# Macular degeneration

**Consultation on draft guideline - Stakeholder comments table**
**30/06/2017 to 11/08/2017**

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| Alliance Pharmaceuticals | Full | 57 | table | Despite being well recognised in the literature and multiple references throughout the document that a diet low in vitamins is a recognised risk factor for AMD (**p53**; line 14-15, **p59**;line 10 and **p29**;line 5), and an agreement from the Committee that patients need to be made aware of this (**p236**;line 1 and p**238**; line 47-48), it has been omitted as a ***"risk factor of interest"*** within the table which sets out any risk factors prioritised as part of the guideline recommendations, which ***"should be ones that are either highly important or specific to AMD"*** (**p56**;line 7-8).<br>There is a concern that by omitting this, patient needs may not be fully addressed by any healthcare professional who may be following NICE guidance, looking towards this table as a reference guide to assist them in their practice of advising their patients of risk factors in those at risk of developing AMD, or who already suffer early/progressive AMD. | Thank you for your comment. Diet is included as a risk factor of interest in this section, and the resulting recommendation states that healthcare professionals should recognise a 'diet low in omega 3 and 6, vitamins, carotenoid and minerals' as one of the factors that make it more likely that a person has AMD. |
| Alliance Pharmaceuticals | Full | 60-72<br><br><br><br><br><br><br>60-72 | general<br><br><br><br><br><br><br>general | The inclusion & exclusion criteria for assessing the clinical evidence in the literature states (**p60**; line 11-18):<br>***"In accordance with the review protocol, only randomised controlled trials (RCTs) and systematic review of RCTs were included if they compared interventions for slowing or preventing the progression of AMD with usual care (including basic advice) or placebo treatment."***<br>We are concerned that this has not been followed, with exclusion of key studies and all relevant available evidence for vitamin supplementation which has been shown to slow progression of AMD. | Thank you for your comment, and for bringing this evidence to our attention.<br><br>1. For each of the specific studies you have mentioned as meeting the RCT criteria:<br>-Akuffo does not report any of the clinical outcomes of interest, with the focus of the study being on other outcomes such as macular pigmentation, contrast sensitivity and concentrations of macular carotenoids.<br>-Beatty only reports visual acuity data as mean changes. Whilst there is an outcome of AMD |

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| | | 60-72 | general | It appears that all but 1 study (Huang 2015), were taken directly from the Cochrane AMD review 2017, but 6 Cochrane studies were not included and the following studies were either excluded or not correctly identified within the literature search, despite meeting the inclusion criteria:<br>**1) x6 high profile RCT's omitted:**<br>- **Akuffo et al.** Sustained supplementation and monitored response with differing carotenoid formulations in early age-related macular degeneration Eye (**MOST study**; 2015) 29, 902–912. *RCT study over 36 months showed sustained supplementation in subjects with early AMD results in significant improvement of MP following 2 years of continuous supplementation, and confers visual benefit in these patients in terms of CS.*<br>- **Beatty S**, Chakravarthy U, Nolan JM, Muldrew KA, Woodside JV, Denny F, et al. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. Ophthalmology. 2013;120(3):600-6<br>- **Chew et al.** Ten-Year Follow-up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study. *JAMA Ophthalm; 272-277:(3)132;2014*<br>- **Moeller SM**, Parekh N, Tinker L, Ritenbaugh C, Blodi B, Wallace RB, Mares JA; **CAREDS Research Study** Group: Associations between intermediate age related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-Related Eye Disease Study | progression, this does not correspond to the specified outcome in the protocol of development of late AMD.<br>-Chew, whilst being a follow-on from the randomised AREDS study, reports data from a non-randomised comparison as people no longer remain in their original treatment groups.<br>-Moeller is not a randomised study<br>-Nolan is a study in people with atypical macular pigment profiles, rather than people with a diagnosis of AMD<br>-Sabour-Pickett again does not report any of the outcomes specified in our protocol, with macular pigment density being the primary outcome in the paper, and visual acuity only reported as mean differences.<br><br>2. For the review papers cited, the majority are narrative reviews or opinion pieces rather than systematic reviews, and therefore do not meet the criteria for inclusion. The exceptions are Garcia-Montalvo (which is excluded as being non-English language) and Vishwanathan, which contains 4 RCTs, all of which were included within the review.<br><br>The protocol for this particular review question did not specify mean change in visual acuity as an outcome measure, but only a dichotomous outcome of significant |

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| | | 60-72 | General | (CAREDS): ancillary study of the Women's Health Initiative. Arch Ophthalmol 2006;124:1151-1162<br>- **Nolan JM**, Akkali MC, Loughman J, Howard AN, Beatty S. Macular carotenoid supplementation in subjects with atypical spatial profiles of macular pigment. Exp Eye Res. 2012;101:9-15. *Head to head RCT study which demonstrated supplementary carotenoids improvement visual performance in terms of observed increases in MP - the precise aim of vitamin supplementation.*<br>- **Sabour-Pickett et al.** Supplementation with three different macular carotenoid formulations in patients with early age-related macular degeneration. Retina. 2014 Sep;34(9):1757-66<br>*RCT study over 12 months demonstrated significant improved visual performance in patients with early AMD after supplementation with meso-zeaxanthin and lutein.*<br><br>**2) x9 RCT systematic reviews have been excluded:**<br>- **Bernstein, P. S et al.** Lutein, zeaxanthin, and *meso*-zeaxanthin: The basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Prog Retin Eye Res. 2016 Jan:* 50;34-66<br>- **Crosby-Nwaobi R** et al. An exploratory study evaluating the effects of macular carotenoid supplementation in various retinal diseases. Clin Ophthalmol. 2016;10:835-44<br>- **García-Montalvo IA**. Nutr Hosp. NUTRITIONAL COMPONENTS AND AGE-RELATED MACULAR | visual acuity loss (e.g. loss of 3 or more lines of visual acuity). This was chosen both to match the Cochrane review, and to capture the intent of the question, which was to ascertain whether these strategies slow the progression of AMD, rather than whether they lead to short term changes in average visual acuity.<br><br>3. The protocol for this question, as agreed in advance by the guideline committee, was written such that observational studies would only be included if no data from randomised controlled trials were identified. The committee agreed this was an area where the well-known advantages of RCTs for addressing questions around interventions (e.g. reduced risk of selection bias) would be important to have confidence in the results found. Since randomised controlled data were identified, observational studies (Chew et al 2014; Moeller et al 2006 etc.) were therefore not included. Also for inclusion within each review question studies had to meet pre-specified inclusion criteria including study population, intervention, comparator, and outcomes of the interest. Inclusion criteria were determined and ratified by the guideline committee. In particular, the committee noted that the initial randomised section of the AREDS study included in the review had a median follow-up of 6.3 years, which the committee agreed was an appropriate length of follow-up in which changes could be detected. Although |

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| | | | | DEGENERATION 2015 Apr 28;32(1):50-4. *Meta-analysis where: Conclusion is substantial evidence that can be applied nutritional support for patients with AMD*<br>- **Hubschman JP** et al. Age-related macular degeneration: current treatments. Clin Ophthalmol. 2009;3:155-66<br>- **Ma.L** et al., "Lutein and zeaxanthin intake and the risk of age-related macular degeneration: a systematic review and meta-analysis,"*The British Journal of Nutrition*, vol.107, no. 3, pp. 350–359, 2012. *….increase in the intake of L/Z was significantly associated with a 26% risk reduction for late AMD*<br>- **Scripsema**,**N** et al. Lutein, Zeaxanthin, and *meso*-Zeaxanthin in the Clinical Management of Eye Disease. J Ophthalmol. 2015; 2015: 865179. *Systematic review epidemiological studies and RCT clinical trials*<br>- **Sin HP et al.** Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration. Acta Ophthalmol. 2013 Feb;91(1):6-11. *Systematic review….patients with documented intermediate risk of AMD or advanced AMD in one eye are recommended to take AREDS-type vitamin supplements*<br>- **Snodderly DM.** Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins. Am J Clin Nutr. 1995;62:1448S-1461S | subsequent analyses have made use of the AREDS data in the form of a case-control or cohort study for other purposes (e.g. in the section of the guideline on classification systems), this question uses the data in its initial randomised form.<br><br>4. Additionally, macular depigmentation was not specified as an outcome, as the committee agreed that this was an intermediate outcome, and changes through this mechanism would be more appropriately captured by looking directly at rates of AMD progression. |

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| | | 60-72 | General | - **Vishwanathan R. et al**. A systematic review on zinc for the prevention and treatment of age-related macular degeneration. Invest Ophthalmol Vis Sci 54, 3985–3998 (2013).<br><br>**3) AREDS study** is the main focus for evidence in this review section, and as a large case control study, there should be equal emphasis awarded to the **x17 other studies** of similar study design and of equal importance.<br>"The decision to only include RCT studies as the only evidence for strategies to slow the progression of AMD is fundamentally flawed, as one would have to follow a very large sample of the population over a long period of time because AMD is a disease that is developed over a persons' lifetime, as a result of cumulative and chronic oxidative stress, which has many contributing risk factors" [quoted with permission from Prof. John Nolan 2017: over 16 years experience conducting clinical trials designed to test the impact of nutrition for vision and age-related macular degeneration]. We are therefore concerned by the omission of any other large and robust Longitudinal Studies as part of your assessment, of which there are many notable studies:<br>- **Chew et al.** Ten-Year Follow-up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study. *JAMA Ophthalmol* 277-272:(3)132;2014 .<br>- **Cho E et al**. Prospective study of intake of fruits, vegetables, vitamins, and carotenoids and risk of age- | |

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| | | | | related maculopathy. Arch Ophthalmol. 2004;122(6):883-92<br>- **Christen WG** et al. Prospective cohort study of antioxidant vitamin supplement use and the risk of age-related maculopathy. American journal of Epidemiology. 1999;149(5):476-84.<br>- **Flood V** et al. Dietary antioxidant intake and incidence of early age-related maculopathy: the **Blue Mountains Eye Study**. Ophthalmology. 2002;109(12):2272-8<br>- **Ho.L** et al., "Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and ω-3 fatty acids: **The Rotterdam study**," *Archives of Ophthalmology*, vol. 129, no. 6, pp. 758–766, 2011. *A total of 2,167 participants from the population-based Rotterdam Study at risk of AMD were followed up for a mean of 8.6 years. They reported that high dietary intake of nutrients with antioxidant properties such as L and Z, β-carotene, omega-3 fatty acids, and zinc reduced the risk of early AMD*<br>- **Holz F. G et al**. Recent developments in the treatment of age-related macular degeneration. J Clin Invest 124, 1430–1438 (2014).<br>- **Kuzniarz M et al**. Use of vitamin and zinc supplements and age-related maculopathy: the Blue Mountains Eye Study. Ophthalmic Epidemiol. 2002;9(4):283-95<br>- **Lim L. S.,** Mitchell P., Seddon J. M., Holz F. G. & Wong T. Y. Age-related macular degeneration. Lancet 379, 1728–1738 (2009) | |

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| | | | | - **Mares-Perlman JA** et al., "Serum antioxidants and age-related macular degeneration in a population based case-control study," *Archives of Ophthalmology*, vol. 113,no. 12, pp. 1518–1523, 1995<br>- **Mares-Perlman JA** et al. Association of zinc and antioxidant nutrients with age-related maculopathy. Archives of ophthalmology. 1996;114(8):991-7<br>- **Mares-Perlman JA et al.** Lutein and zeaxanthin in the diet and serum and their relation to age-related maculopathy in the third national health and nutrition examination survey. Am J Epidemiol 2001;153:424-432<br>- **Meyer zu Westrup** *et al.* Changes of macular pigment optical density in elderly eyes: a longitudinal analysis from **The MARS study** *Int J Retin Vitr (2016) 2:14.* **MARS study (**Münster Ageing and Retina Study) *which looks at slowing progression of AMD with carotenoid supplement intake in patients with early AMD after 4 years*<br>- **Seddon**. J.M et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration,"*JAMA*, vol. 272, no. 18, pp. 1413–1420, 1994. **The Eye Disease Case-Control Study** *reported that subjects with the highest quintile of carotenoid intake had a 43% reduced risk of AMD compared with subjects in the lowest quintile.*<br>- **Snellen EL** et al. Neovascular age-related macular degeneration and its relationship to antioxidant intake. Acta Ophthalmol Scand. 2002;80(4):368-71 | |

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| | | | | - **Tan J.S et al.** Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. Arch Ophthalmol 127, 656–665 (2009). *Blue Mountain Eye Study reported a 65% reduced risk of neovascular AMD between subjects with the highest and lowest intake of L/Z. Subjects above the median carotenoid intake also had a reduced risk of indistinct soft or reticular drusen*<br>- **VandenLangenberg G. M et al.** "Associations between antioxidant and zinc intake and the 5-year incidence of early age-related maculopathy in **The Beaver Dam eye study**," *American Journal of Epidemiology*, vol. 148, no. 2, pp. 204–214, 1998<br>- **Van Leeuwen R** et al. Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA. 2005;294(24):3101-7<br><br>**4)** The review excludes macular pigment studies (**x10 robust studies**) where macular depigmentation is known to increase risk of progression to late AMD in people with early AMD and recognised within this review as, ***"moderate quality evidence"*** (p54;line 1). Please also see a major and well regarded review by Bernstein et al (2016), which outlines the rationale and importance of assessing the totality of evidence available relating to the role of carotenoids for retinal disease including AMD. Please note, we have not included reference to any | |

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| | | | | studies which look at serum concentrations as a proxy, or studies in just healthy study participants.<br><br>- **Akuffo KO et al.** Relationship between macular pigment and visual function in subjects with early age-related macular degeneration. Br J Opthalmol, 2017; 101, 190-197.<br>- **Akuffo KO**, Beatty S, Stack J, Dennison J, O'Regan S, Meagher KA, et al. Central Retinal Enrichment Supplementation Trials (**CREST**): design and methodology of the CREST randomized controlled trials. Ophthalmic Epidemiol. 2014;21(2):111-23 **CREST studies** part funded by the European Research Council.<br>- **Beatty S et al.**The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2000;45(2):115-34.<br>- **Berendschot T** et al. Influence of lutein supplementation on macular pigment, assessed with two objective techniques. Invest. Ophthalm. Vis. Sc. 41, 3322-3326 (2000)<br>- **Bone RA,** Landrum JT, Cao Y, Howard AN, Alvarez-Calderon F. Macular pigment response to a supplement containing meso-zeaxanthin, lutein and zeaxanthin. Nutr Metab (Lond). 2007;4:12.<br>- **Connolly EE**, Beatty S, Thurnham DI, Loughman J, Howard AN, Stack J, et al. Augmentation of macular pigment following supplementation with all three | |

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| | | | | macular carotenoids: an exploratory study. Curr Eye Res. 2010;35(4):335-51<br>- **Dawczynski J, et al.** Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: **The LUTEGA study**. *Graefes Arch Clin Exp Ophthalmol*. 2013;251:2711-2723.<br>- **LaRowe TL et al.** Macular density and are-related maculopathy in the Carotenoids in Age-Related Disease Study. Ophthalmology. 2008 May;115(5):876-883<br>- **Loughman** J, Nolan JM, Howard AN, Connolly E, Meagher K, Beatty S. The impact of macular pigment augmentation on visual performance using different carotenoid formulations. Invest Ophthalmol Vis Sci. 2012;53(12):7871-80.<br>- **Ma** L, Liu R, Du JH, Liu T, Wu SS, Liu XH. Lutein, Zeaxanthin and Meso-zeaxanthin Supplementation Associated with Macular Pigment Optical Density. Nutrients. 2016;8(7)<br><br>By omitting such important and relevant evidence will skew any conclusions drawn which may lead to unintentional inaccurate recommendations and guidance for the medical community to follow, which may ultimately be detrimental to the patient which is of great concern. | |
| Alliance Pharmaceuticals | Full | 68<br>69 | Line 1-41 | Recommendations given by NICE on the subject of vitamin supplementation appear to only include 1 study as the basis per each recommendation to the exclusion of all other studies of | Thank you for your comment. The protocol for this question (as specified by the guideline committee) was written based on the hierarchy of evidence, with |

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| | | | Line 1 - 6 | value (*please refer to comment number 2 above*). We believe that NICE recommendations should be based on the totality of eligible evidence and include all studies within relevant recommendations based on the body of evidence available. | randomised controlled trials being the 'gold standard' type of evaluation study. Non-randomised evidence, including observational studies, is of lower quality and so would only be included if no data from RCTs were available. In this particular area, randomised controlled data were identified, therefore it was not considered necessary to move down the hierarchy of evidence with lower-quality study types.<br>RCTs were agreed by the committee to provide the most robust evidence, and therefore the most appropriate study design on which to base recommendations. |
| Alliance Pharmaceuticals | Full | 69<br>70<br><br>71<br><br><br>71 | Line 8<br>Line 43-45<br><br>Line 7 – 9<br><br><br><br>Line 22-25 | Economic modelling appears to be flawed and we are concerned by the recommendation made on the basis of this. The review states that it is based on two, "***partially applicable cost-utility analyses with very serious limitations"***<br>***"The committee agreed that it was difficult to relate the 2 US-based cost-utility analyses to the NHS perspective as the pricing and reimbursement structures are widely different."***<br>But despite this, a benefit is still shown, ***"….the intervention was reported to confer an extremely small benefit of only 0.004 additional QALYs compared with standard treatment."***<br>The committee does not take into account the calculated QALY and flawed cost utility analysis and goes on to state that vitamin supplements are unlikely to represent value for money, as such:<br>***"On a balance of these considerations, the committee agreed that it was unlikely to represent good value for*** | Thank you for your comment. The committee discussed the 2 economic evaluations identified in the evidence review, and agreed that the study findings were not easily transferable to the NHS. The committee noted the gain of 0.004 QALYs reported by Rein *et al.* (2007), but was sceptical of this result. These uncertainties are reflected in the committee's conclusion. The committee agreed that a research recommendation for a randomised study in this area was appropriate to reduce the uncertainty and further support the evidence base.<br><br>The committee was also presented with evidence from a recent cost–utility analysis by Lee *et al.* (2017), which evaluated the AREDS supplement based on AREDS trial data. This UK study concludes that the supplement |

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| | | | | ***money to offer an intervention with an uncertain – but, in any event, limited – effect on people's quality of life."*** This recommendation does not reflect what was said and the conclusion does not reflect what is already known<br>We are able to provide an economic model which has been independently produced by Prof. Nolan based on all the relevant published studies and is relevant to a UK population which we would be happy to share if this might assist your economic model? Please contact Medical Affairs Manager at Alliance Pharmaceuticals to obtain a copy of this analysis: [address removed] | may be a cost-effective use resources; however, it did not resolve the committee's uncertainty regarding the AREDS data, as described in the 'Trade-off between benefits and harms' section.<br><br>Thank you for your offer of providing an economic model, however, this would be considered unpublished work and should therefore not be included as evidence. |
| Alliance Pharmaceuticals | Full | 72 | 4-7 | ***"Research recommendations***<br>***What is the effectiveness and cost-effectiveness of antioxidant and zinc supplements on AMD disease progression for people with early AMD at high risk of progression?"***<br>Please refer to data in comment number 1-4 and the references for further research which supports this question here, and may even negate the need for it. | Thank you for your comment. The committee, having reconsidered the evidence and comments from stakeholders, agreed that the research recommendation in question remains relevant, as they are unable to make positive clinical recommendations based on the currently available evidence. |
| Bayer PLC | Full<br>Appendix J | 138<br>99 | 44-48<br>2630-2635 and elsewhere | The draft guideline concludes that bevacizumab, injected every 2 months, regardless of whether an eye is the better or worse-seeing eye, and including eyes with VA better than 6/12 is the optimal strategy. However, looking at the studies included in the NMA, it appears that there is only one trial that investigated bevacizumab 2-monthly. This was a small single centre study with only 64 patients included in the bevacizumab 2-monthly arm. It was also noted in the network meta-analysis report (page 15, appendix G) that that the result for bevacizumab given at 2- | Thank you for your comment. The relative effectiveness of bevacizumab given every 2 months is not solely informed by the trial described in your comment. It is instead formed by every aspect of the evidence network that provides data on bevacizumab or continuous treatment regimens (or both) compared with something else. The weight of this additional data neutralises the unexpectedly positive result of the individual trial. The 95% credible interval for 2-monthly |

