Supplementary Online Content

Lindsley KB, Hutfless S, Hawkins BS, et al. Evaluation of clinical questions and patient-important outcomes associated with the treatment of age-related macular degeneration. *JAMA Ophthalmol*. Published online August 16, 2018. doi:10.1001/jamaophthalmol.2018.3456

This supplementary material has been provided by the authors to give readers additional information about their work.

Appendix 1. Study protocol

Research Aims:

The overall aim of this study is to test a framework for setting priorities for systematic reviews and RCTs related to treatment of age-related macular degeneration (AMD). In this study, we will translate statements in the American Academy of Ophthalmology (AAO) clinical practice guideline for management of AMD into answerable clinical questions and map the questions to existing, reliable systematic reviews. We will partner with clinical practice guideline developers, retina experts, healthcare professionals, and patients to prioritize a research agenda for AMD.

By identifying and assessing the available evidence, and the important clinical questions, we aim to provide reliable information to clinicians, researchers, and policymakers; identify where evidence gaps exist; and prioritize important clinical questions for research to answer.

Methods:

1) Extraction of guideline recommendations

Two individuals will independently review and extract every statement that could be considered a recommendation, published in the AAO's Preferred Practice Patterns (PPPs) related to the management of AMD (AAO 2015). We will restate each recommendation as an answerable clinical question. We will consult with AMD specialists who have expertise both in the management of AMD and in forming answerable clinical questions to confirm that our restatements are accurate. The restated clinical questions will constitute a preliminary list of priorities for systematic reviews and clinical trials to address. We will refine this list in subsequent cross-sectional surveys.

2) Survey to identify highly important clinical questions: Survey of the American Academy of Ophthalmology Retina/Vitreous Panel

The purpose of surveying the AAO Retina/Vitreous Panel will be to identify highly important clinical questions to be prioritized. Initial discussions with professional associations and patient groups suggested that their membership would be more likely to respond and complete the surveys if the number of questions could be reduced so that the survey could be completed in 15 minutes or fewer. Members of the AAO Retina/Vitreous Panel will score all clinical questions derived in the first step and we will use their responses to form the shortened list of highly important clinical questions to be prioritized.

We will conduct a two-round web-based cross-sectional modified "Delphi" consensus survey (Custer 1999). We will ask survey participants electronically, using email and the Internet, to score the list of research questions we derived from the AAO's PPP on the management of AMD. The invitation to participate will be sent by an AAO designee and will include the consent to participate (see "Description of the Consent Process"). We will ask participants to score each clinical question on a scale of 0 to 10, with a score of 10 indicating that they view the clinical question as highly important; a score of 0 indicates that they view the clinical question as not important at all. If the participant feels unqualified to rate a particular clinical question, they may select 'no judgment'. There will be space for comments, questions and nomination of items not included in the list. Respondents will be given 4 weeks total to

respond to Round One of the survey. After the initial request, an email reminder will be sent at the end of week 1, week 2, week 3, and 2 days prior to the end of week 4.

In Round Two of the survey we will provide each respondent with the group summary measure (median) for each clinical question asked in Round One and ask the Panel to score additional clinical questions suggested by respondents in Round One. Respondents will be given the opportunity to re-score each item in light of ratings and comments from the previous round. Respondents will be given 4 weeks total to respond to this round of the survey. After the initial request, an email reminder will be sent at the end of week 1, week 2, week 3, and 2 days prior to the end of week 4.

The highest scored clinical questions will represent the highly important clinical questions to be prioritized. We will include the highest scored 10-15 clinical questions, with median scores of at least 7 or higher, in the prioritization surveys. Lower scored clinical questions, considered as moderately important (median at least 4) or not important (median less than 4), will not be included in the prioritization surveys.

3) Survey of healthcare professionals to prioritize clinical questions: Survey of the American Society of Retina Specialists

Using the survey results from the AAO Retina/Vitreous Panel, we will ask members of the American Society of Retinal Specialists (ASRS) to prioritize the order in which the highly important clinical questions should be answered.

