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# Setting Priorities for Diabetic Retinopathy Clinical Research and Identifying Evidence Gaps

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***Purpose:*** Prioritizing comparative effectiveness research may contribute to obtaining answers that clinicians perceive they need and may minimize research that could be considered wasteful. Our objective was to identify evidence gaps and set priorities for new systematic reviews and randomized controlled trials for managing diabetic retinopathy (DR), including diabetic macular edema (DME).

***Design:*** Cross-sectional study.

***Participants:*** Diabetic Retinopathy Clinical Research Network (DRCR.net) investigators.

***Methods:*** We provided recommendations from the American Academy of Ophthalmology's 2012 Preferred Practice Patterns for Diabetic Retinopathy as 91 answerable clinical research questions about intervention effectiveness to 410 DRCR.net investigators to rate each question's importance from 0 (not important) to 10 (very important) using a 2-round Delphi survey and to suggest additional questions. We considered questions as high priority if at least 75% of respondents to both rounds assigned an importance rating of 5 or more in round 2. We also extracted outcome measures relevant to DR and asked respondents to identify those that must be measured in all studies. We mapped Cochrane reviews published up to March 2016 to high-priority clinical research questions.

***Main Outcome Measure:*** Ranking of importance of each clinical question.

***Results:*** Thirty-two individuals (7.8%) completed rounds 1 and 2 and suggested 15 questions. Among the final list of 106 clinical research questions, 22 questions met our definition of high priority: 9 of 22 concerned the effectiveness of anti-VEGF therapy, and 13 of 22 focused on how often patients should be followed up (re-examination) and treatment effectiveness in patients with specific characteristics (e.g., DME). Outcomes that 75% or more of respondents marked as "must be measured in all studies" included visual acuity and visual loss, death of participants, and intraocular pressure. Only 1 prioritized question was associated with conclusive evidence from a Cochrane systematic review.

***Conclusions:*** A limited response rate among DRCR.net members identified 22 comparative effectiveness research questions as high priority for the management of DR, including DME, but few were associated with Cochrane reviews. These results support the need of systematic reviews and randomized controlled trials to address evidence gaps. *Ophthalmology Retina 2016;■:1–9 © 2016 by the American Academy of Ophthalmology*

*Supplemental material is available at www.ophthalmologyretina.org.*

Research that addresses real-world clinical questions may help patients and providers make evidence-informed healthcare decisions.[1,2] In 2011, the Institute of Medicine recognized the critical role of systematic reviews of comparative effectiveness research to provide the best evidence for clinical decision making.[2] Because synthesis of all available evidence in a systematic review is resource intensive,[3] many have recognized the critical importance of prioritizing performance and updates.[1,4–6] Prioritization also reduces unnecessary duplication and failure to build on findings from previous research, both representing considerable waste.[4]

Recognizing that there are many options for prioritizing clinical research needs,[1,5–9] our group developed an alternative framework that we have used in the context of eye and vision topics.[10–12] We begin by identifying research questions addressed in clinical practice guidelines and then asking clinicians to rate the importance of having an answer to the stated research question.[1,11] The advantage of this model is that it assumes that the clinical practice guidelines address the many topics that specialists confront in real-world medical practice.

In the current project, we set out to prioritize systematic review topics for diabetic retinopathy (DR), including diabetic macular edema (DME).[13–16] In 2010, an estimated one third of the 285 million individuals with diabetes worldwide had documented signs of DR. Of those with DR, one third have vision-threatening conditions, including proliferative DR (PDR) or DME.[17] In the United States, the number of



http://dx.doi.org/10.1016/j.oret.2016.10.003
ISSN 2468-6530/16

1) We reviewed the existing 2012 AAO PPP on DR (includes DME) and identified clinical recommendations and outcomes that could be measured in research studies.

2) We restated the recommendations into 91 answerable clinical research questions and identified 31 outcomes that could be relevant to DR. We reviewed the list of recommendations, questions, and outcomes with a retina specialist who suggested wording modifications.

3) We identified DRCR.net members as appropriate survey participants and developed a survey instrument comprising the 91 questions and 31 outcomes. The two-round survey included two questions to ensure that respondents understood the survey purpose.

4) In Round One, we asked the 410 DRCR.net members to assign an importance rating of 0 (low) to 10 (high) to each clinical research question and outcome and to suggest additional questions.

5) In Round Two, we asked them to re-rate the questions and outcomes, showing them ratings and comments by their peers.

6) We considered a question to be high priority when at least 75% of respondents to both rounds assigned a rating of "5" or higher in Round Two.

7) We compared prioritized questions with the AAO PPP's importance to care ratings.

8) We used a database of Cochrane systematic reviews for eyes and vision to match high priority questions to existing evidence supporting a clinical recommendation. This final step allowed identification of CER needs.

**Figure 1.** Summary of research methods. Abbreviations: AAO = American Academy of Ophthalmology; CER = comparative effectiveness research; DME = diabetic macular edema; DR = diabetic retinopathy; PPP = Preferred Practice Patterns (for DR).

people with DR is expected to nearly double from 7.7 million in 2010 to 14.6 million by 2050.[9,18]

Our objective was to set priorities for new systematic reviews and randomized clinical trials of the management of DR and DME using topics identified from the American Academy of Ophthalmology's (AAO) Diabetic Retinopathy Preferred Practice Patterns (PPP) and a 2-round survey of members of the Diabetic Retinopathy Research Network (DRCR.net).[19,20] We matched high-priority questions with existing evidence from Cochrane reviews to identify evidence gaps.

## Methods

Our research involved 8 key steps (see Fig 1). The Johns Hopkins Bloomberg School of Public Health Institutional Review Board classified our proposed research activity as meeting the criteria for exemption under 45 CFR 46.101(b), category 2.

### Identification of Recommendations

In December 2013, we extracted verbatim text from the 2012 PPP that could be considered as a recommendation for care. For each statement, we noted the patient population to which it applied (e.g., a recommendation for patients with nonproliferative DR and PDR, or for patients with DR with or without the presence of clinically significant DME). We also extracted the guideline panel's assessment of the importance of the recommendation and the strength of the evidence supporting it. Most recommendations in the 2012 PPP were not accompanied by references to systematic reviews. The PPP Retina/Vitreous panel included 8 ophthalmologists and 1 methodologist.

### Restating and Refining the Recommendations as Research Questions and Identification of Outcomes

We restated each recommendation as a clinical research question. In keeping with the previous studies using a similar framework,[11,12] we did not include guideline statements on disease definition, disease cause, diagnostic test accuracy; statements classified as ethical or legal statements; or statements that were not recommendations. We also did not specify the outcomes in the clinical research questions, recognizing that the goals of interventions may vary by stage of diabetic retinopathy. Further, it is the responsibility of the investigative group to define key efficacy and safety criteria and study objectives. Two investigators extracted all clinical outcome measures described as pertaining to DR and DME and resolved disagreements through discussion from the DRCR.net.

A retinal specialist (N.M.B.) examined and edited the questions, using the original 2012 PPP text for comparison. He suggested revisions to capture concepts that were current and relevant to care at the time of his review (June 2014). Given the rapid changes occurring in the management of DR, including DME, with the advent of intravitreous anti−vascular endothelial growth factor (anti-VEGF) agents and corticosteroids, questions were modified by one of us (N.M.B.) to capture all but 2 recommendations from the 2014 PPP in the survey.