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| | | | | monthly intervals is 'unexpectedly positive' when taken from this trial, and that it is better than that reported for monthly treatment.<br>Similar reasons were given for the exclusion of TREX and PRNX regimens from the base-case (p136 full guideline): *"Neither 'treat-and extend' regimens,… nor 'PRN-and-extend' regimens are included in our base-case analysis, owing to their reliance on individual trials with relatively small samples. The limited evidence base means our network meta-analysis predicts both approaches to be superior to routine monthly treatment, which is not consistent with the expected dose-response relationship."*<br>The same approach should be applied to bevacizumab 2-monthly for consistency, and this regimen should be removed from the base-case. | bevacizumab (Appendix G, Figure 3) shows that there is significantly less uncertainty in its point estimate than would have been the case had it been informed by the 64-person trial alone.<br><br>The evidence for TREX and PRNX was much less central to the network of evidence. While the synthesis model produced robust estimates of the relative effectiveness of the *agent* used, it was only able to produce highly uncertain estimates attributable to the *regimens*, which were informed entirely by those individual trials with small samples.<br><br>This has now been resolved, to an extent, for TREX. 1-year results from the TREND study (NCT01948830) are now available on clinicaltrials.gov, and an accepted, peer-reviewed trial report has been made available to us in academic confidence. The TREX-AMD study (NCT01748292) has also now reported 2-year follow-up data. These data reduce uncertainty regarding the relative effectiveness of treat-and-extend posology (in particular the large TREND study). These were therefore considered by the guideline committee, and have been included in our clinical evidence synthesis and economic modelling. |

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| | | | | | The relative effectiveness estimates of providing treatment accordingly to a TREX regimen are now sufficiently robust and plausible that they are included in the base case economic analysis. |
| Bayer PLC | Full | 138 | 41-43 | The results of the cost-utility analysis report that "*On average, a patient receives more injections in total when treated with aflibercept than with ranibizumab*."<br>However, this is not supported by the results of large phase III studies (VIEW 1&2) including 2457 patients, which showed that the dosing frequency with aflibercept can be reduced from monthly to 2-monthly with no impact on outcomes. There is an absence of evidence on such a scale for ranibizumab. Furthermore, a post-hoc analysis of the follow-up period of the VIEW studies (weeks 52-96), where both aflibercept and ranibizumab were administered in a 'capped PRN' regimen, reported a lower number of injections in the aflibercept 2mg groups as compared to the ranibizumab group. Patients receiving ranibizumab were also more likely to require frequent dosing (≥6 injections) compared to patients receiving aflibercept (2mg). The authors concluded "these finding suggest that patients with greater disease activity may require fewer injections using intravitreal aflibercept."[32]<br>On page 90 of Appendix J it clarifies that the fewer injections associated with ranibizumab versus aflibercept reflects a higher discontinuation rate with ranibizumab. This should be mentioned in this section of the full guideline.<br>(32) Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD et al. Intravitreal aflibercept injection | Thank you for your comment. We have made the suggested clarification to the full guideline. |

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| | | | | for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014; 121(1):193-201. | |
| Bayer PLC | Full | 146 | 2-3 | The PAS section of the economic evaluation states that *"strategies that use aflibercept or ranibizumab continue to produce ICERs that exceed typical cost-effectiveness thresholds"*<br>We find it of concern that the currently presented analyses question the conclusions of the STAs for ranibizumab and aflibercept in terms of cost-effectiveness.<br>The technology appraisal (TA) for aflibercept solution for injection for treating wet age-related macular degeneration found it to be a cost-effective use of NHS resources, and although the methodology differs, the guideline should not appear to undermine the TA recommendations.<br>The STA process is incredibly rigorous and focused, and the economic model developed for TA294 was extensively tested by the manufacturer and critiqued by the academic review group and the appraisal committee. | Thank you for your comment. It is not surprising that the economic model for this guideline produces results that differ to other analyses, given the differences in this model in terms of the comprehensiveness of the strategies included and the input data used. The key differences are described in Section J.5.7.4 of Appendix J. However, please note that the model has been revised following consultation, as described in detail in other responses and in Appendix J. The revisions made are data-driven, with the availability of additional clinical evidence and the use of more robust and plausible assumptions regarding long-term treatment and effectiveness. Revised model results have therefore been generated, and results are reported accordingly. |
| Bayer PLC | Full | 153 | 28-32 | The guideline states that *"extending current practice to treat eyes with visual acuity better than 6/12 consistently produced additional QALYs…"* (p166 clinical guideline), however goes on to state that extending treatment with aflibercept and ranibizumab *"was associated with ICERs in excess of £20,000 per QALY gained, even when evaluated at their PAS prices".*<br>If the most appropriate analyses are considered (see comment 16) then we believe aflibercept would be cost-effective for this | Thank you for your comment. Additional analyses comparing the treatment of late AMD (wet active) at visual acuity better than 6/12 with no treatment have been undertaken. The revised model generally finds extending treatment this way to have an ICER of less than £20,000 per QALY gained compared with an otherwise identical strategy treating between 6/12 and 6/96, when treatments are evaluated at their list prices. |

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| | | | | group. These analyses should be undertaken and the results reported. | This becomes the case for all main treatment strategies when the discounted, confidential prices are used. For more detail, please refer to Appendix J. |
| Bayer PLC | Full | 156 | Table 47 | There are now two UK retrospective data analyses from electronic medical records that have included results from people with visual acuity >6/12 treated with aflibercept.[5;6]<br>One study (210 eyes) showed a small decline in VA (-2 letters, significance not reported), [5] the other (348 eyes) reported no significant difference (difference not reported),[6] but in both, this group maintained better visual outcomes than treatment groups with worse baseline vision.<br>The conclusion from one of these publications is that *"It is particularly important to improve the number of patients who seek treatment early and can access treatment because the better the starting vision, the more likely a patient is to maintain useful vision."*[5] These publications should be considered so that the full body of clinical evidence has been evaluated.<br>(5) Talks JS, Lotery AJ, Ghanchi F, Sivaprasad S, Johnston RL, Patel N et al. First-Year Visual Acuity Outcomes of Providing Aflibercept According to the VIEW Study Protocol for Age-Related Macular Degeneration. *Ophthalmology* 2016; 123(2):337-343.<br>(6) Lee AY, Lee CS, Egan CA, Bailey C, Johnston RL, Natha S et al. UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice. *Br J Ophthalmol* 2017. | Thank you for your comment, and for bringing these references to our attention. As you correctly state, the Lee 2017 study does not report visual acuity changes for people with better than 6/12 vision at baseline, and therefore this study does not met the criteria for inclusion within the review.<br>For the Talks study, again as you correctly state, no standard deviations or measures of dispersion are reported around the mean estimate, and therefore it is not possible to construct a confidence interval around or assess the confidence we have in the findings reported. For this reason, this study has also been excluded from the review.<br>More generally, the committee agreed the evidence supported that groups with better visual outcomes at baseline will, on average, maintain those better visual outcomes compared to people with worse baseline vision, and that anti-VEGF treatment is clinically effective in people with baseline vision better than 6/12. They therefore agreed the key issue was around the cost-effectiveness of treatment in this population, something extensively analysed in the economic model used in the pharmacological management section of the guideline. |

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| | | | | | The recommendations around treatment in people with visual acuity better than 6/12 were based primarily on the results of that analysis, with the committee's reasoning behind those recommendations given in section 10.2.5 of the full guideline. |
| Bayer PLC | Full | 166 | Anti-VEGF recommendations | The full guideline includes language that is emotive and opinion based e.g. *"The committee agreed that the new model – along with other published economic evidence – showed that treatment with bevacizumab would be cost effective when compared with aflibercept and ranibizumab, and that it would ideally like to make a recommendation in favour of bevacizumab, especially as doing so would enable it to recommend that treatment should be extended to eyes with acuity better than 6/12 (see above)"*). This is not appropriate within the remit of an evidence based clinical guideline and should be removed from the 'evidence to recommendations' section. | Thank you for your comment. The committee have reviewed the wording of the text cited and agreed that it is evidence based and reflects their discussion. The 'evidence to recommendations' sections of the guideline are explicitly intended to capture the committee's interpretation of the evidence.<br>Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, |

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| | | | | | it does not amount to an approval of or a recommendation for such use. |
| Bayer PLC | Full | 170 | 25-26 | Treat and extend regimens should be included in the guideline. There is a recently completed phase 4 study investigating the efficacy of aflibercept with two different approaches of Treat and Extend dosing regimens in Japanese subjects with neovascular (wet) Age-related Macular Degeneration (wAMD) (ALTAIR) https://www.clinicaltrials.gov/ct2/show/NCT02305238. The results of this trial will be presented at EURETINA 2017: http://www.euretina.org/barcelona2017/programme/free-papers-details.asp?id=13292&day=0, and showed that "*two different interval approaches of T&E dosing regimens of IVT-AFL demonstrated significant visual acuity gains and CRT improvement. Majority of patients achieved an intended interval of 12 weeks and more at the last visit.*" The results of this trial should be considered for inclusion in the final guideline. | Thank you for your bringing these data to our attention. Neither study appears to have been published in a peer-reviewed journal at this time, meaning it is not possible to incorporate them into our evidence synthesis.<br>However, as highlighted by other stakeholders, 1-year results from the TREND study have now been published. The TREX-AMD study (NCT01748292) has also now reported 2-year follow-up data. These data reduce uncertainty regarding the relative effectiveness of treat-and-extend posology (in particular the large TREND study). These were therefore considered by the guideline committee, and have been included in our clinical evidence synthesis and economic modelling. |
| Bayer PLC | Full | 172 | Table 49 | The results of the PLANET study have recently been published in conference abstracts[7;8] and are expected to be published in full in Q4 2017. These should be considered for inclusion in the final guideline.<br>The aim of the PLANET study was to evaluate the efficacy, safety and tolerability of aflibercept monotherapy compared with aflibercept plus PDT in patients with PCV. The results show that aflibercept monotherapy (+10.7 letters) was non-inferior to aflibercept plus PDT (+10.8 letters) and more than 80% of patients had no signs of polyp activity at week 52. | Thank you for bringing this evidence to our attention. As the study has not been published in a peer-reviewed journal at this time, it has not been incorporated into the evidence for this guideline. This will be reviewed in future as part of the regular NICE surveillance of evidence that might affect existing guidance. |

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| | | | | These results are in support of recommendations 1.5.11 and 1.5.12.<br>(7) Lee WK, Ogura Y, Iida T, Chen SJ, Wong TY, Mitchell P, Zhang E, Leal S, Ishibashi T. Intravitreal aflibercept for the treatment of polypoidal choroidal vasculopathy. The 3rd Asia-Australia Congress on Controversies in Ophthalmology (COPHy AA). February 2017. Available from: http://www.comtecmed.com/cophy/aa/2017/Uploads/Editor/List%20of%20Posters/14.pdf. Last accessed 24/08/2017.<br>(8) Lee WK, Ogura Y, Iida T, Chen SJ, Wong TY, Mitchell P, Ishibashi T, Zhang E, Leal S. Efficacy and Safety of Intravitreal Aflibercept in Polypoidal Choroidal Vasculopathy: 12-Month Results of the PLANET Study. ARVO 2017 Annual Meeting. May 2017. Available from: http://www.arvo.org/webs/am2017/sectionpdf/RE/Session%20207%20AMD%20and%20anti-VEGF%20therapy.pdf. Last accessed 24/08/2017 | |
| Bayer PLC | Full | 181 | Table 51 | We are aware of several further publications which appear to meet the eligibility criteria as outlined in Appendix C, e.g. which evaluate outcomes for patients who have switched from ranibuzumab or bevacizumab to aflibercept, and which do not appear to have either been included in the evaluation, nor listed as excluded in Appendix F.[9-23] These publications should be considered so that the full body of clinical evidence has been evaluated. Furthermore, there are three publications listed as excluded which we believe may meet the inclusion criteria, presenting relevant subgroups.[24-26] | Thank you for your comment and for supplying these references. After checking of these references, a number have been agreed as meeting the criteria for inclusion in the review, and the guideline and appendices have been updated accordingly.<br>For the studies not included; the Messenger 2014 and Nixon 2017 study was excluded as it did not report measures of dispersion (such as standard deviations) alongside mean changes in visual acuity. The Pfau 2016 study was excluded as not being reported in |

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| | | | | (9) Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol* 2013; 156(1):15-22.<br>(10) Chan CK, Jain A, Sadda S, Varshney N. Optical coherence tomographic and visual results at six months after transitioning to aflibercept for patients on prior ranibizumab or bevacizumab treatment for exudative age-related macular degeneration (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc* 2014; 112:160-198.<br>(11) Gokce G, Durukan AH, Koylu MT, Kucukevcilioglu M. Efficacy of aflibercept on exudative age-related macular degeneration in patients exhibiting complete ranibizumab resistance and tachyphylaxis. *Arq Bras Oftalmol* 2016; 79(6):384-389.<br>(12) Grewal DS, Gill MK, Sarezky D, Lyon AT, Mirza RG. Visual and anatomical outcomes following intravitreal aflibercept in eyes with recalcitrant neovascular age-related macular degeneration: 12-month results. *Eye (Lond)* 2014; 28(7):895-899.<br>(13) Hariri A, Diniz B, Fou LV, Lam LA, Nittala MG, Sadda SR. Quantitative OCT subanalysis of eyes with choroidal neovascularization switched from multiple injections of bevacizumab or ranibizumab to intravitreal aflibercept. *Ophthalmic Surg Lasers Imaging Retina* 2015; 46(2):195-200. | English. The Homer 2015 study was already included within the draft version of the guideline<br><br>The committee agreed that the overall conclusion of the review, that there was no robust evidence that switching treatment led to meaningful improvements for patients, was not changed by this new evidence, and therefore the committee agreed not to make any changes to the current recommendations. |

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| | | | | (14) Hatz K, Prunte C. INTRAVITREAL AFLIBERCEPT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH LIMITED RESPONSE TO RANIBIZUMAB: A Treat-and-Extend Trial. *Retina* 2017; 37(6):1185-1192.<br>(15) Homer N, Grewal DS, Mirza RG, Lyon AT, Gill MK. Transitioning to intravitreal aflibercept following a previous treat-and-extend dosing regimen in neovascular age-related macular degeneration: 24-month results. *Eye (Lond)* 2015; 29(9):1152-1155.<br>(16) Jorstad OK, Faber RT, Moe MC. Two-year functional and anatomical results after converting treatment resistant eyes with exudative age-related macular degeneration to aflibercept in accordance with a treat and extend protocol. *Acta Ophthalmol* 2017.<br>(17) Maksys S, Richter-Muksch S, Weingessel B, Vecsei-Marlovits PV. Short-term effect of aflibercept on visual acuity and central macular thickness in patients not responding to ranibizumab and bevacizumab. *Wien Klin Wochenschr* 2017; 129(9-10):351-357.<br>(18) Nixon DR, Flinn NA. Evaluation of contrast sensitivity and other visual function outcomes in neovascular age-related macular degeneration patients after treatment switch to aflibercept from ranibizumab. *Clin Ophthalmol* 2017; 11:715-721.<br>(19) Pfau M, Fassnacht-Riederle HM, Freiberg FJ, Wons JB, Wirth M, Becker MD et al. [Switching Therapy from Ranibizumab and/or Bevacizumab to Aflibercept in | |

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| | | | | Neovascular Age-Related Macular Degeneration (AMD): One-Year Results]. *Klin Monbl Augenheilkd* 2016; 233(8):945-950.<br>(20) Ruiz RJ, Pascual-Camps I, Cuellar-Monreal MJ, Dolz-Marco R, Fenoll MA, Font-Noguera I et al. Aflibercept in exudative age related macular degeneration refractory to ranibizumab. *Arch Soc Esp Oftalmol* 2015; 90(12):566-571.<br>(21) Seguin-Greenstein S, Lightman S, Tomkins-Netzer O. A Meta-Analysis of Studies Evaluating Visual and Anatomical Outcomes in Patients with Treatment Resistant Neovascular Age-Related Macular Degeneration following Switching to Treatment with Aflibercept. *J Ophthalmol* 2016; 2016:4095852.<br>(22) Tiosano L, Segal O, Mathalone N, Pollack A, Ehrlich R, Klemperer I et al. Aflibercept as a Second Line Therapy for Neovascular Age Related Macular Degeneration in Israel (ASLI) study. *Eye (Lond)* 2017; 31(6):890-898.<br>(23) Wykoff CC, Brown DM, Maldonado ME, Croft DE. Aflibercept treatment for patients with exudative age-related macular degeneration who were incomplete responders to multiple ranibizumab injections (TURF trial). *Br J Ophthalmol* 2014; 98(7):951-955.<br>(24) Hall LB, Zebardast N, Huang JJ, Adelman RA. Aflibercept in the treatment of neovascular age-related macular degeneration in previously treated patients. *J Ocul Pharmacol Ther* 2014; 30(4):346-352. | |

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| | | | | (25) Major JC, Jr., Wykoff CC, Croft DE, Wang R, Mariani AF, Lehmann AE et al. Aflibercept for pigment epithelial detachment for previously treated neovascular age-related macular degeneration. *Can J Ophthalmol* 2015; 50(5):373-377.<br>(26) Messenger WB, Campbell JP, Faridi A, Shippey L, Bailey ST, Lauer AK et al. Injection frequency and anatomic outcomes 1 year following conversion to aflibercept in patients with neovascular age-related macular degeneration. *Br J Ophthalmol* 2014; 98(9):1205-1207. | |
| Bayer PLC | Short<br>Full | 11<br>198 | 1-5<br>1-4 | Recommendation 1.5.14/31 suggests that switching should only be considered if there are practical reasons for doing so, and that the *"clinical benefits are likely to be limited."* We have provided citations of additional publications not currently considered,[9-26] and the vast majority of these publications show that switching appears to improve anatomic outcomes, and maintain/stabilise visual acuity for the group of patients who are resistant to or not reponding to other anti-VEGF treatments. It should also be considered that the reason for switching in these patients is resistance to, or lack of response to current treatment, and therefore maintainance or stabilisation of visual acuity is a legitimate goal, and can be seen as a positive outcome for these patients. We suggest therefore, that for patients resistant to or not responding to their current anti-VEGF treatment, switching to another anti-VEGF may offer clinical benefit. | Thank you for your comment. At its post-consultation meeting, the committee reviewed evidence for this question (including some additional observational studies highlighted by stakeholders in consultation). It agreed that it had been correct in its original conclusion that there is no convincing evidence of meaningful acuity benefit associated with switching anti-VEGF treatment. The committee noted that it was particularly difficult to draw reliable conclusions from before–after studies (which form the majority of the evidence-base), citing evidence that any benefits observed in such studies are very likely to represent regression to the mean (Ferris et al. 2017). Therefore, the committee agreed to retain its recommendation that switching should only be considered if there are practical reasons for doing so. However, it did not believe that it had seen evidence of harm from switching, nor is it clear that switching results in wasted costs (compared with |

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| | | | | | maintaining the original therapy); therefore, the committee agreed that it would not be appropriate to make a strong 'do not' recommendation, in this case. |
| Bayer PLC | Short<br>Full | 11<br>198 | 8<br>7 | Recommendation 1.5.16/33 states "*stop anti-VEGF treatment if the eye develops late AMD (wet inactive)*", but does not define the criteria that should be considered. This is however outlined in the full guideline on page 46 and in Appendix K page 3, and we suggest it would be helpful to either incorporate this into the recommendation or provide a cross-reference to the appropriate section of the full guideline. | Thank you for your comment. The definition of late AMD (wet inactive) is provided in recommendation 1.1.1. |
| Bayer PLC | Short<br>Full | 18<br>9 | 1-4<br>41-43 | The guideline context states *that "estimates indicate that around 26,000 people develop neovascular AMD that that is eligible for treatment in the UK each year (HSCIC, 2014)"* It is difficult to be sure what the reference is for this estimate as 'HSCIC 2014' does not appear to be included in the reference list (Appendix I). However we believe that this is likely to be: Health and Social Care Information Centre (HSCIC). Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics. Published 21 January 2014. Available at: http://content.digital.nhs.uk/catalogue/PUB13413/use-nice-app-med-nhs-exp-stat-eng-12-rep.pdf. If this is the case, we suggest that the underlying references for the incidence of macular degeneration should be updated with the more recent publication by Owen et al. 2012 as cited when discussing the prevalence. Also we note that the figure of 26,000 was reported to relate to England only and so should be extrapolated to the UK population. | Thank you for this information. The committee agreed that it would be helpful to provide an updated estimate of incidence. We have revised the text to reference the suggested study. |