The invitation to participate in the survey will be sent by an ASRS designee and will include the consent to participate (see "Description of the Consent"). We will ask participants to score each clinical question on a scale of 0 to 10, with a score of 10 indicating that they view the clinical question as high priority; a score of 0 indicates that they view the clinical question as not a priority. If the participant feels unqualified to score a particular clinical question, they may select 'no judgment'. There will be space for comments, questions and nomination of items not included in the list. Respondents will be given 4 weeks total to respond to the survey. After the initial request, an email reminder will be sent at the end of week 1, week 2, week 3, and 2 days prior to the end of week 4.

Additionally, we will request survey participants to provide demographic and other information such as occupation/field, specialty, and place of employment (e.g. government, industry, academia, other), experience in clinical trials/systematic reviews (see draft survey). These data will be examined for possible association with the level of importance assigned if sufficient data are available. We will not collect identifiable data and expect that all responses will remain anonymous.

4) Survey of patients to prioritize clinical questions and outcomes: Survey of MD Support

We will ask members of MD Support (www.mdsupport.org), an online patient group for macular degeneration, to prioritize the order in which the highly important clinical questions should be answered by research. The clinical questions will be reworded to lay language, in collaboration with the Director of MD Support, and we will include definitions of clinical terms to make the survey questions clear to non-healthcare professionals. Additionally, we will ask for their assistance in identifying patient-important outcomes for systematic reviews and RCTs related to management of AMD. We will derive the list of outcomes for patients to assess from common outcomes assessed in research related to AMD (Saldanha 2014). We will ask each survey participant demographic and other information, such as having early or

advanced stage AMD (i.e. advanced stage = previously received laser or injections in the eye to treat AMD).

5) Sample size

a. Survey of the American Academy of Ophthalmology's Retina/Vitreous Panel

The size of the AAO Retina/Vitreous Panel varies from 6 to 8 individuals. Because this effort has full collaboration with the AAO, we estimate that all active Panel members will participate in each of the two rounds of the survey.

b. Survey of the American Society of Retina Specialists

We aim to invite about 400 ASRS members. We estimate that a minimum of 25% will participate in the online surveys.

c. Survey of patient and consumer panels

MD Support's online forum consists of about 400 members. We will invite all members with active email addresses to participate in the online survey and estimate that a minimum of 25% with AMD will participate in the online survey.

6) Analysis and Reporting

a. Statistical Plan

We will calculate summary statistics (mean, standard deviation, median, and inter-quartile range) of scores for each clinical question for each survey. We will compare scores by groups of stakeholders, for example healthcare professionals versus patients.

b. Dissemination

We will report our results in a journal article as well as other methods of dissemination (email to survey partners, Twitter, etc.). We will assess the utility of the project by obtaining feedback from CEV editors and authors conducting systematic reviews.

7) Ethical considerations (IRB #2709; exemption status)

a. Inclusion and Exclusion Criteria

The inclusion criterion is to be a member of the respective group that is being asked to complete each specific survey (AAO Retina/Vitreous Panel, ASRS, or MD Support). Consumer patient stakeholders from MD Support will have self-reported AMD or care for a person with AMD to be eligible for analysis.

b. Gender, Age and Locale

We will not exclude participants on the basis of gender, age, or nationality.

c. Recruitment Process

For all surveys, our collaborating partners (AAO, ASRS, and MD Support) will invite participation by email.

d. Risk/Benefits

Description of Risks: There is no foreseeable physical risk to survey participants. Participation in the survey may involve a loss of privacy and a commitment of time.

Description of Measures to Minimize Risks: We will pilot test each round of the survey to provide participants with an estimate of the time it will take to complete. We will ensure participant anonymity and confidentially of responses. Only survey moderators will have access to the anonymous individual survey results. We will report results in an aggregate form without personal identifiers (see "Confidentiality Assurance").

Description of Potential Benefits: By providing their opinions on the importance of a series of clinical questions about AMD, survey participants will contribute to establishing a framework for setting priorities for new systematic reviews and RCTs.

