age-related macular degeneration (geographic atrophy): some light at the end of the tunnel? *J Clin Med*. 2023;12(15):5131.
43. Ecken P, Gnatzy T, von der Gracht HA. Desirability bias in foresight: consequences for decision quality based on Delphi results. *Technol Forecast Soc Change*. 2011;78(9):1654−1670.

Pictures & Perspectives



Dilated Conjunctival Vasculature in a Patient Up-Titrating Treprostinil Therapy

A 61-year-old man with a history of heritable pulmonary hypertension (+BNPR2) was hospitalized for up-titration of treprostinil. The patient developed acute, bilateral "red eye" without visual symptoms, visual acuity of 20/20, normal intraocular pressures, and symmetrically reactive pupils. Examination demonstrated bilateral, dilated circumferential conjunctival vasculature surrounding the limbus with temporal extension (**A**) and relative nasal sparing (**B**). Computed tomography angiography was reassuring against carotid-cavernous fistula. Dilated conjunctival vasculature has been reported secondary to epoprostenol; however, this is the first reported case secondary to treprostinil therapy. He remained asymptomatic with preserved afferent function on follow-up. (Magnified version of Figure **A**-**B** is available online at www.aaojournal.org).

John Wilson, MD[1]
Eli Pratte, MD[1]
Nathaniel Blecher, MD[1]

[1]*Department of Ophthalmology, Washington University School of Medicine, St. Louis, Missouri*