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| | | | | It is also interesting to note that the reported prevalence of late AMD in adults aged 65 years and older estimated by Owen et al[1] (4.8%), has recently been supported by a UK cross-sectional study by Wilde et al 2017[2] which reported a prevalence of 4.6% in this population. We suggest that this publication is also cited to add weight to the statements.<br>(1) Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol* 2012; 96(5):752-756.<br>(2) Wilde C, Poostchi A, Mehta RL, MacNab HK, Hillman JG, Vernon SA et al. Prevalence of age-related macular degeneration in an elderly UK Caucasian population-The Bridlington Eye Assessment Project: a cross-sectional study. *Eye (Lond)* 2017; 31(7):1042-1050. | |
| Bayer PLC | Short<br>Full | 7<br>109 | 19-21<br>1-3 | Recommendation 1.4.6/9 states that people should be 'urgently' referred to hospital eye services, but does not specify a timeframe for this referral. We note from page 106 of the full guideline that an appropriate target was considered by the committee to be 'a maximum of 7 days from presentation to referral', and also that an 'urgent' referral is "*universally understood as one that should be made within 7 days*." We reject that this would be 'universally understood', and suggest that a timeframe should be included in this recommendation so that it is clear what is intended by 'urgent'. We note the concerns regarding setting a shorter specified timeframe of 1 working day, and also of explicitly specifying a 7-day target, therefore we suggest that an appropriate target may be 5 working days. | Thank you for your comment. Following discussion of stakeholder feedback, the committee agreed that to improve the clarity of the recommendations, the time from suspicion of late AMD (wet active) to referral should be defined as 1 working day, with an additional clarification that emergency referral is not required. |

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| Bayer PLC | Short<br>Full | 8<br>109 | 3-5<br>11-13 | Recommendation 1.4.10/12 states that treatment should be offered with 21 days of referral to the hospital eye service. This extends the timeframe from that currently recommended by the Royal College of Ophthalmologists (2 weeks). As the committee acknowledge on page 106 of the full guideline, the evidence provides a clear mandate for the swiftest possible patient journey from suspicion to treatment of late AMD (wet active). It is not therefore acceptable to make allowances for capacity issues and extend this timeframe; this could lead to a delay in treatment for people newly diagnosed with AMD which in turn could have an important impact on their visual acuity. Clinical guidelines should provide aspirational recommendations based on the available evidence, with the intention that they will drive improvements in care, and should not accede to 'compromises' due to resourcing issues. | Thank you for your comment. Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise the chances of preserving vision. |
| Bayer PLC | Short<br>Full | 8-9<br>169 | 26-6<br>10-17 | Bayer strongly supports the inclusion of recommendation 1.5.4/21. It is important that this clinical guideline is consistent with and clearly reflects European law in this area, in particular the Human Medicine Regulation 2012, alongside the guidance issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and the General Medical Council (GMC) reiterating this legal position. | Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers |

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| | | | | | to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| Bayer PLC | Short<br>Full | 9<br>169 | 7-9<br>18-20 | Recommendation 1.5.4/21 includes that *"no clinically significant differences in effectiveness and safety between aflibercept, ranibizumab and bevacizumab have been seen in the trials considered by the guideline committee."* The 'evidence to recommendations' section of the full guideline also states that *"the committee agreed that the adverse event risks of different treatments were sufficiently similar and low for safety outcomes not to be crucial to their decision making."*<br>Bevacizumab is formulated for intravenous administration and is not manufactured to ophthalmology standards. For unlicensed administration into the eye, individual vials of bevacizumab are often repackaged or compounded into multiple units. The quality, safety and efficacy of such unlicensed products is uncertain, and whilst clinical trials have investigated bevacizumab for the treatment of wAMD, the data generated on safety and efficacy may not be applicable to other sources of reformulated bevacizumab for ocular use.<br>The compounding process can increase the risk of contamination, and there have been multiple reports of adverse events after the injection of compounded bevacizumab into the eye, including serious intraocular infections. The bevacizumab | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use.<br>The evidence reviewed by the committee included a scenario analysis in which the likelihood of |

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| | | | | Summary of Product Characteristics warns of this safety risk: *"Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness."* Such reports include a precautionary recall of 27 Avastin batches by Moorfields Pharmaceuticals after an increased number of reports of suspected sterile endophthalmitis were received in 2012.[3]<br>A publication by Palmer et al (2013) also showed variable quality of bevacizumab repacked into pre-filled plastic syringes among five different compounding pharmacies in the UK.[4]<br>Therefore it is imperative that an additional statement is included to clarify that the trial results may not be generalisible to those achieved in clinical practice, and to remind prescribers that inappropriate handling and storage could lead to serious adverse outcomes for patients.<br>An important aspect of the drug licensing process is to ensure consistent quality of manufacture for licensed medicines, such that patients and prescribers can be confident that the safety and efficacy of marketed products can be directly related to the | endophthalmitis associated with bevacizumab in the model was increased to an implausibly high level (20% per year). This demonstrated that this had no material effect on the net balance of benefits and harms between the different agents (see appendix J.5.6.4). Therefore, it concluded that the evidence was robust to any uncertainty, in this area. |

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| | | | | data produced by the clinical trials used in the regulatory process.<br>(3) PRNewswire. Patient Safety Group Calls for Urgent Action on Unlicensed Medicines. 20/03/2012. Available from: http://www.prnewswire.co.uk/news-releases/patient-safety-group-calls-for-urgent-action-on-unlicensed-medicines-144603055.html. Last accessed 24/08/2017.<br>(4) Palmer JM, Amoaku WM, Kamali F. Quality of bevacizumab compounded for intravitreal administration. *Eye (Lond)* 2013; 27(9):1090-1097. | |
| Bayer PLC | Appendix J | general | general | As aflibercept and ranibizumab are available to the NHS with confidential discounts we believe there is a large overemphasis on the list price cost-effectiveness analyses. As the analyses are currently presented there is a significant risk of misleading the reader.<br>As list price cost-effectiveness analyses are of no relevance to the NHS it would seem more appropriate to lead with PAS price analyses. Should this not be considered appropriate for some reason we would suggest prominently stating upfront that analyses based on list prices are not reflective of value to the NHS given the availability of both treatments at confidential discounts. The reader should be referred earlier to the PAS price analyses. | Thank you for your comment. It was not possible to present a full array of results with the confidential discounts of aflibercept and ranibizumab in the guideline documentation, as doing so would potentially allow a reader to estimate those discounts, thereby breaching their confidentiality.<br>However, the committee was presented with all analyses conducted using the confidential prices to inform decision-making. The committee therefore considered the evidence most relevant to the NHS in making recommendations.<br>While the results in Appendix J were obtained using list prices, the decision to present them was taken to: (1) ensure full transparency in the economic modelling work undertaken, and (2) to allow the direction and magnitude of changes in results in scenario analyses and sensitivity analyses to be scrutinised. |

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| | | | | | To add further clarity we have now emphasised, at the beginning of the results section, that list price results are presented first, followed by those based on PASs. We have also ensured that all table and figure captions state whether results are based on list or PAS prices.<br>We have also been able to include more information on the PAS-price analyses. However, we remain cautious to protect the confidentiality inherent in these figures. |
| Bayer PLC | Appendix J | general | general | Given that bevacizumab is not licenced, and licensed treatments are available for AMD, we consider that there is too much focus on bevacizumab in the cost-effectiveness analyses. Bevacizumab should only be included in a scenario analyses and not the 'base-case' analyses. Including bevacizumab as the treatment against which all others are referenced in terms of cost-effectiveness does not seem logical given the overall recommendation that it cannot be prescribed where another licensed product meets the need. | Thank you for your comment. We took the approach of first presenting the largest possible array of theoretically feasible strategies, then systematically reducing the set of strategies until reaching the set that most closely represents current practice. Cost–utility results with bevacizumab omitted from the decision space are presented as part of this process.<br><br>This decision was taken to ensure full transparency in the economic modelling work undertaken. |
| Bayer PLC | Appendix J | general | general | Following the comments above, we believe that the most relevant analyses for decision making should include:<br>- PAS prices<br>- only regimens on product labels<br>- exclude 'no treatment' (no treatment is no longer a reasonable clinical option)<br>exclude unlicensed treatments | Thank you for your comment. Results for the decision-set specified here are available in the full guideline and appendix J (details are however limited because confidentiality is asserted regarding the inputs to the PAS-price analyses).<br><br>We took the approach of first presenting the largest possible array of theoretically feasible strategies, then systematically reducing the set of strategies until |

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| | | | | | reaching the set that most closely represents current practice. Cost–utility results with bevacizumab omitted from the decision space are presented as part of this process.<br><br>This decision was taken to ensure full transparency in the economic modelling work undertaken. |
| Bayer PLC | Appendix J | 25 | 783-5 | The text states that "Effectiveness data were derived from the VIEW trials and an indirect comparison conducted by Kliejnen Systematic Reviews as VIEW did not compare aflibercept with ranibizumab." This statement is not accurate. The VIEW trials did directly compare aflibercept with ranibizumab; the indirect comparison was carried out to compare aflibercept 2 mg every 8 weeks with ranibizumab 0.5 mg in a 'treatment as needed' regimen which was not included in the trial. | Thank you for highlighting this oversight, which has now been rectified. |
| Bayer PLC | Appendix J | 142 | Network meta-analysis and transition probabilities | The economic evaluation includes a whole range of treatment regimens that are off-label and not used in clinical practice. The economic analyses give unwarranted focus to these off-label regimens. Their inclusion affects the cost-effectiveness of regimens used in clinical practice and which are supported by strong evidence bases. We believe these unlicensed regimens should only form part of exploratory scenario analyses and not the main analyses on which economic decisions are based. | Thank you for your comment. Randomised controlled trials exist for regimens that represent off-label use of some treatments. We took the approach of estimating separate treatment effects for the intervention used and for the dosing schedule used, allowing us to capture all theoretical treatment strategies in our evidence synthesis and economic model.<br><br>This decision was taken to best utilise the available clinical evidence, to determine the relative effectiveness of different dosing regimens that could theoretically be used. |

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| | | | | | We then took the approach of first presenting the largest possible array of theoretically feasible strategies in our economic evaluation, before systematically reducing the set of strategies until reaching the set that most closely represents current practice. Cost–utility results with off-label treatment schedules omitted from the decision space are presented as part of this process.<br><br>This decision was taken to ensure full transparency in the economic modelling work undertaken. |
| Bayer PLC | Appendix J | 142 | 3481-3484 | A meta-regression approach has been employed to establish the efficacy of each 'agent' and 'characteristic' combination - the explicit assumption in this approach being that the relative effect of each 'characteristic' is shared between the agents.<br>However, the guideline acknowledges that *"This will be a potential simplification if treatment effects are in fact interdependent; say, if the effect attributable to '2-monthly dosing' varies depending on whether the drug being given this way is aflibercept or ranibizumab."*<br>There are data suggesting a plausible difference in durability between the 2 molecules therefore it is inappropriate to make the assumption that the treatment effects are interdependent.<br>The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of ranibizumab.[27] It has been hypothesized that this greater affinity could translate into a | Thank you for raising this issue. In hindsight, the example that you quote from Appendix J was perhaps an unhelpful one for us to use to describe this methodology. This is because the meta-regression does contain separate covariates for treatment frequency that are specific to aflibercept and ranibizumab. Theoretically, separate duration covariates should capture any difference in durability between aflibercept and ranibizumab.<br><br>We have revised our reporting of this methodology by providing a more appropriate example. |

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| | | | | substantially longer duration of action in the eye,[28] thus allowing for less frequent dosing. This is supported by studies showing a greater mean duration of VEGF suppression with aflibercept,[29-31] and by results from large phase III clinical trials (VIEW 1&2) including 2457 patients,[32] which showed that the dosing frequency with aflibercept can be reduced from monthly to 2-monthly with no impact on outcomes. There is an absence of evidence on such a scale for ranibizumab. The VIEW studies also showed that 2-monthly aflibercept (after 3 months loading doses) is non-inferior to monthly ranibizumab in the first year of treatment.[32] Furthermore, a post-hoc analysis of the follow-up period of the VIEW studies (weeks 52-96), where both interventions were administered in a 'capped PRN' regimen reported a lower number of injections in the aflibercept 2mg groups as compared to the ranibizumab group. Patients receiving ranibizumab were also more likely to require frequent dosing (≥6 injections) compared to patients receiving aflibercept (2mg). "*These finding suggest that patients with greater disease activity may require fewer injections using intravitreal aflibercept."*[32]<br>The regimen of ranibizumab administered every 2 months has not been investigated in clinical trials, nor is it commonly used in clinical practice. What is more, a study by Wang X et al.[33] comparing VEGF and ranibizumab concentrations after monthly and 2-monthly ranibizumab injections, concluded that intraocular VEGF suppression with ranibizumab is not sustained to 2 months. | |

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| | | | | This increased durability of aflibercept is in opposition to the assumption that the characteristics are shared between the agents. The effect of this assumption biases against aflibercept, particularly when extended intervals between injections are considered.<br>(27) Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012; 15(2):171-185.<br>(28) Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008; 92(5):667-668.<br>(29) Muether PS, Hermann MM, Droge K, Kirchhof B, Fauser S. Long-term stability of vascular endothelial growth factor suppression time under ranibizumab treatment in age-related macular degeneration. *Am J Ophthalmol* 2013; 156(5):989-993.<br>(30) Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. *Am J Ophthalmol* 2014; 158(3):532-536.<br>(31) Fauser S, Muether PS. Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times. *Br J Ophthalmol* 2016; 100(11):1494-1498. | |

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| | | | | (32) Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014; 121(1):193-201.<br>(33) Wang X, Sawada T, Kakinoki M, Miyake T, Kawamura H, Saishin Y et al. Aqueous vascular endothelial growth factor and ranibizumab concentrations after monthly and bimonthly intravitreal injections of ranibizumab for age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2014; 252(7):1033-1039. | |
| Butterflies Healthcare Ltd | Full | 111 | general | There is no reference to the potential benefit appropriate supplements have been shown by AREDS and AREDS 2 to have in reducing the progression of macular degeneration. | Thank you for your comment. The potential benefits regarding supplements are reviewed and discussed in chapter 6 (strategies for slowing AMD progression).<br>Having reviewed the evidence, the committee agreed that the benefits described in the AREDS RCT could not be relied on as the basis for a positive recommendation. For details of the committee's considerations, please see section 6.2.4). |
| Butterflies Healthcare Ltd | Short | 11 | general | There is no reference to the potential benefit appropriate supplements have been shown by AREDS and AREDS 2 to have in reducing the progression of macular degeneration. | Thank you for your comment. The potential benefits regarding supplements are reviewed and discussed in chapter 6 (strategies for slowing AMD progression).<br>Having reviewed the evidence, the committee agreed that the benefits described in the AREDS RCT could not be relied on as the basis for a positive recommendation. For details of the committee's considerations, please see section 6.2.4). |

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| Central Manchester University Hospital NHS Foundation Trust - Manchester Royal Eye Hospital | Full | 108 | general | A recommendation has been made that treatment be commenced within 21 days of initial referral. We are concerned that this is inappropriate for this urgent sight-threatening disease especially when there is already a long-established target of 14 days set by The Royal College of Ophthalmologists. It would be more beneficial for patients if efforts were made to improve on this not relax it further. The rate of vision loss is not predictable in wet AMD patients and some forms of disease can be rapidly progressive, in particular predominantly classic choroidal neovascular membranes. In the natural history arm of Lucentis PIER study a mean of 5 letters are lost by 1 month. A three week target is too close to this time by which a clnically significant loss of vision of vision may have recurred. Patients waiting for wet AMD treatment are also at risk of devastating sudden macular haemorrhages. Visual outcomes are also potentially worse if treatment initiation is delayed (Rasmussen et al 2015 Acta Ophthalmologica 93:7).<br><br>A 14 day target is well within achievable targets. We are happy to share our own practice through which we are able to triage patients within 48 hours, sometimes even same day and consistently deliver a two week target which we are aiming to bring down further and agree key performance indicators with commissioners. | Thank you for your comment.<br>Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |
| Central Manchester University Hospital NHS | Full | 165 | | The recommendation re: PRN treatment versus treat and extend approach relates primarily to this approach being used in the randomised controlled trial setting. PRN approach is effective in this setting with capacity for tight monthly review but this | Thank you for your comment. The evidence base on which the committee made its recommendations has been focused on randomised, comparative studies. For proactive, treat-and-extend dosing additional data (1 |

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| Foundation Trust - Manchester Royal Eye Hospital | | | | realistically has been historically difficult to deliver in real world practice. We are concerned at the consistent evidence emerging from real world data reports that this approach leads to poorer outcomes which are likely due to the difficulty in delivering necessary capacity for timely review appointments (Tufail et al. 2014. Opthalmology 121(5):1092-101) A treat and extend pro-active approach which limits the number of reviews required and maintains a more pro-active treatment approach has already shown benefits in randomised controlled trials and real world data studies (e.g Arnold et al. 2015 Ophthalmology 122(6):1212-9). Our own experience and audit shows that outcomes achieved during years when a prn reactive approach was the norm are inferior to those achieved since switching to more proactive treatment approaches (initial fixed dosing with Eylea then treat and extend or treat and extend Lucentis) | year from TREND, 2 year from TREX-AMD) have increased certainty regarding its effectiveness. Long-term data regarding treat-and-extend regimens are non-comparative. The randomised data have now been incorporated into our evidence synthesis, such that we now feel this provides the most appropriate estimation of the benefits of treat-and-extend protocols relative to PRN. This shows treat-and-extend to be marginally superior to PRN over 1 year, on average, and slightly inferior to PRN over 2 years, on average. The committee was also aware that treat-and-extend regimens do not appear to be a cost-effective use of NHS resources, when compared with PRN strategies or regimens with regular injections (for example, 2-monthly). |
| Central Manchester University Hospital NHS Foundation Trust - Manchester | Full | 166 | general | The recommendation to remain within the current visual acuity range and wait for patients to lose vision to 6/12 or worse is an opportunity lost in these guidelines.<br>Treating patients whilst they have quality vision before the disease does irreversible damage to their vision, their lifestyle and independence is important. 6/12 vision is the cut off for | Thank you for your comment. The committee considered stakeholder comments and revised health economic modelling of relevance to the upper acuity threshold for initiating anti-VEGF treatment at its post-consultation meeting. It noted that the revised model suggested that, compared with restricting antiangiogenic therapy to the range recommended in TA155 and TA294, offering treatment to eyes with |

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| Royal Eye Hospital | | | | driving legality and withholding treatment until vision is lost from a good baseline level with a clear diagnosis of wet AMD is hard to justify.<br><br>Patients treated at better than 6/12 level do well with treatment and are more likely to maintain good vision on treatment. Their net vision gain will inevitably be less than patients with worse vision because of a ceiling effect but in practice these patients have more to gain from treatment and more to lose from treatment being witheld. If patient treatment is delayed the vision lost may not be recoverable.<br><br>Delaying treatment for health economic reasons is also only delaying the inevitable and moving the time point at which treatment would need initiating anyway by a matter of months. Assuming patients with wet AMD but better than 6/12 start at a baseline of 5-10 letters better than the 6/12 threshold, the natural history arms of the PIER study and ANCHOR study show vision loss of 5 letters at between 1-3 months so the time at which apparently the treatment becomes cost-effective may not be long whilst the patient may suffer long term impairment to wait for this time point. | acuity greater than 6/12 invariably provides benefits at a cost that would conventionally be considered an effective use of resources. However, the committee understood that, unless the agent used was either bevacizumab or very low-intensity ranibizumab, extending treatment was only cost effective compared with something that was, in itself, not cost effective. Because the analysis had convincingly shown that there are many strategies that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation explicitly mandating such an approach. However, the committee noted that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used. |