Description of Level of Research Burden: We anticipate that the time commitment for each survey will vary, decreasing with each round. No survey should take more than 30 minutes to complete.

e. Compensation

There will be no monetary compensation for participating in any survey, although each group participating will be thanked and acknowledged in publications and on the CEV website.

f. Description of the Consent Process

For all surveys, the initial invitation will contain a description of the research we are conducting. Invitees will be given a total of 4 weeks to consider whether they will participate. An email reminder will be sent at the end of each of the 4 weeks that the survey is active. We will consider a response to the survey as evidence of consent to participate. We will consider the invitee as declining participation if s/he sends a declining email or if s/he does not respond to the survey after four weeks.

g. Data Security

All survey invitations and reminders will be sent by the partnering groups; none by CEV.

CEV will not solicit the contact information of members from our partner groups; however, email, mail, or phone correspondence from a survey participant to CEV moderators may include information that would enable the moderators to know who the participant is. In any case, participant names will not be used on any survey instrument or data file. We will report results in an aggregate form without personal identifiers.

We will store paper forms in an office building that has very good external security (615 N. Wolfe Street Baltimore, MD 21205). The building has a 24-hour manned security desk, and photo ID is required to get in. We will store the electronic data file on a password-protected server. We will back up data files on a regular basis with a CD-ROM version stored off-site.

8) Protocol amendments

In August 2016, after receiving the Panel's Round 2 survey responses, we increased the number of highly important clinical questions to be prioritized from 10-15 to 17 based on the median score of 7 or higher.

In December 2016, after observing low response rates to the online surveys, we decided to survey another group of healthcare professionals to increase the absolute number of respondents. We printed paper copies of the prioritization surveys and distributed them at the registration table during the Atlantic Coast Retina Conference and Macula meetings held in Baltimore, Maryland in January 2017.

9) References

AAO 2015
Preferred Practice Pattern: Primary Open Angle Glaucoma. Available at: http://one.aao.org/CE/PracticeGuidelines/PPP.aspx?p=1

Custer 1999
Custer, Rodney L.; Scarcella, Joseph A.; Stewart, Bob R. The Modified Delphi Technique - A Rotational Modification," Journal of Vocational and Technical Education, 1999; 15 (2): 50-8

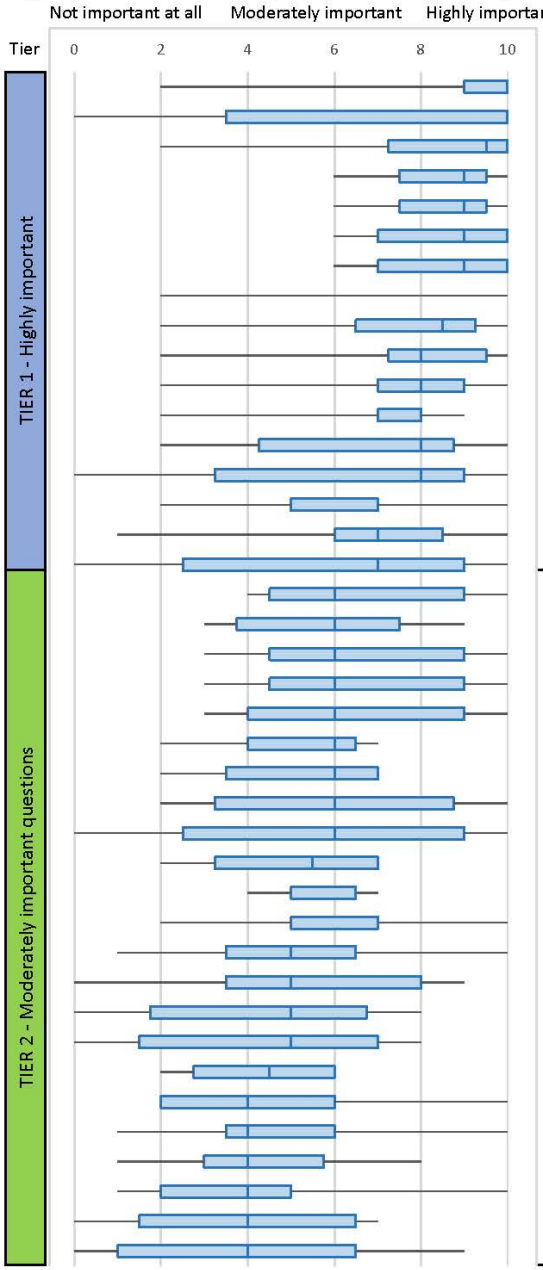
Guyatt 2000
Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, Wilson MC, Richardson WS. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group.JAMA. 2000 Sep 13;284(10):1290-6.