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| Central Manchester University Hospital NHS Foundation Trust - Manchester Royal Eye Hospital | Full | 176 | general | We disagree that there isn't already sufficient evidence for using PDT and anti-VEGF therapy in combination for patients with confirmed polypoidal disease.<br>This is more prevalent in some racial groups and studies conducted in parts of the world with greater prevalence, the Everest 1 and 2 studies (the Everest 2 study has been presented and will be publishing soon) have shown best outcomes with combination therapy. We also have experience of treating patients local and referred in from the region who have had numerous injections (at significant cumulative expense) before photodynamic therapy after which the injection requirement reduced or was no longer required.<br>Patients with ICG confirmed polypoidal disease could be managed in specialist centres with ICG angiography and photodynamic therapy. Please can NICE clarify whether they would consider treatment in specialist centres with clearly defined protocols based on the Everest studies as part of prospectively audited cohorts an acceptable approach. | Thank you for your comment. The committee discussed the stakeholder comment however it agreed that it could not make an evidence-based recommendation in favour of PDT as an adjunct to anti-VEGF for eyes with PCV. Although it noted that there is some evidence of improvement in surrogate measures of disease activity, no benefit for patients has been demonstrated. In particular, Everest 1 showed no significant differences in visual acuity between people receiving PDT+anti-VEGF or ant-VEGF alone. Indeed, in the meta-analysis combining all types of late AMD (wet active), a significantly lower proportion of people randomised to combination therapy achieved a gain of 15 letters or more in BCVA, and there was no evidence that results were significantly different in the PCV-only stratum (see appendix H.6.3.1). Additionally preliminary data from the PLANET study (see ID267) reinforce the absence of acuity gains with combination therapy, compared with anti-VEGF monotherapy, in PCV. |
| College of Optometrists | Full | General | General | The College of Optometrists welcomes the development of a NICE guideline on age-related macular degeneration (AMD).<br><br>AMD is a very common eye condition and the number of people affected is very likely to increase due to an ageing population. | Thank you for your comment and recognition of the importance of this guidance. |

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| College of Optometrists | Full | 105 | 25 | We welcome the recognition of the evidence regarding the role of optometrists.<br><br>This evidence acknowledges the important role optometrists play in the referral pathway and the importance of an urgent referral once people with suspected late AMD (wet) present to optometrists. | Thank you for your comment and recognition of the importance of evidence regarding the role of optometrists. |
| College of Optometrists | Full | 29 | 42 | We appreciate that the list of examples as listed in the guideline is neither exclusive nor proscriptive, but we would suggest adding Optometrists to the list of examples of suitably trained healthcare professionals able to give intraocular injections. There are examples of suitably trained optometrists providing intraocular injections across the country in hospitals. | Thank you for your comment. The committee agreed that optometrists were a relevant example to add to this list, and the recommendation has been amended accordingly. |
| College of Optometrists | Full | 79 | 6 | We welcome this research recommendation. | Thank you for your comment and endorsement of the recommendation. |
| College of Optometrists | Full | 92 | 18 | We would suggest adding the following research recommendation:<br>- What is the diagnostic accuracy of optometrists in community practice?<br>- Would using OCT in primary practice for diagnosing people with AMD improves that accuracy of diagnosis?<br><br>Why this is important: Committee members used their clinical experience and expertise to consider the potential consequences for both patients and services associated with different diagnosis strategies. The committee agreed by | Thank you for this suggestion. The committee agreed to add a new research recommendation "What is the diagnostic accuracy of OCT offered in primary care?" in line with the suggestion made.<br>The committee also agreed the key issue to address was the accuracy of the tests themselves, rather than the person conducting them, and therefore agreed not to make specific reference to optometrists as part of this recommendation. |

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| | | | | consensus that clinical examination, including slit lamp biomicroscopy, should be used as the first-line diagnostic strategy when people present with any signs or symptoms of AMD. Where the committee discussed the findings of Muen (2011) Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study, a relatively small study looking at diagnostic accuracy of optometrist referral, further research would be needed to ensure the effective and efficient use of community pathways and referral from sight tests. In addition, further research would be required to investigate the impact of the use of OCT in optometric practice on the referral rate and accuracy of wet AMD diagnosis. | |
| College of Optometrists | Short | 12 | 1 | We would suggest adding the following recommendation:<br><br>- Advise people with late AMD (dry) to continue to attend their optometrist for a sight test regularly.<br><br>Clinical monitoring involves the assessment of visual functional and any structural changes to the macula. An optometrist performing a sigh test could detect the onset of new symptoms or visual changes. They have the right clinical knowledge of the symptoms and progression of the disease and a sound understanding of the need to access services promptly when deterioration in vision or distortion is detected. It is important to ensure that people with AMD are monitored and managed in the right part of the care pathway. | Thank you for this suggestion, which the committee agreed was sensible. Accordingly, a bullet-point recommending advice on sight-tests was added to recommendation 1.7.2. |

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| College of Optometrists | Short | 3 | 2 | We welcome this recommendation and clarity of the proposed classification for AMD using table 1.<br><br>The classification is easy to understand while being clinically useful to support decision-making. | Thank you for your comment and endorsement of the recommendation |
| College of Optometrists | Short | 8 | 7 | We welcome this recommendation.<br><br>We would like to suggest that this recommended local pathway also cover feedback and replies to referrals as it will help improving the relevance and the quality of referral letters, which will support the implementation of NHS England RightCare principles ensuring people access the right care, in the right place at the right time.<br><br>We suggest amending the recommendation 1.4.11 as follows:<br><br>"Commissioners and providers should agree a clear local pathway for people with AMD, which should cover:<br>• referral from primary to secondary care, with direct referral preferred<br>• discharge from secondary to primary care, covering ongoing 10 management and re-referral when necessary<br>• **feedback to the primary referring practitioner**." | Thank you for your comment. The committee agree this was an important issue, but also that the evidence available did not allow them to make specific recommendations around feedback to referrers. |

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| Elecktron Eye Technology | Full | **29** | **16-17; 31** | If early-stage AMD is not referred to hospital eye services many patients will not have access to advice concerning preventative measures.<br><br>The NHS should be (and is) concerned with prevention.<br><br>This recommendation should be modified to suggest patients be advised then managed by their local optometrist. This could include advice on lifestyle and diet and measurement/monitoring of macular pigment (MP). | Thank you for your comment. The guideline looked for evidence on effective strategies to slow the progression of AMD. However, on reviewing the evidence, the committee was unable to recommend any such measures as no clear evidence of effectiveness was identified. |
| Elecktron Eye Technology | Full | 34 | 5-7; general | *Effectiveness of supplementation*<br>Retinal carotenoids are known to accumulate in the Fibres of Henle in the central 5 degrees of the retina and are known as macular pigment (MP). (See selected references below.)<br><br>There is a large and substantial literature describing both the effectiveness of retinal carotenoid supplementation and the benefits of increasing and measuring MP which is not considered in these guidelines. Not least of these is the important observation that lutein has powerful anti-inflammatory and antioxidant properties.<br><br>Further to the above, it is well known that many UK-based ophthalmologists advise symptom-free early stage ('dry') AMD patients (currently diagnosed according to drusen) to improve their diet/lifestyle and consider lutein/zeaxanthin supplements. | Thank you for your comment and providing us with information regarding the evidence on supplementation. This protocol as agreed by the guideline committee, was written such that observational data would only be included if randomised controlled data on the effectiveness of supplement were not identified. RCTs were found for this review question, and observational data were therefore not included in the evidence review.<br>As noted within the committee's discussions in the guideline, some supplements are widely available in other countries such as the USA, but there is a lack of evidence on the effectiveness of supplementation in the context of UK health services. |

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| | | | | *Cost effectiveness*<br>It is true that there is less material available on the cost-effectiveness of supplementation, particularly in a state-funded healthcare system such as the NHS.<br><br>Elektron Eye Technology (EET) manufactures the MPS II, the most widely adopted MP screener currently available to eye care professionals. Developed with visual science experts at the University of Manchester and scientifically validated through use in multiple research studies, the MPS II is used both for detecting AMD risk – in the form of low macular pigment optical density (MPOD) – and monitoring the ongoing effectiveness of retinal carotenoid supplementation on at-risk patients and those with early stage AMD. [See comment 3, below, for further discussion of MPOD.]<br><br>Supplementation and macular pigment (MP) screening is widely adopted by primary care eye doctors in the United States with millions of eyes having been successfully screened by the MPS II and many patients having benefited from macular re-pigmentation. (The MPS II is known as 'Quantifeye' in the US.) MP screening/monitoring using MPS II is also growing in the German and South African primary care settings.<br><br>EET is well positioned to participate in the trial of an evidence-based early AMD pathway between optometrists and ophthalmologists in the UK with the aim of assessing the effectiveness/cost-effectiveness of supplements on early stage | |

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| | | | | AMD patients. In addition to technical knowledge, EET is able to draw on scientific expertise from strategic partners in academia and the nutraceutical industry to complement the expertise on the NICE panel.<br><br>Selected references:<br><br>• Kamoshita et al (2016). Lutein acts via multiple antioxidant pathways in the photo-stressed retina. *Nature*, Scientific Reports 6, Article number: 30226<br>• Loane E et al (2008) The rationale and evidence base for a protective role of macular pigment in age-related maculopathy. *Br J Ophthalmol.* Sep;92(9):1163-8<br>• Murray IJ, et al (2013) Visual Acuity changes in early AMD after lutein supplementation; the CLEAR study. *Invest Ophthalmol Vis Sci*. Mar 11;54(3)<br>• Richer SP et al (2011) Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry*. Nov;82(11):667-680.e6<br>• Tian Y et al (2013) The effects of Lutein Supplementation on Blood Plasma Levels of Compliment Factor D, C5a and C3d. *PLoS One*. 8(8): e73387<br>• Van der Veen et al (2009) A new desktop instrument for measuring macular pigment optical density based on a | |

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| | | | | novel technique for setting flicker thresholds. *Ophthalmic Physiol Opt.* Mar;29(2):127-37<br>• Weigert G et al (2011) Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. Oct 17;52(11):8174-8 | |
| Elecktron Eye Technology | Full | 48 | 1 | Low Macular Pigment Optical Density (MPOD) is an established risk factor for AMD. These data are excluded from Table 14 (risk factors) and the wider document.<br><br><u>Selected references:</u><br><br>• Beatty S et al (2001) Macular pigment and risk for age-related macular degeneration in subjects from a Northern European population. *Invest Ophthalmol Vis Sci.* Feb;42(2):439-46<br>• Bernstein et al (2010) The value of measurement of macular carotenoid pigment optical densities and distributions in age-related macular degeneration and other retinal disorders. *Vision Res.* Mar 31; 50(7): 716–728<br>• Nolan et al (2007) Risk factors for age-related maculopathy are associated with a relative lack of macular pigment. *Exp Eye Res* 2007; 84: 61–74 | Thank you for your comment. Our review included pigmentary changes as a factor of interest. However, the cited papers do not meet the eligibility criteria for the relevant review – none presents time-to-event or time-adjusted data on the impact of a risk factor for development or progression of AMD. |
| Elecktron Eye Technology | Full | 69-71 | General | Randomized control trials (RCTs), though commendable have substantial resource implications. | Thank you for your comment. The committee agreed that, in the absence of effective treatments to slow |

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| | | | | There is a need for clear information/guidance for the many millions of patients with early stage disease. Instead of an RCT, an evidence based early-AMD pathway between optometrists and ophthalmologists should be established. | progression of early AMD, it would not be an effective use of ophthalmologists' time to receive referrals at this stage in the disease.<br>The research recommendation for additional RCT evidence on the subject of antioxidant and zinc supplementation is intended to encourage research that will provide clarity about any benefit that may be expected from supplementation. |
| Fight for Sight | general | | | We are concerned that within the proposed guidance some areas lacks detail. The guideline should be upgraded to provide the level of detail that is necessary to enable clinicians to treat macular degeneration appropriately and effectively. We have proposed a number of specific recommendations:<br><br>1. There is a lack of guidance on the specifics of delivering patient care: for example on the use of antibiotic drops and airflow in clean rooms. The guideline should contain more detail on these areas.<br>2. The guideline does not address the issues of patients with co/multi morbidities.<br>3. It would be beneficial to update the prevalence of age-related macular degeneration, as this would be more useful for the commissioners.<br><br>Question 1: This recommendation will be a challenging change in practice because …… | Thank you for your comment.<br>The use of antibiotic drops and airflow in clear room is outside the scope of this guideline (as consulted on with stakeholders earlier in the process), and therefore it was not possible to make recommendations on this topic.<br>On considering this comment and others around multimorbidity, the committee agreed it would be useful to add a cross-reference to NICE's guidance on the assessment and management of multimorbidity.<br>The incidence figure in the introduction has been updated, in line with this comment and others (we believe the prevalence was already drawn from the most appropriate source). |

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| | | | | Question 3: Our trust has had experience of implementing this approach and would be willing to submit its experiences to the NICE shared learning database. Contact…….. | |
| Fight for Sight | Short | 19-22 | General | Recommendations for Research<br><br>We welcome the focus of research recommendations. Fight for Sight led the sight loss sector patient priority consultation on setting priorities for eye research, with the James Lind Alliance. We would very much want to see the findings in this report related to age-related macular degeneration feature in the research recommendations, in particular the commitment to find a treatment to stop dry AMD progressing and/or developing into the wet form. | Thank you for your comment and endorsement of the research recommendation. |
| Fight for Sight | Short | 5 | | 1.2 Information and Support<br><br>We would like to see recognition and information provided about the potential treatments that are available and also ways to participate in related eye research. | Thank you for your comment. Recommendation 1.2.2 recommends that healthcare professionals should 'Provide opportunities to discuss AMD with the person… [including] treatment options, including possible benefits and risks'.<br>An additional point has been added to 1.4.5, suggesting it may be appropriate to refer people with late AMD (dry) to hospital eye services if there is ongoing research which may be accessed in this way. |
| Fight for Sight | Short | 7 | 1.4.6 | 1.4 Diagnosis and Referral<br><br>We would like to see a time limit for urgent referral within the guidance. | Thank you for your comment. Following discussion of stakeholder feedback, the committee agreed that to improve the clarity of the recommendations, the time from suspicion of late AMD (wet active) to referral |

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| | | | | | should be defined as 1 working day, with an additional clarification that emergency referral is not required. |
| Fight for Sight | Short | 8 | 1.4.10 | The standard referral time of 21 days does not align with guidance provided by the Royal College of Ophthalmologists, which states, 'Patients should be seen by a specialist with medical retinal expertise within one week of diagnosis, and, there should be no more than one week between evaluation and treatment'. | Thank you for your comment. Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise its guidance to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |
| Macular Society | Full | General | General | The Macular Society is the leading charity fighting to end sight loss caused by macular disease. Every day over 200 people in the UK face the shock of a diagnosis of macular disease. This sight loss can rob people of their independence, leaving them unable to drive, read or recognise their family. Our members tell us what a profoundly isolating condition it is. People with macular disease are seven times more likely to feel distressed or depressed. We help people adapt to life with sight loss, regain their confidence and independence and take back control of their lives. We are one of the few sight loss charities that | Thank you for your comment and recognition of the importance of this guidance.<br>Regarding the consultation period, NICE's guideline manual (2014) states that consultation of draft guidelines will be for a standard period of 4 weeks. Whilst NICE appreciates that for large guidelines this can present challenges for stakeholders it endeavours through regular communication to ensure that stakeholders are provided with sufficient notice to |

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| | | | | actively fund and support medical research into macular disease. This is the research that will one day find a cure. Our work is solely funded by donations.<br><br>The Macular Society welcomes the NICE Clinical Guideline on age-related macular degeneration (AMD) as an opportunity to improve and provide consistency across the country for the diagnosis and management of AMD. What we hear from those with AMD is that depending on where you live, prompt access to hospital services and timely treatment (where required) is highly variable. It is acknowledged that demand for treatment of late AMD (wet active) is severely straining NHS ophthalmology departments and we welcome the creative ways in which some hospitals are adapting their services to meet the timescales for diagnosis and treatment recommended by the Royal College of Ophthalmologists in their AMD: Guidelines for management.<br><br>There is much that we agree with among the recommendations, such as the importance of providing information for those with AMD as well as their family and those who support them and self-monitoring to detect any changes in their vision. The areas where we do not support the recommendations are referral and treatment pathways and treatment where visual acuity is better than 6/12.<br><br>We generally support the recommendations for research, particularly where a lack of evidence led to the committee being unable to make a recommendation. We hope that the | enable them to prepare for publication of draft guidance. |

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| | | | | recommendations will be taken forward by the NHS to address these gaps in evidence.<br><br>We would like to highlight that we do not feel that a 6 week consultation period was adequate time to fully develop our comments. The delays in publishing the draft guideline affected our ability to plan preparation of our response and the consultation period fell in the summer holiday period when many staff and members were not available. The full guideline is a 241 page document developed over 2 years which needs careful consideration by stakeholders and we consider that a longer consultation period would have been more appropriate. | |
| Macular Society | Full | | | **Omissions**<br><br>An omission from the guideline is the use of blue light filtering intra-ocular lenses after cataract surgery. We think that the evidence to date does not support routine use but it would be useful if NICE would issue guidance. | Thank you for your comment. The use of blue-light filtering lenses after cataract surgery was not included within the scope of this guideline, but this question was explicitly considered within the scope of the NICE guideline on cataract surgery. |
| Macular Society | Full | 106/107 | | **Referral and treatment pathways**<br><br>We question the maximum of 7 days from initial presentation to referral implied by 'urgent' in Recommendation 9 on referral to hospital services of people with suspected late AMD (wet active). We would like to see evidence to support the statement that optometrists 'universally understand an 'urgent' referral as one that should be made within 7 days'. | Thank you for your comment. Following discussion of stakeholder feedback, the committee agreed that the time from suspicion of late AMD (wet active) to referral should be defined as 1 working day, with an additional clarification that emergency referral is not required.<br>Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance |

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| | | | | Not with standing this, we do not understand why referral cannot take place immediately and, where possible, the same working day. We question the concern that specifying referral should take place on a shorter timescale than 'urgent' would lead to the 'drastic' steps imagined.<br><br>We strongly object to any lengthening of the current recommended maximum timescales for the referral pathway set out in the Royal College of Ophthalmologists AMD: Guidelines for management. We consider that Recommendation 12, which extends the time limit from referral to treatment from 14 to 21 days runs counter to statements in the guideline, such as:<br><br>"The committee noted that included evidence demonstrated a clear association between visual loss and time delay in diagnosis and treatment for people with AMD. In some studies, the rate of loss was as rapid as 1 ETDRS letter every 3 days. Evidence from the included RCTs in section 10.1 was also considered. This suggests that eyes with late AMD (wet active) that were randomised to placebo anti-VEGF or sham PDT lost approximately 15 ETDRS letters over 1 year's follow-up. The committee interpreted this evidence as providing a clear mandate for the swiftest possible patient journey from suspicion to treatment of late AMD (wet active)."<br><br>Wet AMD is an urgent sight threatening condition and vision loss occurring due to disease progression may not be recovered. | was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |

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| | | | | Some forms of disease can be aggressive and lead to rapid vision loss. Patients are also at risk of severe sight-threatening macular haemorrhages when disease is active. It is not possible at the time of referral to work out which types of patient are at higher risk so it is best to treat all patients with an equal level of urgency.<br><br>As supporting evidence we would like to highlight the natural history arm in the PIER study because all subgroups of wet AMD were enrolled (Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1 Regillo, Carl D. et al. American Journal of Ophthalmology , Volume 145 , Issue 2 , 239 - 248.e5). There was a 5 letter ETDRS loss by 4 weeks and 5 letters is a clinically significant drop in vision. Setting a target close to a time interval at which this much vision might be lost is not appropriate. If treatment is commenced early there is also the potential for better visual outcomes (Rasmussen, A., Brandi, S., Fuchs, J., Hansen, L. H., Lund-Andersen, H., Sander, B. and Larsen, M. (2015), Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Ophthalmol, 93: 616–620. doi:10.1111/aos.12781).<br><br>We do not consider it acceptable to extend the target on the basis that it is not currently achievable in some areas. The fact | |

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| | | | | that it is achievable for some hospital eye clinics should be something to which other clinics aspire. | |
| Macular Society | Full | 28 | 3 | **Classification**<br><br>We welcome the proposed classification system, particularly the distinction between active and inactive wet AMD. We consider it achieves the aim stated on page 36: A useful classification should be simple enough for all – doctors, patients and carers – to understand but sufficiently sophisticated to support clinical decision-making. | Thank you for your comment and endorsement of the recommendation. |
| Macular Society | Full | 69 | 16 | **Risk Factors**<br><br>**Strategies to slow the progression of AMD**<br><br>**Antioxidant vitamin and mineral supplements**<br><br>We consider that the committee has been unduly negative about the lutein and zeaxanthin supplements as used in the AREDS2 formula.<br><br>The first AREDS trial showed benefit in category 3 and 4 patients, which persisted for seven years, with a modest but useful slowing of progression, which could mean that 30% of people expected to progress to advanced AMD over a 5-year period, would not. The trial did not have enough power to confirm, or not, effects in categories 1 and 2, because | Thank you for your comment. The committee agreed that, as the evidence suggesting slower progression to late AMD with supplementation from AREDS1 was based on post-hoc analyses, and these findings have not been replicated in other RCTs (nor in the context of primary prevention), it could not conclude that an effect had been reliably demonstrated.<br>The committee agreed that, if an effect of the magnitude reported in this trial could be expected in practice, supplementation would be very likely to be cost effective. This has recently been demonstrated by a cost–utility analysis conducted by Lee *et al.* (2017), which evaluated the AREDS supplement based on AREDS1 trial data. This UK study concludes that the supplement may be a cost-effective use resources; however, it did not resolve the committee's uncertainty |

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| | | | | progression from those states was very low so the slightly lower progression in the lower risk AREDS categories could not be statistically significant.<br><br>The draft guideline raised concerns about the generalisability of the AREDS 1 results, because the trial recruited a well-educated and well-nourished group, who might not be representative of the general population (of the USA). However the key point is that if AREDS 1 recruited people who were more health-conscious than the average and were eating a healthier diet, the AREDS 1 results would under-estimate the benefits in the general population. Mortality amongst the AREDS recruits was about half that in the general population, confirming the healthier habits. Over 65% were educated beyond high school level and only 6.7% were smokers.<br>The AREDS 1 supplement has been assessed as cost-effective in both the USA and Singapore.<br>At the time when AREDS 1 was being carried out (1992-1998), neither lutein nor zeaxanthin were available as supplements for research purposes. Observational studies suggested that higher intake of these carotenoids protected against AMD. The draft guideline on lutein and zeaxanthin supplements appears to be based on the updated Cochrane review, which includes only RCTs, as is traditional with Cochrane reviews.<br><br>One observational study came from the AREDS 1 study, where participants aged 60 or over (4519 people) completed a food frequency questionnaire at recruitment. Recruits reporting the highest intake of lutein and zeaxanthin were less likely to have | regarding the AREDS1 data, described in the 'Trade-off between benefits and harms' section of 6.2.4 in the full guideline. The absence of robust evidence therefore makes it impossible to judge whether the supplementation from AREDS1 would indeed be cost-effective.<br>In view of the large population for which supplementation would be indicated, and the extended length of time for which people would need to take the supplements, the committee was also bound to consider the potential resource impact of a positive recommendation. It noted its responsibility, as set out in *Developing NICE guidelines*, that, 'In general, the Committee will want to be increasingly certain of the cost effectiveness of a recommendation as the cost of implementation increases. Therefore, the Committee may require more robust evidence on the effectiveness and cost effectiveness of recommendations that are expected to have a substantial impact on resources' (7.2). In this case, any evidence of effectiveness and cost effectiveness is highly uncertain, and the committee felt unable to make any recommendation that would impose significant additional costs on the NHS.<br>Accordingly, the committee recommended that additional research was necessary to confirm or refute the post-hoc findings from AREDS1.<br>With regards to some of the specific points made: |

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| | | | | advanced AMD, with ORs versus the lowest quintile of intake of 0.65 (95% CI 0.45-0.93) for wet AMD, 0.45 (0.24-0.86) for GA, and 0.73 (0.56-0.96) for large or extensive drusen.<br><br>The AREDS 2 investigators noted that their recruits tended to have higher intakes of lutein and zeaxanthin than the general population (about 20% higher than the NHANES population), which reduced the power of the study to show benefit from supplementation. Some of those in the highest decile of dietary lutein and zeaxanthin intake were already taking more than was in the supplement. A daily intake of 10mg of lutein may be rather more than is required.<br><br>The aim of AREDS 2 was to refine the AREDS 1 supplement, and in particular to test the effects of lutein and zeaxanthin. The key results of AREDS 2 were that:<br><br>• Neither lowering the zinc dose nor omitting beta-carotene affected progression to advanced AMD<br>• Lutein and zeaxanthin supplements were more effective than beta-carotene – HR 0.82 (%% CI 0.69-0.96) for progression to advanced AMD, HR 0.78 (95% CI 0.64-0.94) for development of wet AMD and 0.94 (95% CI 0.70-1.26) for central GA.<br>• Analysis by quintiles of baseline lutein and zeaxanthin, versus no lutein and zeaxanthin, showed a significant reduction in progression to advanced AMD only in the lowest quintile; HR 0.74 (95% CI 0.59-0.94) | • The committee noted that hypothesis around larger effects being expected in people with poorer baseline nutrition. However, in the absence of RCT evidence to confirm this they were not confident to rely on this as the basis for making recommendations, when there are other hypotheses that could also be made, e.g. adherence rates (to either supplementation or other treatments) could be different in this group, which may alter effectiveness estimates.<br>• Thanks you for pointing out the poor phrasing of the evidence statements around the AREDS2 results, which has now been corrected to make clear this is compared to other formulations, rather than no supplementation.<br>• The committee noted the focus of the AREDS2 study on optimising the AREDS formulation. They also noted that a number of variations to the original formulation were proposed, of which others (such as the inclusion of omega-3 fatty acids) were found not to be an improvements. This issue around multiple testing within the study strengthened the committee's view that the new formulation needed to be tested in its own right in a stand-alone RCT. |

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| | | | | • Adding DHA and EPA to the AREDS 1 formula conferred no benefit.<br><br>One finding was that serum levels of lutein and zeaxanthin were lower when recruits also took beta-carotene, probably because beta-carotene competes with lutein and zeaxanthin for absorption.<br><br>The conclusion of AREDS 2 was that lutein and zeaxanthin should replace beta-carotene in the AREDS formula, and that the zinc could be reduced to 25mg.<br><br>We therefore think that there is good evidence that the AREDS 2 supplement should be used for patients meeting the AREDS 3 and 4 categories. It would be interesting to have data to compare quintiles of intake in the UK general population over 65 with the AREDs group.<br><br>Paragraph 6.2.3.4.2 states: "Moderate quality evidence with 5 years follow-up showed lutein/zeaxanthin supplements had no effect on preventing progression to late AMD". This is incorrect. The Cochrane review which underpins this section of the draft guidelines (page 2, paragraph 2) states: "People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94)". This statement is technically correct (though the AREDS2 paper has RR 0.91) but misleading if taken out of context. All the people in AREDS 2 got a form of the AREDS 1 supplement. AREDS 2 was not primarily | |

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| | | | | about whether lutein and zeaxanthin supplementation reduced the risk, but was about optimising the AREDS 1 supplement.<br><br>And there was some benefit from lutein and zeaxanthin, shown in the comparison, in effect, of the AREDS 1 and AREDS 2 formulae, where for any advanced AMD the relative risk with AREDS 2 is 0.82 (0.69-0.96, p = 0.02). For wet AMD, the RR is 0.78 (0.64-0.94, p = 0.01) and for GA the RR is 0.94 (0.70-1.26). This was a post-hoc analysis but it would be wasteful to dismiss it. The risk of wet AMD was reduced in all subgroups in the AREDS 1 trial (AREDS paper 36), but in the lowest risk subgroups, the progression rates were too low for differences to reach statistical significance.<br><br>So if the AREDS 1 formula reduces progression to wet AMD with RR 0.70, we might expect the AREDS 2 formula to reduce it further: 0.70 x 0.78 = 0.55. For categories 3 and 4 patients in AREDS, progression occurred in 28% on placebo and 20% on the AREDs 1 formula. If we apply the AREDS 2 correction, the 20% would become 16%. So treating 100 patients for 5 years might prevent 12 patients (28-16) developing wet AMD, at a cost of £100,000 (the AREDS 2 supplement costs around £200 a year). If each of the 12 patients avoids treatment with ranibizumab, offsetting savings accrue. In year 1 of ranibizumab treatment, the average patient might have three initial injections followed by perhaps another five in year 1, at a cost of (800 x 8 = £6,400) for injections and perhaps £60 x 3 for monitoring visits = £6850 per patient in year 1, or £82,200 for 12 patients. These figures are only illustrative and do not allow for | |

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| | | | | discounting, which affects the cost of ranibizumab more than the supplements. However if we fed them into an economic model, the cost per QALY would be low.<br><br>We suggest that the NICE GDG economists do some analyses of the cost-effectiveness of the AREDS 2 supplement on reducing progression to wet AMD in AREDS categories 3 and 4 separately, and within category 3, for those with and without large drusen. In category 3, progression was 27% in those with, and 6% in those without, large drusen.<br><br>**The Olk study**<br>The prospective cohort study by Olk and colleagues assessed the effects of zeaxanthin plus triple therapy versus triple therapy alone (bevacizumab, dexamethasone, photo-dynamic therapy with verteporfin) on the development of CNV in the fellow eyes of people with unilateral CNV. A significantly lower proportion (6.25%) of people who received zeaxanthin and triple therapy developed CNV in the fellow eye than those receiving triple therapy (12.5%; p=0.03). The Olk study had its weaknesses. It compared two consecutive cohorts of people with unilateral wet AMD, with zeaxanthin 20mg daily being added after a specific date, and added a control group from a study of six RCTs of anti-VEGF treatment. The people were already taking an AREDS 1 supplement, which may, because of the beta-carotene content, have reduced the bio-availability of zeaxanthin. Olk et al suggested that an RCT of zeaxanthin supplementation should be done, but that seems unnecessary after the AREDS trials. | |

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| | | | | The reduction in progression to wet AMD in the zeaxanthin cohort was statistically significant (p = 0.03).<br><br>The draft guideline (page 70) is dismissive of this study, saying; "agreed it was not directly applicable to the question of preventing onward progression of AMD as the mean VA of the cohort was 20/200, indicating significant ocular morbidity"<br><br>and<br><br>"It was also mindful that the included clinical evidence had not demonstrated a benefit of this form of supplementation" (meaning lutein and zeaxanthin as per AREDS 2)<br><br>We think both these statements are wrong. The second is discussed above. As regards the first, 20/200 (6/60) is significant visual impairment but vision can get much worse. At 20/200, utility is 0.66. At 20/800 (counting fingers) it is 0.52. So to dismiss this study because of the poor starting vision, seems inappropriate. In addition, it is likely that the effect on progression to wet AMD is independent of baseline VA, and could apply at better baseline VA, though we have as yet no evidence for that.<br><br>This study is not included in the clinical effectiveness section 6.2.3.4 or in Table 20, which seems an omission. It is dealt with in section 6.2.2, page 66, on health economic evidence. | |

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| | | | | Treating 100 people with zeaxanthin for 9 years would cost (undiscounted) about £180,000 (based on AREDS 2 formula cost) and based on the Olk study, prevents six developing wet AMD. The costs of treating wet AMD with ranibizumab in its first year alone would be about £41,000 for the six patients, so the supplement cost is offset, to about £140,000, which equates to a cost per case of wet AMD prevented of about £23,000. If we assumed that avoidance of wet AMD gave a utility gain of, say 0.2 (the difference between VA 20/20 and 20/50), then that would have to be maintained for 4 years in order to get a cost per QALY under £30,000.<br><br>If bevacizumab was used the cost per QALY would be far higher and supplementation probably not cost-effective. Note that these costings assume that the NHS funds supplements. At present patients largely do, so encouraging patients to use supplements would reduce NHS costs.<br><br>**Evidence for cost effectiveness of antioxidant vitamin and mineral supplements**<br><br>The Macular Society funded a study to assess the cost effectiveness of antioxidant vitamin and mineral supplements, the results of which were published on 24 August 2017 in the British Journal of Ophthalmology:<br><br>Cost-effectiveness of age-related macular degeneration study supplements in the UK: combined | |

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| | | | | trial and real-world outcomes data. Lee AY, Butt T, Chew E, Agron E, Clemons T, Egan C, Lee CS, Tufail A. *Br J Ophthalmol* 2017;0:1–8. doi:10.1136/bjophthalmol-2017-310939<br><br>http://bjo.bmj.com/cgi/content/full/bjophthalmol-2017-310939<br><br>The study concluded:<br><br>"In conclusion, this model demonstrates that the use of AREDS supplements is a dominant cost-effective intervention for use for AREDS category 4a patients with nAMD in one eye in the UK.<br><br>Previous studies have supported the effectiveness of AREDS supplements for category 3 and 4 patients. From this study, the recommendation to publicly fund AREDS supplements to category 3 patients would depend on the healthcare system willingness to pay. In contrast AREDS supplements are a dominant cost-effective intervention for category 4 AREDS patients, as they are both less expensive than standard care and more effective and therefore should be considered for public funding."<br><br>We would refer NICE to this publication and note the ongoing consultation by NHS England on guidance to CCGs on items which should not be routinely prescribed in primary care. The draft guidance includes lutein and antioxidants for AMD and bases their inclusion on 'low clinical effectiveness'. The Macular Society will be responding to the consultation to highlight this | |

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| | | | | latest publication as evidence as to why such supplements should continue to be available on prescription. | |
| Macular Society | Short | 11 | 22<br><br><br><br>24<br><br>26 | **Non-pharmacological management**<br><br>It is proposed that the guideline include specific information about low vision aids. We would recommend that patients should be made aware of the benefits of a low vision and lighting assessment. The Macular Society would further recommend the provision of low vision services locally and within Eye Clinics.<br><br>The Macular Society supports the recommendation for rehabilitation through peer support groups, relieving isolation and promoting independence.<br><br>The Macular Society would like to see referrals to Eccentric Viewing and steady eye strategy where there is central vision loss in both eyes, helping people to use their remaining vision more effectively, maintaining independence and wellbeing. | Thank you for your comment. The committee agreed with the importance of low vision services, but did not identify specific evidence that would enable them to comment on what those services should involve. As a result, the committee agreed a recommendation to consider referral to low-vision services was most appropriate, as people's individual needs could then be addressed and support tailored to them within that setting.<br>Thank you for your support for the recommendations on group rehabilitation and eccentric viewing training. |
| Macular Society | Short | 12 | 8 | **Monitoring AMD**<br><br>Recommendation 1.7.2<br><br>It is questioned whether 'healthcare professional' is the most helpful term for patients insofar as who to contact if their vision changes. It may be more helpful for patients if this reference | Thank you for your comments.<br>1.7.2 has been revised to refer to 'eye-care professional' to improve the clarity of this recommendation<br>The cross-reference in 1.7.2 has been corrected.<br>1.7.5 the committee agreed that 'as soon as possible' conveys an appropriate sense of urgency without |

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| | | | 15 | were more specific to their eye health, so that they do not consider consulting their GP, for example.<br><br>It appears that there is a mistake and the recommendation referred to should be 1.7.5 not 1.8.5.<br><br>We suggest adding the words 'in accordance with the agreed local pathway' to the end of the bullet point.<br><br>Recommendation 1.7.5<br><br>Replace 'as soon as possible' with 'immediately'. | inducing a disproportionate reaction such as presentation at eye casualty |
| Macular Society | Short | 12 | 12/13 | **Self-monitoring**<br><br>Recommendation 1.7.4<br><br>While self-monitoring of AMD is important for patients, it is questioned whether the draft guideline provides sufficient guidance as to how patients should do this. It is proposed that the guideline include specific information about strategies that can be used and is explicit about monitoring both eyes independently. | Thank you for your comment, and endorsement for the recommendation. In the guideline, a list of important signs or symptoms is included to prompt patients to seek health professional care. However, none of the evidence identified for this question supported the recommendation of particular strategies. |
| Macular Society | Short | 5 | | **Information and support**<br><br>Having to give up driving when their sight deteriorates is a very sensitive issue with people with late AMD. It is suggested that an additional bullet point be added to this section: | Thank you for these suggestions. The committee agreed it would be helpful to add 'vision standards for driving' and 'the possibility of developing visual hallucinations associated with retinal dysfunction |

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| | | | 17<br><br>20 | • Sight loss and driving<br><br>Low vision aids are of great benefit to many people with AMD. It is suggested that this be specifically included as a topic to cover in this section.<br><br>Charles Bonnet Syndrome (CBS) should be specifically included as an example of possible complications. In the region of 50% of people with late AMD experience CBS hallucinations. Many of the Society's members were not told about CBS by their eye clinic. People who experience CBS without prior knowledge of the condition are more likely to suffer emotional distress and require additional support such as counselling.<br><br>It is disappointing that the committee felt it was not able to include a recommendation on the benefits of Eye clinic liaison officers (ECLOs) due to the lack of AMD specific evidence in the literature. However, we are pleased that the committee acknowledge the importance of ECLOs in providing information to patients and their key role as part of the service provided at hospital eye clinics.<br><br>ECLOs, while not universally available, are a valuable resource to provide patient support and it is suggested that ECLOs are specifically included in this point. | (Charles Bonnet syndrome)' to the list of topics that should be discussed with people with AMD (1.2.2) |

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| Macular Society | Short | 8 | 13 | **Pharmacological management of AMD**<br><br>The Macular Society is disappointed that there is no recommendation for treatment of eyes with late AMD (wet active) where vision is better than 6/12 given the evidence on cost effectiveness of ranibizumab presented in:<br><br>Butt T, Lee A, Lee C, et al. The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes. BMJ Open 2015;5:e006535. doi:10.1136/bmjopen-2014- 006535<br><br>We note that bevacizumab is not licensed for intraocular use for late AMD (wet active) but we support the finding that the optimal strategy for treating wet AMD is:<br><br>• Bevacizumab<br>• Every 2 months<br>• No restriction to better seeing eye<br>• Include eyes with VA >6/12.<br><br>We note that recommendations in a NICE clinical guideline cannot contradict recommendations in NICE technology appraisal guidance and this is why the guideline cross refers to TA155 and TA 294 in relation to the use of ranibizumab and aflibercept. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use.<br>The committee considered stakeholder comments and revised health economic modelling of relevance to the upper acuity threshold for initiating anti-VEGF treatment at its post-consultation meeting. It noted that the revised model suggested that, compared with restricting antiangiogenic therapy to the range recommended in TA155 and TA294, offering treatment to eyes with acuity greater than 6/12 invariably provides benefits at a cost that would conventionally be |

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| | | | | We note from the EMA website that ranibizumab and aflibercept are licensed for treatment of late AMD (wet active) with no limitation regarding visual acuity.<br><br>http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf<br><br>and<br><br>http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf<br><br>This does not appear to be widely known and has implications for the current use of bevacizumab to treat late AMD (wet active) when patients present with visual acuity outside the circumstances specified in TA155 and TA294. We are disappointed that all stakeholders have not been made aware of this important information and therefore able to tailor their comments accordingly. People with wet AMD can have vision better than 6/12 and should be treated immediately. | considered an effective use of resources. However, the committee understood that, unless the agent used was either bevacizumab or very low-intensity ranibizumab, extending treatment was only cost effective compared with something that was, in itself, not cost effective. Because the analysis had convincingly shown that there are many strategies that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation explicitly mandating such an approach. However, the committee noted that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used. |
| Manchester Consultants Eye Partnership LLP | Full | General | General | Manchester Consultants Eye Partnership provides NHS macular services to patients in several areas of North-West England: Heywood, Middleton and Rochdale; Tameside and Glossop; Greater Preston, Chorley and South Ribble. We are the only ophthalmology service rated as Outstanding by the CQC, achieving clinical trial outcomes at population-wide scale. | Thank you for your comment, and sharing your experience in current practice. |