Li 2015
Li T, Vedula SS, Hadar N, Parkin C, Lau J, Dickersin K. Innovations in data collection, management, and archiving for systematic reviews. Ann Intern Med. 2015;162(4):287-94.

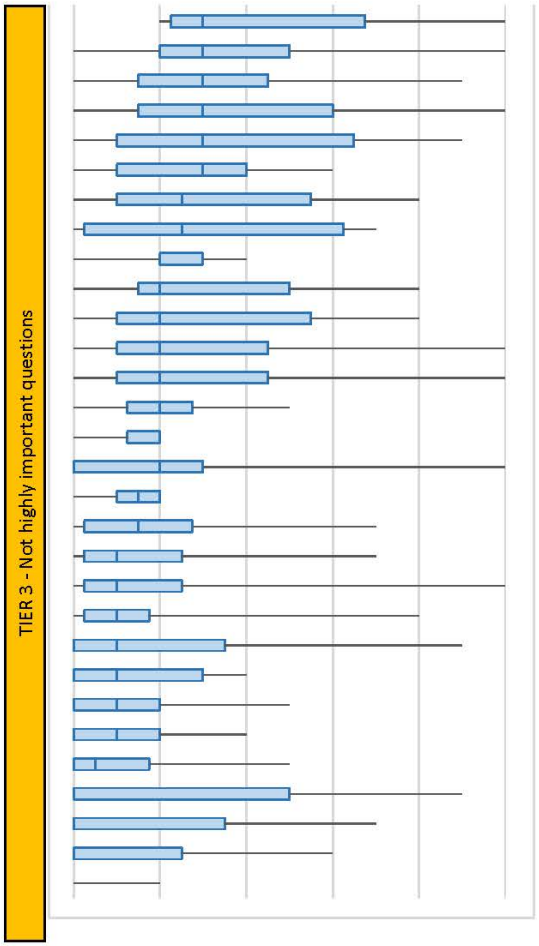
Lindsley 2016
Lindsley K, Li T, Ssemanda E, Virgili G, Dickersin K. Interventions for age-related macular degeneration: are practice guidelines based on systematic reviews? Ophthalmology 2016. 123(4):884-97.

Saldanha 2014
Saldanha IJ, Dickersin K, Wang X, Li T. Outcomes in Cochrane systematic reviews addressing four common eye conditions: an evaluation of completeness and comparability. PLoS One. 2014;9(10):e109400

Appendix 2. American Academy of Ophthalmology Retina/Vitreous Panel scoring of importance of clinical questions related to the treatment of age-related macular degeneration (AMD)