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| | | | | The results from this service, which operates a fast-track, see-and-treat model at CCG scale, have been published (Ophthalmology Times March 2016), but were not included within the recent assessment. We treat Wet AMD as an urgent condition, aiming to initiate treatment within 48-hours of referral, and subsequently maintain 100% adherence to treatment regimes. Outcomes are exceptional, with Visual acuity improvements in line with Anchor and Marina clinical trials, with a decreased requirement for injections. Now at 3 years since launch, outcomes continue to be aligned with pivotal studies, and capacity is managed within a small and efficient unit.<br><br>Our comments on the draft specification should be viewed in this context. Our experience and data contribute to existing studies showing that early and accurate intervention correlates with outcome. We demonstrate that gold-standard operational models do exist and are fully deliverable within the NHS. | |
| Manchester Consultants Eye Partnership LLP | Full | General | General | We have considerable experience in the delivery of exceptional outcomes in wet AMD and would be delighted to share our expertise and experience with the committee, and to help in any way to disseminate our approach, which is based on early and accurate intervention. | Thank you for your comment, your experience will be valuable to disseminate the guideline in clinical practice. |
| Manchester Consultants | Full | 106-107 | | **Referral to treatment time (RTTT)** | Thank you for your comment. Following discussion of stakeholder feedback, the committee agreed that the |

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| Eye Partnership LLP | | | | Results from our service are consistent with a substantial body of data, some of which is presented directly and recognised explicitly within the draft guidelines, that early intervention is associated with improved visual acuity outcomes, and hence cost-effectiveness.<br><br>In sharp contrast, real-life data suggests that late and poorly regimented therapeutic intervention is widespread within current NHS practice (references below). Overall one-year mean VA improvements of 1-2 letters compare poorly to outcomes of 8.8 letters, which are achieved with accelerated RTTT. Detailed economic assessment is likely to demonstrate that the cost-effectiveness gains associated with shortened RTTT are dramatically more significant in real-world implementation than any other aspects identified within the revised guidelines.<br><br>Whilst service model recommendations may be beyond its current reach, clinical guidelines relating to RTTT and treatment accuracy lie firmly within the current scope of the proposed guidelines. To positively impact both clinical outcomes and cost-effectiveness, we would urge the committee to strengthen RTTT recommendations and wherever possible, mandate these aspects of service provision. In particular:<br><br>**Referral to treatment time – optometrist referral** | time from suspicion of late AMD (wet active) to referral should be defined as 1 working day, with an additional clarification that emergency referral is not required.<br>Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |

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| | | | | In our practice, all optometrist referral takes place as an urgent priority through a same-day fast-track process, with simplified referral processes and the use of IT-based referrals placing no additional burden on referrers. An extension to a 7-day turnaround jeopardies patient outcomes with no meaningful gain to referrers.<br><br>A NICE guideline that pathways must ensure referral from optometrists within 24 hours of presentation would achieve considerable acceleration in RTTT with no additional cost or administrative burden, and would inject much needed urgency into downstream patient pathways.<br><br>**Referral to treatment time (RTTT) – change from 14 to 21 days**<br><br>Several studies have demonstrated the poor performance of many NHS AMD services. Rather than basing its recommendation to lengthen RTTT on clinical evidence, the draft guidelines relax standards, explicitly so that they are more achievable. Targets which have been rationally designed by experts based on clinical evidence are at risk of being relegated to aspirations, setting a precedent for subsequent targets.<br><br>If implemented, this change will adversely impact the urgency for the dramatic service improvements which are undoubtedly required. There will be further deterioration of achieved RTTT, a weakening of CCG standards, and considerable avoidable sight loss (and its associated societal and financial costs). There will | |

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| | | | | be no improvement in cost-effectiveness, and because early intervention results in a requirement for fewer injections, revised standards will actually increase the demand burden on struggling units.<br><br>The belief that RTTT is an unachievable target appears to be based on a subjective, and inaccurate view of the mechanics of service provision. We continue to demonstrate that urgent RTTT is fully deliverable at relevant scale within the NHS, and that RTTT has a greater impact on outcome and cost-effectiveness than any other factor.<br><br>We would urge the committee to extend its data assessment to review the cost-effectiveness of early intervention, both with respect to outcome and reduced injection requirements, and in the light of this assessmen,t to consider more robust and firmer guidelines, including mandating <14 day RTTT.<br><br>NICE guidance is strongly influential in defining service and commissioning priorities, and if the committee genuinely seek to improve AMD standards and cost-effectiveness, RTTT should be an immediate priority and the subject of maximally effective guideline recommendations. It is the *sine qua non* of AMD.<br><br>Tufail et al. The neovascular age-related macular degeneration database: multicenter study of 92976 ranibizumab injections: | |

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| | | | | report 1: visual acuity. Ophthalmology 121(5): 1092-1101. May 2014<br><br>Chevan R et al. Bilateral visual outcomes and service utilization of patients treated for 3 years with ranibizumab for neovascular age-related macular degeneration. Clinical Ophthalmology, 2014; 8: 717-23<br><br>Holz FG, Tadayoni R, Beatty S et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular Degeneration. Br J Ophthalmol.2014<br><br>London Medicines Evaluation Network Review. Evidence behind change in treatment regimen recommendations and monitoring for ranibizumab and data on use in clinical practice for age related macular degeneration. September 2014 | |
| Manchester Consultants Eye Partnership LLP | Full | 106-107 | | **Importance of compliance with treatment regimes**<br><br>In our experience, and consistent with the clinical trials of VEGF inhibitors, compliance with treatment protocols is of fundamental importance in translating clinical trial outcomes into the real-world setting. Whilst specific data relating to compliance is relatively sparse, we do know that poor overall performance is widespread in NHS AMD services (references above). | Thank you for your comment. |

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| | | | | The committee is right to highlight the need to balance the requirements of new and existing patients, and the Royal College of Ophthalmologists has previously highlighted that treatment guidelines and tariff both contribute to distortion of NHS priorities, in particular improving first appointment delays at the expense of follow-on care.<br><br>Accuracy of follow-on care goes hand-in-hand with RTTT in determining the real-world outcomes and cost-effectiveness of VEGF treatment. Guidance on RTTT must therefore be accompanied by a parallel requirement for adherence to care schedules. | |
| Manchester Consultants Eye Partnership LLP | Full | 110 | | **Importance of research into models of care**<br><br>We would wholeheartedly support a call for extended research into models of care, particularly those associated with accelerating RTTT and improving adherence to treatment regimes. In our experience, this is the single most important area of AMD service delivery and the key driver of outcome and hence cost-effectiveness.<br><br>We note the paucity of existing data. Given the established importance however of early intervention, randomised studies with delayed treatment arms are unlikely to gain approval. Given the limitation of the performance of many services, nor is it | Thank you for your comment, and endorsement of research recommendation on models of care.<br>The committee acknowledged that current evidence on models of care were based on non-randomised studies and future research should take this into account when designing any study. |

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| | | | | realistic that capacity will be identified to perform meaningful systematic studies, even within the tertiary setting, in which <20% pathway compliance has previously been recorded.<br><br>There needs to be recognition therefore that non-randomised, non-systematic studies comparing different models of care across CCGs are likely to be the highest available standard of data. We would highlight that these results from our Service, published in March 2016 but not included within the present draft, demonstrate both the importance of RTTT, and that outstanding models of care are fully deliverable within the NHS. | |
| Moorfields Eye Hospital NHS Trust | Full | General | General | We are concerned about the time allowed to respond to this review over the summer holiday period when many people are away. While we welcome the attentive work that led to this draft guidance, the NICE panel has considerable resources, and took 2+ years to produce a several hundred page document that was put out to consultation over the summer, a time when the ability to respond is limited. This is a very important document and should have an additional 3 months review period as there was no clinical peer review (unlike say Health economics). The NICE panel has very limited clinical input given the document title is Age-related macular degeneration: diagnosis and management. Given the delays in timelines the NICE panel had in getting this document out in draft form, is seems reasonable that the community is allowed more time to comment. A | Thank you for your comment, and your efforts to get comments back within agreed the timeframe.<br>NICE's guideline manual (2014) states that consultation of draft guidelines will be for a standard period of 4 weeks. Whilst NICE appreciates that for large guidelines this can present challenges for stakeholders it endeavours through regular communication to ensure that stakeholders are provided with sufficient notice to enable them to prepare for publication of draft guidance. |

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| | | | | document of this size will inevitably have errors and omissions that additional time will allow for help to optimise the guidance | |
| Moorfields Eye Hospital NHS Trust | Full | 155 | general | **Treatment in people presenting with visual acuity better than 6/12. We are concerned that there has been no recommendation to treat at vision better than 6/12 for a number of reasons,**<br>a- The guidance summary recommendations 37-42 on page 32 all deal with monitoring/self monitoring. The purpose of monitoring/self monitoring is to pick up active wet early before visual acuity drops, to achieve better visual acuity outcomes as for the majority of patient anti_VEGF prevents visual loss, but does not recover lost vision ( Anchor/Marina/ABC/VIEW trials). Early pick up of vision could likely mean patient present with visual acuities better than 6/12. The NICE draft guidance does not recommend treatment at acuities better than 6/12 (which we strongly disagree with and present evidence to support this). If NICE do not change stance on funding eyes with good vision and progressive wet AMD, then they should remove the recommendations for monitoring and timelines for giving the first treatment- which would put the patient and physician in a difficult position.<br>The guidance on monitoring but not being allowed to treat early are inherently contradictory and this should be justified. A key outcome stated by the panel for monitoring (page 205 full draft) is visual acuity. | Thank you for your comment. The committee considered stakeholder comments and revised health economic modelling of relevance to the upper acuity threshold for initiating anti-VEGF treatment at its post-consultation meeting. It noted that the revised model suggested that, compared with restricting antiangiogenic therapy to the range recommended in TA155 and TA294, offering treatment to eyes with acuity greater than 6/12 invariably provides benefits at a cost that would conventionally be considered an effective use of resources. However, the committee understood that, unless the agent used was either bevacizumab or very low-intensity ranibizumab, extending treatment was only cost effective compared with something that was, in itself, not cost effective. Because the analysis had convincingly shown that there are many strategies that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation explicitly mandating such an approach. However, the committee noted that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used. |

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| Moorfields Eye Hospital NHS Trust | Full | 159 | general | **Visual acuity at 1 year follow-up**<br>There are additional studies that have been not included such as CATT, LUCAS, GEFAL – which has an entry criteria of 6/9 and 1 to 2 years follow up. These data are clinical trial data that could be used as additional evidence of better visual acuity status in eyes initiated on treatment with better baseline visual acuities. Analysis should be repeated using these data from studies<br>The product licence for ranibizumab and aflibercept contain no lower acuity limit. It is not ethical to have an RCT of untreated patients with good vision. Butt et al (BMJ Open. 2015 May ) and Lee et al (Br J Ophthalmol. 2015), mined data in untreated patients in the UK to demonstrate their progression of visual loss, in centres using EMR systems looking at all patients in these systems, which would minimise bias. We feel these data together with the clinical trials mentioned above proved ample clinical evidence of the benefits of early intervention when eyes are more likely to maintain driving visual acuity. Change in visual acuity letter score is of less functional importance than maintenance of a good visual acuity state, so treating and maintaining a patient at 6/9 and keeping them driving is more beneficial than treating at 6/24 and gaining 5 letters. The clinical section on page 159 seems confused about this fundamental point. | Thank you for your comment.<br>CATT, LUCAS, GEFAL were included in our review of choice of agent (full guideline section 10.1). Although the upper bound for eligibility for these trials was higher than in previous trials, we are unaware of any publications presenting results for eyes with vision better than 6/12, which would be necessary to be included in the review on acuity thresholds for treatment (full guideline section 10.2).<br>The evidence statements on p. 159 of the consultation draft state that 'people presenting with visual acuity better than 6/12 had better visual acuity after 1 year's anti-VEGF treatment than those with those with baseline VA 5 between 6/12 and 6/96'.<br>The committee's interpretation of this evidence was in line with what is suggested in your comment: 'The committee acknowledged that the evidence presented in this review suggested treating AMD when visual acuity is good leads to the eye maintaining good visual acuity over time. The committee noted that this was in line with clinical experience, where treating AMD before significant visual impairment occurs commonly leads to maintenance of vision (and may lead to fewer injections being required overall).'<br>We have now added the additional comment that 'The committee agreed that maintenance of good visual acuity is likely to have more impact on a person's |

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| | | | | | quality of life than ostensibly larger changes in acuity, when absolute acuity remains poor.' |
| Moorfields Eye Hospital NHS Trust | Full | 159 | general | **There seems to some inaccuracy regarding how vision changes in eyes treated with wet AMD with anti-VEGF and should be corrected,**<br>**1-** Change is dependent on baseline visual acuity – so it is inaccurate to compare potential acuity change in eyes with different baseline acuities.<br>**2-** The best predictor of final visual acuity state is baseline visual acuity – so loss or gain of letters is less important than preserving visual acuity state and this should be stated both from a patient and utility perspective.<br>**3-** The committee ignore the fact that the delta between the treated and placebo arm is similar for different strata of starting vision in the Anchor/Marina trials – this work has been previously presented, and these data could be obtained from Novartis to support this easily, and would help clarify the misconceptions in this section.<br>**4-** When untreated eyes at vision better than 6/12 progress – they do not progress smoothly with a gradual reduction of VA but may precipitously drop ( as per EMR data collection Butt et al (BMJ Open. 2015 May ) and Lee et al (Br J Ophthalmol. 2015). There is a danger therefore that eyes left untreated with wet AMD between follow up visits will have a sudden irreversible drop in vision while waiting for the vision to drop below 6/12 to allow for treatment. This is contradictory to work in large sections in the guidance that discus monitoring | Thank you for your comments. The committee agreed there may well be correlations between baseline visual acuity data and visual acuity change, but were constrained by the data available from trials both to implement the economic model and for the purpose of making recommendations.<br>The committee agreed that preserving visual acuity through treatment, compared to an untreated group who decline, would be a relevant and important outcome. This outcome would be captured by comparing changes in visual acuity between treated and untreated groups (where this data is available).<br>The committee noted that patient's individual trajectories are likely to be heterogeneous, with some experiencing fast drops in visual acuity. However, in the absence of the ability to identify and predict the individuals in which this is likely to occur, the committee agreed they were only able to make recommendations for the average individual, and could not make specific recommendations about people at risk of sudden losses of acuity. |

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| | | | | which uses visual acuity as metric for monitoring effectiveness | |
| Moorfields Eye Hospital NHS Trust | Full | 159 | general | We believe the draft guidance should review the recommendations on not funding eyes presenting with acuity better than 6/12, based on the Butt et al paper (BMJ Open. 2015 May ). However even if this work is dismissed and the NICE committee own model used instead, on the assumption that the Heath economic model used not flawed then:<br><br>Given that treatment of eyes better than 6/12 with ranibizumab or aflibercept is likely to be effective but not deemed cost effective in table 54 appendix, we ask that the manufacturers are given the opportunity to renegotiate the PAS to bring the ICER within generally acceptable willingness to pay thresholds. The previous PAS would have been negotiated with only evidence on treatment of eyes better than 6/12 available. Given the new evidence that treatment of eyes better than 6/12 may be cost effective at a lower drug price, we suggest that NICE and the manufacturers should discuss whether a financial agreement can be reached to extend treatment to this effective, but less cost effective population at an acceptable price. It may be that Table 54 represents list and not PAS price and the intervention is already within generally acceptable willingness to pay thresholds | Thank you for your comment. Additional detail has been added to the evidence table for the Butt et al. study in Appendix J, section J6, listing limitations of the model more comprehensively.<br>It is not within NICE's remit to negotiate PAS arrangements (though, of course, we will consider the implications of any revised PAS that is agreed with the Department of Health). |
| Moorfields Eye Hospital NHS Trust | Full | 160 | general | **Heath Economics - visual acuity better than 6/12**<br>As a basic principle, it seems self-evident that maintaining a better VA status and hence accumulating more QALY should be | Thank you for highlighting that our discussion regarding the Butt et al. model is unclear. Additional detail has now been added to the evidence table for this study in |

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| | | | | cost effective provided the additional clinical are and injection number is not excessive. Butt et al. (BMJ Open. 2015 May ) have clearly shown this to be cost effective using very conservative model, in fact the criticism of the model if taken on board would likely make intervention at acuity less than 6/12 even more cost effective. It is unclear from the long and complex appendix on health economics what the precise concerns that invalidate the model are. We think that it is essential that a precise evidenced reason for why Butt et al limitations make it invalid, all models have limitations including the ones generated by the authors of the draft guidance.<br><br>In terms of the limitations of Butt et al model, stated in the appendix, the draft guidance say the limitations were of the Butt et al model included:<br><br>• Use of list price of ranibizumab so not assuming discounts. Given that the NICE guidance looks at list price first, it's quite a small limitation that if anything makes Butt et al paper more conservative given that the current PAS price is much lower than list price used.<br>• Only including treatment costs, not a 'cost of blindness'. This is difficult to quantify from an NHS perspective and again would make Butt et al more conservative. Treating | Appendix J, section J6, listing limitations of the model more comprehensively.<br>While it does appear intuitive that early treatment should be more cost effective, 2 issues complicate this:<br>Treatment does not cost the same regardless of when it was given. Being treated earlier will maintain an eye's VA above 6/96 for longer, therefore the eye will receive more injections over a lifetime. The total treatment cost associated with eyes with VA better than 6/12 is therefore more than treating eyes once they reach 6/12.<br>The influence of an individual's fellow eye on their quality of life. Unaffected fellow eyes will typically possess superior VA compared with the affected eye. The reduction in quality of life when a unilaterally affected eye deteriorates to 6/12 will be mitigated if the fellow, better-seeing eye retains superior VA. This limits the potential QALY gain associated with treating a unilaterally affected eye with VA better than 6/12.<br><br>We have updated our economic evaluation, particularly assumptions regarding long-term treatment. We should note that, while our model has major differences with the Butt et al. model, our revisions have made its cost-effectiveness results closer to those of Butt et al. |

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| | | | | in the better eye is also more likely to preserve driving vision. | |
| Moorfields Eye Hospital NHS Trust | Full | 28 | 3 | The panel have confused the nomenclature as not all pseudodrusen are reticular in type – The term reticular needs to be removed.<br>The progression risk of pseudodrusen alone or with drusen and/or pigmentary change is not as well defined as conventional drusen and placing them in risk strata is problematic<br><br>The term 'adult vitelliform' is loaded and implies a monogenic disorder (PRP2, Bestrophin), I think the panel mean vitelliform which is a non-specific clinical feature | Thank you for your comment.<br>Reference to pseudodrusen has been removed.<br>There is potential to confuse adult vitelliform macular dystrophy with an age-related vitelliform lesion as part of AMD. We have therefore dropped the descriptor "Adult". |
| Moorfields Eye Hospital NHS Trust | Full | 28 | 3 | **Indeterminate AMD**<br>Although I understand the need to classify serous PEDs – calling them intermediate AMD will lead to MARKED CONFUSION as it differs from the definition of intermediate AMD in classification systems such as Beckman ( see comment 2 - https://www.ncbi.nlm.nih.gov/pubmed/23332590). The subretinal fluid definition could be late onset CSR and the definition given would not differentiate the two and is problematic. Central serous retinopathy can occur in the AMD at risk age-population. | Thank you for your comment highlighting this potential confusion. This appears to have arisen because the word indeterminate might be interpreted to refer to whether a patient has AMD or not. The intended definition is that the patient has AMD, but their category of Late AMD is indeterminate. To avoid this, it has been altered to: Late AMD (indeterminate). The first clinical description has also been altered to clarify.<br>The type of AMD in this category is recognised by clinicians but not present in other classification systems. Other terms were considered, but none were judged to be entirely suitable. Intermediate AMD is |

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| | | | | | used in other classification systems for other sub-types, and implies progression to other, more advanced categories. Late AMD (indeterminate) does not necessarily progress to Late AMD (wet active) although it is at risk of doing so. |
| Moorfields Eye Hospital NHS Trust | Full | 28 | 3 | **Late AMD(dry)**<br>Strongly recommend avoiding the role of Visual acuity in this definition given the fact that cataract and PCO occur in this age group – and the noise in VA testing ( 7-10 letters repeatability Patel PJ, et al. Intersession repeatability of visual acuity scores in age-related macular degeneration. Invest Ophthalmol Vis Sci.2008 Oct;49(10):4347-52.) – meaning a dichotomous type definition is problematic.<br>Adult vitelliform is NOT a form of late AMD, however vitelliform lesion may be a feature of AMD– Vitelliform lesions may resolve in a minority without atrophy – this should be removed<br>As should confluent drusenoid and pigmentary change!!<br>The authors use the term 'non-geographic' atrophy without adequately defining the term geographic atrophy.<br>The progression of early to late atopic AMD is a continuum, and there is a global consensus academic panel defining this (Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration: Recommendations from Classification of Atrophy Consensus Meetings. Ophthalmology. 2017 Apr;124(4):464-478). I would strongly recommend following this and not attempting to define this themselves, this will add to future confusion. The NICE panel have not referenced current | Thank you for your comment. We acknowledge that there may be other causes of visual loss and so wording has been changed to specify that it should be due to AMD, not other causes. The use of vision has been retained to avoid milder forms of dry AMD being included in Late AMD (dry). It is reasonable to use an easily understood and measurable functional assessment for this. |

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| | | | | imaging papers on pre-GA and the fact that atrophy can be of the RPE, photoreceptor layer or both. There seems to be limited referencing of this whole area. | |
| Moorfields Eye Hospital NHS Trust | Full | 28 | 3 | **Late AMD (wet inactive)**<br>Fibrosis is a continuum and very subjective on OCT – the main imaging modality using in clinical follow up. Subretinal hypereflective material (SHRM) and fibrosis can be indistinguishable on OCT testing, and SHRM may have an excellent response to treatment.<br><br>How is atrophy different from geographic on imaging modalities is not defined?<br><br>YOU CAN HAVE THE LISTED FEATURES AND STILL HAVE ACTIVE wet AMD – this area needs extensive review and redefining, although we understand the need for this classification approach. Even if you have these features and there is no currently active wet AMD the wet AMD can reactivate after a pause in treatment. Madhusudhana KC, et al Neovascular Age-Related Macular Degeneration Database. Report 6: time to retreatment after a pause in therapy. Outcomes from 92 976 intravitreal ranibizumab injections. Br J Ophthalmol. 2016 Dec;100(12):1617-1622.<br>WET inactive can be temporary halt to therapy or a permanent one – this definition is therefore problematic and may lead to misinterpretation and confusion by patients, physicians and | Thank you for your comment. Recommendation 1.5.18 has been revised to state that anti-VEGF should be stopped if the eye develops late AMD (wet inactive) (in which category RPE tear is included) only if there is no prospect of functional improvement.<br>If these features are present along with features of Late AMD (wet *active*), then wet active is the dominant category and the patient would be in this latter category. Patients may move from Late AMD (wet inactive) to Late AMD (wet active) with a recurrence or reactivation; and a comment has been added to clarify this. We acknowledge that it is possible to have an RPE tear and Late AMD (wet active), so wording has been changed to clarify the presence of permanent structural damage due to an RPE tear in the Late AMD (wet inactive) category.<br>Fibrosis is a valuable clinical sign which informs management decisions. It is best identified by the combination of clinical examination/colour photos and OCT. We acknowledge that fibrosis is one of the causes of Sub-retinal Hyper-reflective Material (SRHM) on OCT, but can be distinguished from neovascularisation by fluorescein angiography if necessary. |

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| | | | | payers. These definition need more clinical and evidence based input. | |
| Moorfields Eye Hospital NHS Trust | Full | 39 | General | There are numerous issues with the proposed classification system<br>1- The terminology will ADD to confusion – e.g. 'Beckmann' definition of intermediate AMD (https://www.ncbi.nlm.nih.gov/pubmed/23332590)<br>2- There is a lack of evidence to support the classification changes and as these are arbitrary – it would be better for consistency to have a national/international consensus panel. There are also new proposed ICD definitions and an RCOphth AMD dataset that any proposed classification system should map onto<br>3- European wide studies starting on AMD (IMI-2 Macustar) , are using the 'Beckman Classification' – these studies have wide stakeholder input ( HTA, patient groups, and regulatory bodies (FDA and EMA). These studies will define more accurately natural history progression. Arbitrarily redefining entities such as intermediate AMD will cause significant future confusion for all concerned managing or researching AMD | Thank you for your comment. Other classification systems have been developed primarily for research, including epidemiological research. This classification was developed to aid communication between healthcare professionals, who may or may not be specialised in eye care; and also to aid communication with patients. The Beckman and ICD classification systems do not capture all the phenotypes of AMD clinicians are faced with. |
| Moorfields Eye Hospital NHS Trust | Full | 70 | General | Antioxidant vitamin and mineral supplements<br>We feel the recommendation to use AREDS supplements should be reconsidered in light of a recent publication that addresses the concerns raised by the committee regarding the applicability of previous health economic analysis of AREDS. The concerns given in the draft guidance are listed below | Thank you for informing us of the recent cost–utility analysis by Lee et al.<br>Upon reviewing the new economic evaluation study, and consultee comments, the committee remains concerned that the clinical benefits of AREDS1 and AREDS2 remain unclear. The committee are not aware |

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| | | | | together with how they have been addressed in the study by Lee et al (BJO 2017) in bold following each concern<br><br>With regard to Rein et al. (2007) the committee was sceptical of the way in which the assumed benefit of the AREDS vitamin supplementation had been parameterised to affect transitions between states reflecting pathological manifestations of early AMD, rather than preventing transitions from those early AMD states to more advanced and visually debilitating states (as per the AREDS trial data).<br>***We agree and hence the health economic modelling we have undertaken, that looks at preventing late neovascular AMD (Lee et al. BJO 2017 http://bjo.bmj.com/content/early/2017/08/03/bjophthalmol-2017-310939.full).***<br><br>Another key assumption of the analysis is that all patients are identified at standard optometry appointments, and the committee agreed that additional resources may be needed to screen patients for their suitability for vitamin treatment.<br><br>***We agree some of the previous studies involved screening patients for intermediate AMD, or late AMD in one eye. The work by Lee et al. just examines opportunistic presentation that matches how patients currently present on the NHS. (Lee et al. BJO 2017 http://bjo.bmj.com/content/early/2017/08/03/bjophthalmol-2017-310939.full).*** | that the results of the AREDS1 study has been replicated with a similar compound or any of its formula components, and agreed that such evidence would increase their confidence in its conclusions. The recent cost–utility model (Lee et al. 2017) was based on AREDS1 study data, and as the committee were not convinced in those clinical findings, it could not be certain regarding the conclusions of the model.<br>Although the committee concluded that it had not seen sufficient reliable evidence to make a recommendation in favour of supplementation, there is clearly clinical expertise in favour of it in practice, and the AREDS trials suggest there may be some degree of benefit. Given this, and in the absence of compelling evidence in either direction, the committee chose not to make a negative recommendation regarding the use of supplementation. Instead, it made a research recommendation encouraging the collection of additional data that could ultimately lead to confident (positive or negative) guidance. |

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| | | | | On a balance of these considerations, the committee agreed that it was unlikely to represent good value for money to offer an intervention with an uncertain – but, in any event, limited – effect on people's quality of life. The committee's caution, in this regard, was increased by the large population for which the intervention would potentially be indicated, meaning that the overall resource impact could be significant, even if the cost per person was perceived to be small.<br><br>***If the AREDS provision is restricted to AREDS group 4 patients only– the intervention is dominant in its cost – effectives, and would target a population already in hospital eye services who do not require screening and are likely to be compliant (Lee et al. BJO 2017 http://bjo.bmj.com/content/early/2017/08/03/bjophthalmol-2017-310939.full).***<br><br>***The work by Lee at al. address the shortcomings of previous work highlighted in the draft guidance and therefore funding AREDS should be reconsidered..*** | |
| Moorfields Eye Hospital NHS Trust | Full | research recommendations | | The recommendations to do a AREDS2 vs placebo trial should be removed<br><br>This trial design would be very difficult to do given the positive result in AREDS (Cochrane review and the committees' own admission to its positive findings etc), specifically for AREDS 4 patient who would derive most benefit. It is likely that an ethics | Thank you for your comment. The committee discussed your comment however it does not agree that there would be any ethical impediment to an RCT seeking to confirm or refute the findings of a post-hoc analysis of a trial in a non-UK setting, when the treatment in question is not routinely provided in NHS practice at present. |

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| | | | | committee would allow a placebo arm – hence the design of AREDS 2 and was in part the reason for its complex design. IF the committee are worried about side effects in smokers – this subgroup could be either given AREDS 2 or simply stop smoking. There are side effects from giving anti-VEGF ( stroke, endophthalmitis and loss of vision) which would be prevented by AREDS. There is 10 year follow up data on AREDS.<br><br>The draft guidance states '… the effects of each of the formula components in the AREDS1 formula on AMD progression are unclear'. First this does not matter as the result is positive and nutritional studies are about a particular combination –the combination does not necessarily equal each individual component in isolation. Secondly how would and AREDS2 vs placebo study answer questions about AREDS1. TO some extent the 'AREDS 2 answered this in part, but the committee complained it was 'complicated. We strongly feel the proposal for AREDS2 vs placebo would be a waste of resources and would not be ethical to run and should be removed. | |
| Moorfields Eye Hospital NHS Trust | Appendix J | 44 | 1425 | The appendix states – "Distribution of eyes on diagnosis: "*The distribution of these eyes between VA states, upon diagnosis, is informed by our distribution of first-treated eyes, adjusted to account for the higher likelihood of fellow eyes having VA ≥6/12 due to being diagnosed earlier. First-treated eyes are 17% likely to have VA of 6/12 or better, compared with 47% of second-treated eyes, based on data from the UK AMD database (Zarranz- Ventura et al. 2014)*"" | Thank you for your comment. Our use of these data relate only to fellow eyes that develop late AMD (wet active). At baseline in our model, late AMD (wet active) is present in at least one eye (the "first eye"). The VA of first eyes is determined by observational data obtained by members of the committee from 2 UK centres.<br>We use the Zarranz-Ventura data to make this first-eye distribution more representative of VA in fellow eyes at the point of diagnosis. People with neovascular AMD in |

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| | | | | **This is the same source as Butt et al (BMJ Open 2014), but did they end up with the same distributions? Please clarify as this would affect the validity of the model.** | one eye will have their fellow eye monitored, which is why 47% of second eyes have VA better than 6/12 at diagnosis, compared with just 17% of first eyes. The average second-treated eye will be identified earlier than the average first-treated eye.<br>In the Butt et al. model, it appears that the distribution of eyes once they reach acuity of 6/12 or less, on the "delayed treatment" arm, is informed by the distribution of all eyes at the point of diagnosis, in the ARMD dataset. This is likely to underestimate the average VA of these eyes, because if an eye is known to have neovascular AMD – but is above the treatment threshold – it is likely to be monitored closely to identify the point at which treatment can be given as early as possible. This critique been added to the evidence table for this study in Appendix J, section J6. |
| NHS Clinical Commissioners (NHSCC) | Full | 72 | 5 | Given the current lack of evidence for the effectiveness and cost-effectiveness of antioxidant and zinc supplements on the progression of AMD it would be helpful to have a stronger statement from the GDG about NOT using them. If the committee feel that these supplements are 'unlikely to represent good value for money' then a 'do not do' recommendation would seem appropriate until further research has been undertaken. | Thank you for your comment. Although the committee concluded that it had not seen sufficient reliable evidence to make a recommendation in favour of supplementation, there is clearly clinical expertise in favour of it in practice, and the AREDS trials suggest there may be some degree of benefit. Given this, and in the absence of compelling evidence in either direction, the committee chose not to make a negative recommendation regarding the use of supplementation. Instead, it made a research recommendation encouraging the collection of additional data that could |

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| | | | | | ultimately lead to confident (positive or negative) guidance. |
| NHS Clinical Commissioners (NHSCC) | Full | 126 | 35-36 | "Moreover, the UK government has previously decided that it will not disregard drug licensing purely to save money on drug costs". This statement is not referenced and we would be grateful for clarity on the source of this policy. | Thank you for your comment. See Macular Degeneration: Written question – 227588 (http://www.parliament.uk/written-questions-answers-statements/written-question/commons/2015-03-16/227588 and http://qna.files.parliament.uk/qna-attachments/227552/original/NHS%20Commissioner%20Letter.pdf) |
| NHS Clinical Commissioners (NHSCC) | Short | 8 of 22<br><br>9 of 22 | 26-27<br><br>1-24 | We would like to focus our response on behalf of our members to the recommendations relating to Bevacizumab and Ranibizumab with reference to the economic assessment that was shared in support of the recommendations.<br><br>The recommendation that Bevacizumab should not be used for the treatment of age related macular degeneration simply because it is cheaper or more cost effective will have significant cost implications for the NHS and will impact on patients' ability to access these treatments. The financial challenges currently being experienced by the NHS are well documented as funding fails to keep pace with increasing demand and the rising cost of services. The statement that "Bevacizumab may not be prescribed for intraocular use for AMD simply because it is cheaper or more cost effective" will place considerable limitations on a prescriber's ability to deliver the best value for members of the public. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, |

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| | | | | We have previously raised this issue in May 2015 highlighting views from over 120 CCGs that this is a long standing challenge within the NHS and that there is a need to ensure that we have all the available options to be able to deliver the best possible care for our patients. One of the benefits of clinical commissioning groups has been the involvement of clinicians in the commissioning process. Our members report that there has been an increase in the incidence of this chronic eye condition due to an ageing population, and as commissioners we have a responsibility to ensure that the limited NHS pound is spent most effectively.<br><br>The economic analysis shows that there are considerable savings to be made from the use of Bevacizumab when compared to other treatments, particularly Ranibizumab, and that there is clinical equivalence in terms of outcomes. The committee "noted the clear evidence that all the strategies providing best value for money were those based on Bevacizumab" and "were satisfied that the visual acuity outcomes were neither clinically nor statistically significantly different between aflibercept, bevacizumab and ranibizumab, such that they can be considered equally effective." There would therefore seem to be considerable benefits to be accrued directly for CCGs from making this switch which could then be reinvested for the benefit of the local population. We have heard that the failure to effectively licence a product for a specified purpose is a limitation on a CCG's ability to change prescribing habit as clinicians legally require a clear justification for | it does not amount to an approval of or a recommendation for such use. |

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| | | | | administering a drug on an unlicensed basis which is not based upon cost-effectiveness.<br><br>We therefore call on NICE to:<br>1. Withdraw the recommendation that Bevacizumab should not be prescribed simply because it is cheaper or more cost effective than a licensed alternative. We believe this goes beyond the remit of the NICE role in assessing the suitability of products based on clinical effectiveness and economic analysis.<br><br>Given the acceptance that there is no clinically significant differences between Aflibercept, Ranibizumab and Bevacizumab identified in the clinical trials considered by the guideline committee and considerable cost savings could be released, undertake to support partners such as Department of Health and MHRA in reviewing the licensing arrangements for Bevacizumab for the treatment of wet age-related macular degeneration. | |
| NHS Coastal West Sussex CCG | Full | General | General | Data analysis in Appendix F and summarised in the main document is not consistent with the economic evaluation in TA155. TA155 is overdue for review and this should be done PRIOR to any guidance recommending its use as a further economic evaluation may reveal that the intervention is not cost-effective to make it an option for treatment. TA 155 should be reviewed prior to the publication of this NICE AMD guidance. TA294 should also be reviewed at the same time for similar reasons. | Thank you for your comments, which will be passed to the technology appraisal programme for consideration as part of their review of TA155 and TA294 in due course. |

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| NHS Coastal West Sussex CCG | Full | 169 | 14 | 'bevacizumab may not be prescribed for intraocular use for AMD simply because it is cheaper or more cost effective than a licensed alternative' This we believe is an incorrect statement and should not be included in the final guidance.<br><br>The following letter has been submitted to the GMC:<br><br>Professor Terence Stephenson<br><br>Chair of Council<br><br>General Medical Council<br><br>350 Euston Road<br><br>London NW1 3JN<br><br>09/08/2017<br><br><br>Dear Professor Stephenson<br><br>I am writing as both a general practitioner and a CCG Clinical Lead for Medicines Management. However, in addition, my views are supported by the NHSCC Medicines Task Group that represents CCGs in delivering medicines optimisation and by the wider medical community. I am also writing to the GMC as the relevant 'regulatory body' as I am required to do so by the GMC under section 88 C of 'Leadership and management for all | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |

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| | | | | doctors' (GMC 2012), as I am 'concerned about how management decisions might conflict' with my 'primary duty to patients'.<br><br>On 13/07/2017 NICE produced draft guidance on the diagnosis and management of age-related macular degeneration (AMD). As part of the necessary evidence appraisal it was confirmed that there were 'no clinically significant differences in effectiveness and safety' between bevacizumab (Avastin) and the alternative intravitreal injection therapies for wet AMD. This is consistent with the findings of the earlier Cochrane reviews.<br><br>The use of bevacizumab (Avastin) as an intravitreal injection therapy for wet AMD is accepted clinical practice across the world, but as the off-label use of a licensed drug the GMC considers it to be unlicensed for this indication. In the GMC publication 'Good practice in prescribing and managing medicines and devices' (2013), it is stated that unlicensed medicines may be prescribed when 'there is no suitably licensed medicine that will meet the patient's need'. However, the licensed alternatives to bevacizumab that are currently preferentially recommended and used because of the current GMC guidance are at a substantially higher cost to the NHS. This was highlighted in an economic evaluation of the data provided by the IVAN trial (BMJ 2014), emphasising the significant savings to the NHS in switching from ranibizumab (Lucentis) to bevacizumab (Avastin). In its position statement in | |

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| | | | | support of the use of bevacizumab (Avastin) in wet AMD, The Royal College of Ophthalmologists subsequently stated that 'ophthalmologists should be in a position to treat patients according to sound scientific and clinical evidence that includes information about the overall costs to the health service'. The potential cost savings in using bevacizumab (Avastin) are now likely to be considerably higher because of both increased usage in wet AMD and also wider indications for use.<br><br>CCGs have fixed resources and are legally required to remain within budget, although many currently are in financial deficit and some under NHSE 'special measures'. In order to address a financial deficit, not only is it necessary to prioritise expenditure but also to rationalise healthcare provision through setting higher thresholds for treatment, decrease activity by increasing waiting times, removal of patient access to procedures and drugs deemed of lower clinical value, and in some cases decommissioning of existing clinical pathways and services. All of these adversely impact on 'the needs' of the individual patient affected. The GMC recognises this in stating 'All doctors must make the care of patients their first concern. However, the treatment options that can be offered to patients may be affected by limits on resources' (Leadership and management for all doctors GMC 2012).<br><br>There are reasons, both commercial and non-commercial, why some cost-effective drugs remain unlicensed or more | |

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| | | | | specifically 'off-label', despite being current accepted practice; but this does not mean that a license would not be granted if applied for. For example, amitriptyline is used 'off-label' for the treatment of neuropathic pain, and indeed conforms to NICE guidance (CG 173). This was addressed by the GMC in the consultation document 'Good practice in prescribing and managing medicines and devices' (GMC 2011) which stated that an unlicensed drug could be prescribed if: 'you are satisfied, on the basis of authoritative clinical guidance, that it is as safe and effective as an appropriately licensed alternative'. Although this draft version went to stakeholder consultation, the final changed published document critically did not, and states: 'You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient' (Good practice in prescribing and managing medicines and devices GMC 2013). This however fails to address the 'specific needs' of the population, whose access to healthcare may be directly affected by the further limitation of available resources caused by a restriction on the necessary cost-effective approach to resource allocation when a fixed financial budget exits. Indeed, in addition, this appears contradictory to the 'you must make good use of the resources available to you' (Good medical practice GMC 2013) and 'when making decisions about using resources, you must…. provide the best service possible within | |

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| | | | | the resources available, taking account of your responsibilities towards your patients and the wider population' (Leadership and management for all doctors GMC 2012).<br><br>It is appreciated that the MHRA has an important regulatory function in ensuring the safety of prescribed medicines, but unlicensed medicines could be safely prescribed provided a robust evidence appraisal for both efficacy and safety was carried out by an independent body, for example NICE. A recommendation for use as a treatment option by the relevant Royal College would add a further protective mechanism for patients. The following amendment to section 68 of 'Good practice in prescribing and managing medicines and devices' (GMC 2013) would serve this purpose:<br><br>**68 You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where either:**<br><br>**a on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.** | |