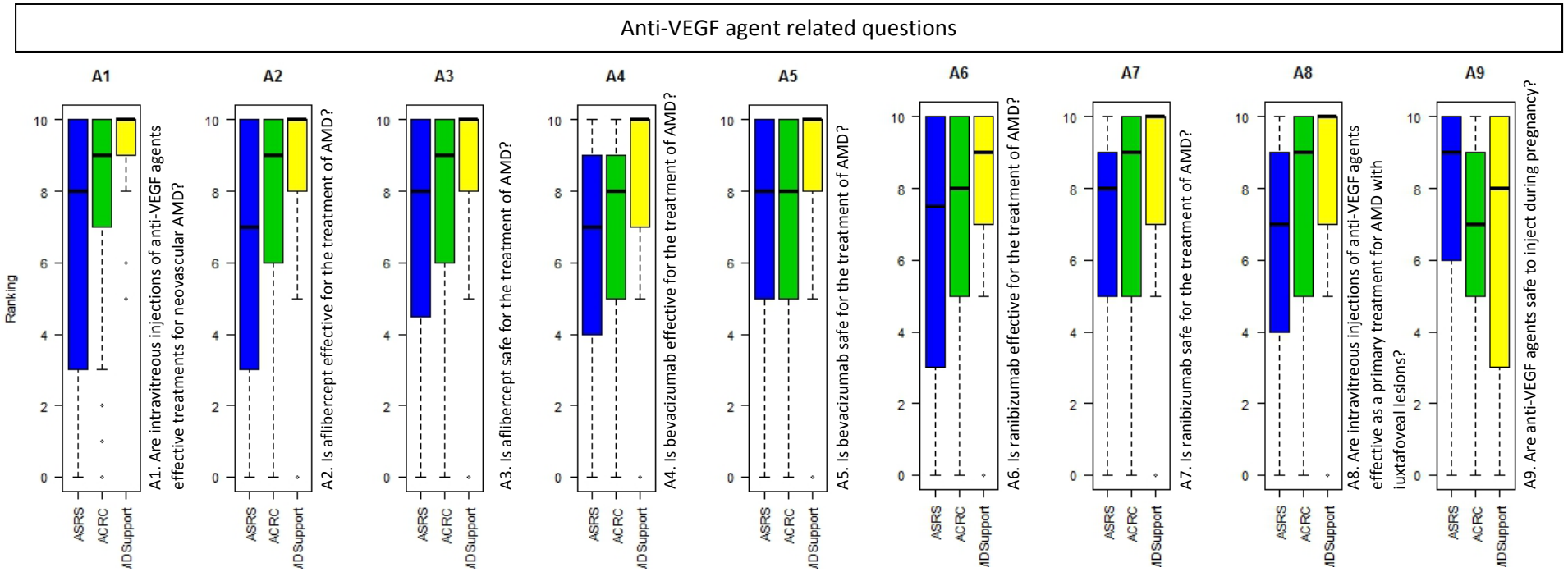


Tier		Clinical question
TIER 1 - Highly important	1	Is aflibercept effective for the treatment of AMD?
	2	Are intravitreous injections of anti-VEGF agents effective treatments for neovascular AMD?
	3	Is ranibizumab effective for the treatment of AMD?
	4	Is long-term supplementation with high-dose antioxidants safe for the general patient with AMD?
	5	Is long-term supplementation with high-dose antioxidants safe for smokers with AMD?
	6	Are antioxidant vitamin and mineral supplements an effective treatment for intermediate AMD?
	7	Are antioxidant vitamin and mineral supplements an effective treatment for advanced AMD in only one eye?
	8	Is aflibercept safe for the treatment of AMD?
	9	Is ranibizumab safe for the treatment of AMD?
	10	Is self-monitoring by patients at high-risk effective in preventing progression of advanced AMD?
	11	Is bevacizumab effective for the treatment of AMD?
	12	Is bevacizumab safe for the treatment of AMD?
	13	Is surgery for cataracts in people with AMD safe?
	14	Does avoiding sunlight after verteporfin photodynamic therapy prevent or reduce photosensitivity reactions?
	15	Are anti-VEGF agents safe to inject during pregnancy?
	16	Does smoking cessation prevent progression of AMD?
	17	Are intravitreous injections of anti-VEGF agents effective as a primary treatment for AMD with juxtafoveal lesions?
TIER 2 - Moderately important questions	18	Does the effectiveness of anti-VEGF agents differ by agent, treatment regimen or the combination of agent and treatment regimen?
	19	Is verteporfin photodynamic therapy effective for polypoidal choroidal vasculopathy?
	20	Are intravitreous injections of anti-VEGF agents for AMD safe in terms of acute inflammation?
	21	Are intravitreous injections of anti-VEGF agents for AMD safe systemically (i.e., cardiovascular events)?
	22	Are intravitreous injections of anti-VEGF agents for AMD safe overall?
	23	Are zinc supplements for AMD safe?
	24	Are implantable miniature telescopes (IMT) for vision loss due to end-stage AMD effective?
	25	Are antioxidant vitamin and mineral supplements an effective treatment for patients who have less than intermediate AMD?
	26	Are intravitreous injections of anti-VEGF agents for AMD safe for the eye (i.e., endophthalmitis, infection)?
	27	Do omega 3 fatty acids prevent or slow the progression of AMD?
	28	Is vitamin E supplementation above the AREDS levels safe in patients with AMD?
	29	Are intravitreous injections of anti-VEGF agents more effective than laser photocoagulation for extrafoveal neovascular lesions?
	30	Is observation without medicine, surgery or repeat testing an effective treatment strategy for advanced AMD with bilateral disciform scars?
	31	Is thermal laser photocoagulation surgery an effective treatment for AMD with juxtapapillary CNV?
	32	Is verteporfin photodynamic therapy effective for patients with AMD who are pregnant or breast-feeding?
	33	Is submacular surgery (e.g., vitrectomy) an effective treatment for AMD with large submacular hemorrhage?
	34	Are intravitreous injections of anti-VEGF agents effective treatments for polypoidal choroidal vasculopathy (PCV)?
	35	Does genetic testing improve the effectiveness of interventions used to treat AMD?
	36	Is observation without medicine, surgery or repeat testing an effective treatment strategy for advanced AMD with bilateral subfoveal geographic atrophy or disciform scars?
	37	Are complement inhibitors effective for AMD?
	38	Is observation without medicine, surgery or repeat testing an effective treatment strategy for asymptomatic non-neovascular AMD?
	39	Are intravitreous injections of corticosteroids for AMD safe?
	40	Are intravitreous injections of corticosteroids an effective treatment for AMD?



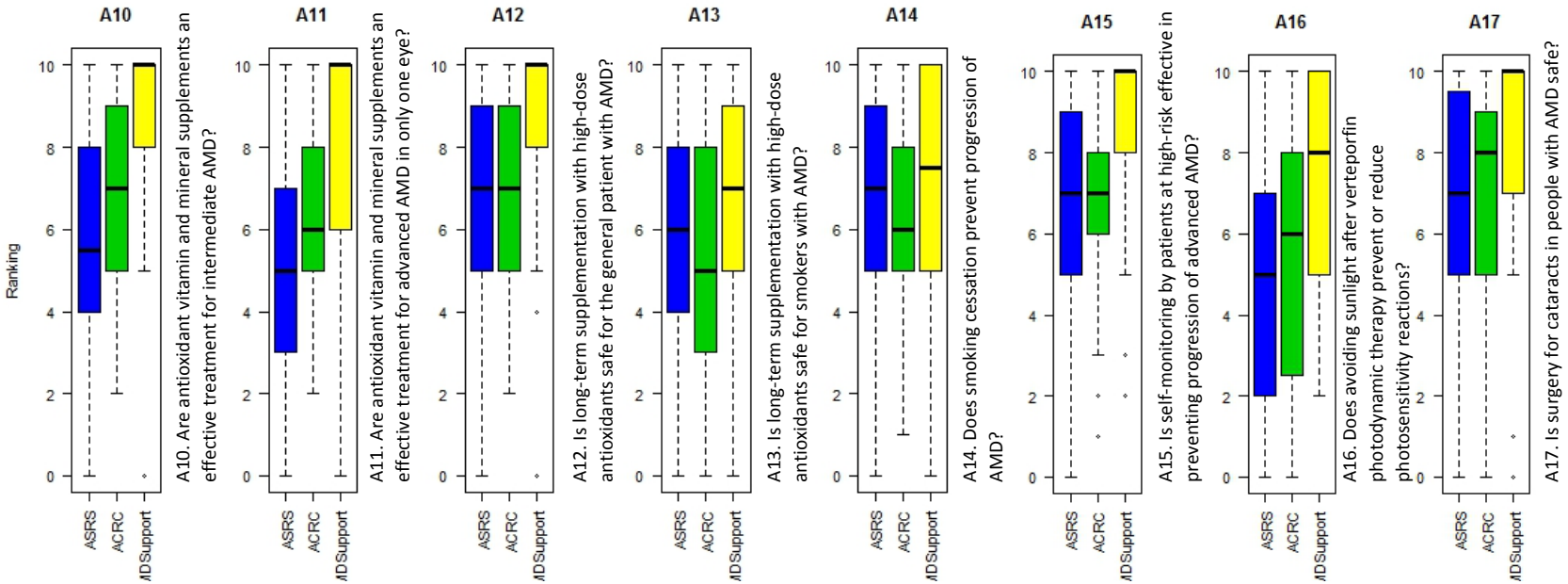
41 Is aspirin safe to use in patients being treated for AMD?
42 Is thermal laser photocoagulation surgery for AMD safe?
43 What is the incidence of a new scotoma or enlargement of a pre-existing scotoma with or without visual acuity loss after thermal laser photocoagulation surgery for AMD?
44 Is radiotherapy (e.g., with strontium) an effective treatment for AMD?
45 Is thermal laser photocoagulation surgery an effective treatment fornew extrafoveal classic CNV?
46 How long does thermal laser surgery for AMD prevent recurrence, persistence or new choroidal neovascularization (CNV)?
47 Is radiotherapy (e.g., with strontium) for AMD safe?
48 Is verteporfin photodynamic therapy safe for patients with AMD who are pregnant or breast-feeding?
49 Is verteporfin photodynamic therapy effective for treating juxtafoveal CNV in AMD?
50 Is verteporfin photodynamic therapy combined with pharmacologic therapy an effective treatment for AMD?
51 Is the combination of intravitreous injections of anti-VEGF agents with other treatments (e.g., transpupillary thermotherapy) more effective than anti-VEGF agents alone for advanced AMD?
52 Is verteporfin photodynamic therapy effective for occult CNV when PDT with vision 20/50?
53 Is verteporfin photodynamic therapy effective for new or recurrent subfoveal CNV where the classic component is >50% of the lesion and the entire lesion is <=5400 microns in greatest linear diameter?
54 Is adjunctive use of intravitreous injections of corticosteroids with verteporfin photodynamic therapy an effective treatment for AMD?
55 Is acupuncture an effective treatment for AMD?
56 Is verteporfin photodynamic therapy safe for the general patient with AMD?
57 Is electrical stimulation an effective treatment for AMD?
58 Is verteporfin photodynamic therapy safe for patients with AMD and liver dysfunction?
59 Is macular translocation surgery for AMD safe?
60 Is macular translocation surgery an effective treatment for AMD?
61 Is verteporfin photodynamic therapy effective for patients with AMD and liver dysfunction?
62 Is interferon for advanced AMD safe?
63 Is verteporfin photodynamic therapy effective for the general patient with AMD?
64 Is thermal laser photocoagulation surgery a more or similarly effective treatment than intravitreous injections of anti-VEGF agents for subfoveal CNV in AMD?
65 Is rheopheresis for advanced AMD safe?
66 Is rheopheresis an effective treatment for advanced AMD?
67 Is thermal laser photocoagulation surgery an effective treatment for recurrent extrafoveal classic CNV?
68 Are intravitreous injections of anti-VEGF agents effective treatments for the general patient with AMD?
69 Is interferon an effective treatment for advanced AMD?
70 Is thermal laser photocoagulation surgery an effective treatment for the general patient with AMD?

Appendix 3. Results of prioritization of Tier 1 clinical questions (n=17) by healthcare professionals and patients



Antioxidant related questions

Other treatment modality related questions



A10. Are antioxidant vitamin and mineral supplements an effective treatment for intermediate AMD?

A11. Are antioxidant vitamin and mineral supplements an effective treatment for advanced AMD in only one eye?

A12. Is long-term supplementation with high-dose antioxidants safe for the general patient with AMD?

A13. Is long-term supplementation with high-dose antioxidants safe for smokers with AMD?

A14. Does smoking cessation prevent progression of AMD?

A15. Is self-monitoring by patients at high-risk effective in preventing progression of advanced AMD?

A16. Does avoiding sunlight after verteporfin photodynamic therapy prevent or reduce photosensitivity reactions?

A17. Is surgery for cataracts in people with AMD safe?