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| | | | | **b there is a NICE evidence appraisal that demonstrates at least the same efficacy and safety as a licensed alternative medicine for the condition to be treated, and a recommendation for use of the unlicensed medicine for that condition as an option for treatment by the relevant Royal College.**<br><br>In the example of the treatment of wet AMD, this would enable the needs of the population to be considered by the appropriate cost-effective use of limited, fixed NHS resources.<br><br>The proposed changes to the GMC guidance on unlicensed medicines should be considered immediately and, if agreed, implemented prior to the final publication of the NICE AMD guidance. This would allow changes to the current draft statement: 'bevacizumab may not be prescribed for intraocular use for AMD simply because it is cheaper or more cost-effective than a licensed alternative', which as it stands would inappropriately direct NHS funding away from patient care, with no additional benefit to the individual treated patient, but would have continued negative impact on patients who do not have the condition.<br><br>This is further supported by the economic evaluation of the comparative net health benefits (NHB) of anti-VGEF therapies in | |

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| | | | | the 2017 NICE macular degeneration draft guidance where it states:<br><br>'At an opportunity cost of £20,000 per QALY, only 40 of the 112 base-case active treatment strategies provide a higher NHB value than providing AMD patients with no treatment. This means they produce net health outcomes to the NHS that are better than offering no active AMD treatment, taking into account both the health benefits to AMD patients and the costs involved, which could alternatively have been used elsewhere in the system. Of the 40, 38 involve treatment with bevacizumab. The remaining 2 strategies that produce better net health outcomes than providing no treatment involve treatment with ranibizumab, but only for better-seeing eyes. Here, treating worse-seeing eyes achieves health gains for the patient that are small relative to their additional costs. Both of the ranibizumab strategies that are superior to providing no treatment involve the lowest intensity treatment level modelled (3-12 month intervals between injections). Unlike bevacizumab, 3-monthly regimens produce higher NHB than 2-monthly regimens for ranibizumab, due to the large incremental costs associated with more frequent injections. All other (72) active treatment strategies provide worse net health outcomes' (NICE 2017).<br><br>Further comprehensive data analysis is provided in Appendix F of the NICE macular degeneration draft guidance and this must question the validity of the original NICE TA economic appraisal | |

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| | | | | data. The base-case NHB results, at an opportunity cost of £20,000 per QALY, showed the following strategy to be optimal:<br><br>'bevacizumab, injected every 2 months, regardless of whether an eye is the better or worse-seeing eye, and including eyes with VA better than 6/12. This produces the highest NHB, generating 3.329 QALYs per patient for the healthcare system as a whole. Treating eyes every 3 months with bevacizumab, rather than every 2, produces less overall NHB, and also fewer QALYs to the person being treated (3.822 vs. 3.913), reflecting the improved clinical outcomes gained from providing more frequent treatment. Bevacizumab delivered every 2 months also produces the largest NHB if the opportunity cost of a QALY forgone is £30,000' (NICE 2017).<br><br>In a recent appeal judgement on pharmaceutical drug pricing (Flynn Pharma Ltd vs Competition and Markets Authority January 2017), the wider impact of drug costs on the general public dependent on a financially struggling NHS with fixed resources was considered more important than an individual pharmaceutical company's profit. Peter Freeman QC in turning down the appeal by Flynn Pharma Ltd for interim relief for decreasing the price of phenytoin caps following the CMA order in December 2016 stated: 'The over-riding consideration is that, taking all the circumstances into account, the harm to the public from allowing the continuation of higher prices for this product outweighs the harm to Flynn that this may cause. A relevant | |

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| | | | | factor in this finding is that it is not only the pecuniary effect of high prices on the resources of the NHS that is in issue, although that is serious enough, but the consequent effect on the health and well-being of affected patients and hence to public health overall and the public interest'.<br><br>Concerns have been raised by the GMC both during the consultation for the 2013 document, and in the GMC Council meeting 23/04/15 about the legality of prescribing an unlicensed drug when a licensed drug is available for that condition. It is important to note that section 68 of **'**Good practice in prescribing and managing medicines and devices' (GMC 2013) relates only to the individual prescribing doctor, and David Lock (Queen's Council) is adamant that 'there is nothing to suggest that a doctor who appropriately prescribes bevacizumab for someone with wet AMD acts in breach of the criminal law' and 'no court has stopped a clinician from using bevacizumab rather than ranibizumab' (BMJ 2015). Furthermore, if this were the case then every single doctor who prescribes amitriptyline for neuropathic pain, that is every GP in the country, would currently be liable to prosecution. The pharmaceutical industry is also required to operate within the law. The GMC may be aware of the use of competition law in Italy against Novartis and Roche and it is unlikely that the proposed change to the current GMC guidance would be challenged by a pharmaceutical company as this would result in a referral to the Competition and Markets Authority (CMA) for a potential abuse of a dominant market | |

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| | | | | position under the 1998 Competition Act. Significantly, on 24/02/2017, the French State Council upheld the decision in September 2015 to award a RTU ('temporary use recommendation') for bevacizumab (Avastin) in treating wet AMD by the ANSM (The agence nationale de securité du médicament et des produits de santé), the French equivalent of the MHRA. Other European countries have also authorised the use of bevacizumab (Avastin) in wet AMD and an overview is provided in 'Study on off-label use of medicinal products in the European Union' (European Commission February 2017).<br><br>The current GMC guidance that restricts the treatment of wet AMD to expensive licensed medicines only, when a considerably cheaper unlicensed drug with the same efficacy and safety could be used is therefore unethical and contradictory to other GMC guidance that emphasises the importance of making the best use of limited NHS resources for the benefit of the wider population. With the current unsustainable pressure on CCG finances with the consequent restriction of access to healthcare for that wider population, treatment of the individual patient must take into account the most cost-effective therapeutic intervention. It is therefore imperative that the GMC reconsiders its current position on the use of unlicensed drugs where there is supporting evidence of efficacy and safety.<br><br>Dr Stephen C Pike MSc FRCGP GMC No 3116308 | |

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| | | | | Clinical Lead Medicines Management Coastal West Sussex CCG<br><br>General Practitioner, Northbourne Medical Centre, Shoreham-by-Sea<br><br>Member NHSCC Medicines Task Group<br><br>August 2017 | |
| NHS East and North Hertfordshire CCG | Full<br>Short | general | general | There is an evidence evaluation in the full guideline concerning statins, omega-3 fatty acids and antioxidant vitamin and mineral supplements to slow progression of AMD. The evidence summary appears to indicate that the evidence is not sufficient to recommend for use. However, there are no subsequent recommendations within the full and short guidelines that these are not recommended for use to slow AMD progression. It is uncertain why this is the case and it would appear appropriate that specific recommendations that these are not recommended for use are added to the full and short guidelines (while acknowledging that there is a research recommendation for antioxidant and zinc supplements, this implies that there is insufficient evidence to recommend for use but there is no recommendation not to use in the main text). | Thank you for your comment. Although the committee concluded that it had not seen sufficient reliable evidence to make a recommendation in favour of supplementation, there is clearly clinical expertise in favour of it in practice, and the AREDS trials suggest there may be some degree of benefit. Given this, and in the absence of compelling evidence in either direction, the committee chose not to make a negative recommendation regarding the use of supplementation. Instead, it made a research recommendation encouraging the collection of additional data that could ultimately lead to confident (positive or negative) guidance. |
| NHS East and North | Short | 8 | 26 | The recommendations for bevacizumab are so restrictive that it would appear that in practice the only circumstances when it could be used is when ranibizumab or aflibercept cannot be | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. |

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| Hertfordshire CCG | | | | used (the circumstances where bevacizumab could be used when the others couldn't would appear negligible). While acknowledging the medico-legal issues with the use of unlicensed medicines, where the evidence indicates that bevacizumab is as safe and effective as alternatives and is more cost-effective it would appear inappropriate for the NHS not to be able to use bevacizumab when there is substantial pressure on the NHS to optimise medicines, ensure best value for money and make savings. While appreciating that this may be outside of the remit of NICE it would be helpful to understand how this issue could be taken forward at a national level. | These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| NHS East and North Hertfordshire CCG | Short | 11 | 1 | There is no recommendation on switching anti-VEGF when there has been no response or loss of response. This was considered within the full guideline and if, as appears to be the case, there is insufficient evidence for improved outcomes from switching anti-VEGF when there has been no response or loss of response then it would appear appropriate that there is a recommendation that switching is not recommended under these circumstances. | Thank you for your comment. The committee agreed that there is a lack of evidence regarding the effectiveness of switching, with no randomised, comparative trials in this area. As such, the committee did not feel able to state that there is no benefit associated with switching, nor any benefit at all. A negative, 'do not do' recommendation is just as strong as a positive, 'offer' recommendation, and should therefore be supported by sufficient evidence. In the absence of such evidence, the committee chose to recommend randomised, comparative research to reduce uncertainty in this area. |

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| NHS East and North Hertfordshire CCG | Short | 11 | 6 | It is uncertain why the recommendation is only to 'Consider' stopping anti-VEGF treatment if the eye experiences severe, progressive loss of visual acuity despite treatment. If there is severe, progressive loss of visual acuity which indicates that treatment is no longer working and the benefits no longer outweigh the risks it appears uncertain under what circumstances stopping treatment would not be appropriate and should only be considered. Therefore it would appear appropriate that the recommendation should state 'Stop anti-VEGF treatment if the eye experiences severe, progressive loss of visual acuity despite treatment'. A definition of severe, progressive loss of visual acuity would be helpful. | Thank you for your comment. The committee discussed your comment however it agreed that in the absence of a counterfactual (such as would be provided by a randomised trial of objective stopping rules), it cannot be assumed that a severe, progressive loss of visual acuity necessarily indicates that 'treatment is no longer working' – it is possible that the deterioration would be even more rapid without treatment. For this reason, the committee agreed that clinicians should use their judgement in considering the benefits and harms of treatment cessation. |
| NHS Enfield CCG | Full | 169 | 12-15 | As a CCG under legal directions and an ageing population we have concerns about the recommendation not to use bevacizumab. From examining the evidence it is our view that for many patients bevacizumab is an appropriate option for treatment of Wet AMD and is the most cost effective option. We note that other NICE guidelines( e.g neuropathic pain) advocate the use of drugs "off-label" and cannot see why NICE cannot make recommendation for bevacizumab to be used "off-label" for treatment of Wet AMD. If bevacizumab was the preferred treatment it would save the NHS considerable expense and fund treatment for the increasing number of patients requiring treatment now and in the future. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use |

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| | | | | | of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| NHS Enfield CCG | Full | 72 | 5 | Due to the current lack of evidence for the efficacy and cost-effectiveness of antioxidant and zinc preparations on the progression of AMD it is hoped that NICE could give a message that these preparations should not be made currently available on the NHS. | Thank you for your comment. Whilst the committee agreed there was insufficient evidence to recommend antioxidant and zinc supplementation be routinely offered on the NHS, they also agreed there was sufficient evidence of possible benefits that it would also be inappropriate to make a 'do not offer' recommendation in this case. |
| NHS North Derbyshire CCG | full | 169 | 12/13 | We are concerned that bevacizumab appears from all the evidence to be by some way the most cost-effective treatment and yet there is a specific recommendation not to use it. Several other NICE guidelines (e.g. lipid modification, neuropathic pain) recommend the use of drugs 'off-label' and this would seem to be a chance to save the NHS a significant amount of money which is not being taken. Recommending bevacizumab first-line would offer scope for patients being treated earlier, or for the money to be reinvested in other areas of patient care. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, |

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| | | | | | it does not amount to an approval of or a recommendation for such use. |
| NHS North Derbyshire CCG | full | 72 | 5 | Given the current lack of evidence for the effectiveness and cost-effectiveness of antioxidant and zinc supplements on the progression of AMD it would be helpful to have a stronger statement from the GDG about NOT using them. If the committee feel that these supplements are 'unlikely to represent good value for money' then a 'do not do' recommendation would seem appropriate until further research has been undertaken. | Thank you for your comment. Although the committee concluded that it had not seen sufficient reliable evidence to make a recommendation in favour of supplementation, there is clearly clinical expertise in favour of it in practice, and the AREDS trials suggest there may be some degree of benefit. Given this, and in the absence of compelling evidence in either direction, the committee chose not to make a negative recommendation regarding the use of supplementation. Instead, it made a research recommendation encouraging the collection of additional data that could ultimately lead to confident (positive or negative) guidance. |
| NHS Northern, Eastern and Western Devon CCG | Full | 146 | 2-3 | **At the current patient access scheme (PAS) prices neither ranibizumab nor aflibercept are cost effective. The PAS prices therefore need to be renegotiated.** The NICE Guideline Development Group considers the new model provides the most robust health economic evidence available to it**. The modelling shows that** at current PAS prices, ranibizumab and aflibercept produced ICERs that exceeded typical cost effectiveness thresholds. This guideline incorporates TA155 and TA294 which recommend ranibizumab and aflibercept on the basis that they provided cost effective options compared with alternative treatments. Thus if the current PAS prices of ranibizumab and aflibercept are continued, the NHS is required to fund treatments which have been shown to be not cost effective. This will be | Thank you for your comment. It is not within NICE's remit to negotiate PAS arrangements (though, of course, we will consider the implications of any revised PAS that is agreed with the Department of Health). |

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| | | | | inequitous compared to other recommendations from NICE. The solution to this is that the **PAS prices for ranibizumab and aflibercept should be renegotiated to produce ICERs which fall below the £20,000 per QALY gained threshold based on a product label regimen used for AMD in clinical practice**. It is imperative that the PAS prices for ranibizumab and aflibercept are renegotiated to avoid this situation continuing. | |
| NHS Northern, Eastern and Western Devon CCG | Appendix J | 139 | 3338-43 | **If the PAS is renegotiated in line with our previous comment then with a renegotiated PAS there is a likelihood that extending treatment with ranibizumab and aflibercept to a visual acuity better than 6/12 would be cost effective.** A Probabilistic Sensitivity Analysis (PSA) in appendix J comparing aflibercept and ranibizumab PRN regimens at PAS price for the current practice visual acuity range and extending to visual acuity better than 6/12 shows that no one option is clearly cost effective over the other. Extending treatment to eyes with visual acuity better than 6/12 should be reconsidered. | Thank you for your comment. The committee considered stakeholder comments and revised health economic modelling of relevance to the upper acuity threshold for initiating anti-VEGF treatment at its post-consultation meeting. It noted that the revised model suggested that, compared with restricting antiangiogenic therapy to the range recommended in TA155 and TA294, offering treatment to eyes with acuity greater than 6/12 invariably provides benefits at a cost that would conventionally be considered an effective use of resources. However, the committee understood that, unless the agent used was either bevacizumab or very low-intensity ranibizumab, extending treatment was only cost effective compared with something that was, in itself, not cost effective. Because the analysis had convincingly shown that there are many strategies that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation |

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| | | | | | explicitly mandating such an approach. However, the committee noted that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used. |
| NHS Solihull CCG | Full | General | General | [Comment from NHS South Worcestershire Clinical Commissioning Group, NHS Redditch & Bromsgrove CCG and NHS Wyre Forest CCG]<br>The draft guideline includes estimates of costs per QALYs/ICERs/net health benefits for bevacizumab as a treatment option in wet AMD; as detailed above it would appear that only bevacizumab strategies are associated with an ICER of less than £20,000 per QALY and 2 monthly bevacizumab has the highest net health benefit. Whilst aware of the unlicensed nature of bevacizumab in wet AMD, the need to prioritise the use of NHS resources cannot be underestimated. The evidence suggests that bevacizumab is equally effective to other antiangiogenic therapies and that there is little difference in the adverse effects between the three agents. There ought to be a solution to using a currently unlicensed treatment, where there is a body of evidence sufficient to support safety and clinical effectiveness, as an alternative to other (licensed) less cost-effective treatments. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| NHS Solihull CCG | Full | General | General | [Comment from NHS South Worcestershire Clinical Commissioning Group, NHS Redditch & Bromsgrove CCG and NHS Wyre Forest CCG]<br>We note that an updated economic model has been used as part of this guideline, that is, a single model which includes | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF |

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| | | | | interdependent decisions in the single pathway, with treatment and visual acuity of both eyes included rather than the one (better seeing) eye. This modelling has suggested that bevacizumab regimens were the only strategies with incremental cost-effectiveness ratios (ICERs) of less than £20,000 per QALY gained; aflibercept and ranibizumab regimens were associated with much higher ICERs – this was also the case when the confidential patient access scheme (PAS) prices of aflibercept and ranibizumab were used in the model, noting that only low-intensity ranibizumab (for better-seeing eyes only) produced superior net health benefits than providing no treatment.<br>Commissioners have a duty to ensure appropriate use of NHS resources and have to balance limited financial resources to meet a variety of local health needs. Based on the updated economic modelling of aflibercept and ranibizumab it would seem pertinent to review the recommendations included in the previous related Technology Appraisals (TA) as it would seem that the ICERs estimated within this draft guideline, certainly for ranibizumab, are higher than suggested by the previous TA. | agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| NHS Solihull CCG | Full | 161 – 169 | | Bevacizumab: The committee clearly accepted that in terms of efficacy "its members were satisfied that the visual acuity outcomes were neither clinically nor statistically significantly different between aflibercept, bevacizumab and ranibizumab, such that they can be considered equally effective." The committee were also of the opinion that "the safety profiles of all 3 anti-VEGF therapies can be considered to be comparable" | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. |

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| | | | | and on the basis of this made a recommendation for the use of anti-VEGF therapies for the treatment of wet AMD.<br>The committee also "noted the clear evidence that all the strategies providing best value for money were those based on bevacizumab".<br>However, the committee were unable to recommend the use of bevacizumab as it is not licensed for this indication.<br>We note that NICE CG 173, the management of neuropathic pain in adults includes recommendations for products which are not licensed for the indication in question (within the guidance from professional bodies), and would strongly suggest that this sets a precedent which should be applied in this guideline.<br>Furthermore, we understand that policy-makers in France have taken the line that bevacizumab should be used in this indication. | The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| NHS Solihull CCG | Full | 170 | 25 | [Comment from NHS South Worcestershire Clinical Commissioning Group, NHS Redditch & Bromsgrove CCG and NHS Wyre Forest CCG]<br>We welcome the recommendation to undertake further research on the effectiveness and cost effectiveness of 'treat-and-extend' regimen compared with alternative regimens. | Thank you for your comment and your endorsement of this research recommendation. However, the TREND study (NCT01948830, see clinicaltrials.gov) has recently reported its 1-year outcomes, from 650 subjects randomised to ranibizumab 0.5 mg given either monthly or by a treat-and-extend protocol. In light of this new evidence, the committee has revised the research recommendation by specifying that outcomes beyond 1 year are required. The committee has also reduced the priority level for this research (relative to their other research recommendations). |

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| NHS Solihull CCG | Full | 197 | | The committee concluded "it would not usually be a reasonable use of resources to try a second agent in the hope that it will succeed where the first choice has failed."<br>We strongly suggest that this statement should result in a "do not do" recommendation in relation to switching agents under these circumstances. | Thank you for your comment. The committee agreed that there is a lack of evidence regarding the effectiveness of switching, with no randomised, comparative trials in this area. As such, the committee did not feel able to comment on the likely benefits or harms associated with switching. A negative, 'do not do' recommendation is just as strong as a positive, 'offer' recommendation, and should therefore be supported by sufficient evidence. In the absence of such evidence, the committee chose to recommend randomised, comparative research to reduce uncertainty in this area. |
| NHS Solihull CCG | Full | 198 | 2 | [Commesnt from NHS South Worcestershire Clinical Commissioning Group, NHS Redditch & Bromsgrove CCG and NHS Wyre Forest CCG]<br>As the currently available evidence suggests that treatment switches are seldom associated with obvious therapeutic benefit, it would be helpful to be more explicit in the recommendation re switching, for example, that it would not usually be a reasonable use of resources to try a second agent in the hope that it will succeed where the first choice has failed. | Thank you for your comment. The committee agreed that there is a lack of evidence regarding the effectiveness of switching, with no randomised, comparative trials in this area. As such, the committee did not feel able to comment on the likely benefits or harms associated with switching. A negative, 'do not do' recommendation is just as strong as a positive, 'offer' recommendation, and should therefore be supported by sufficient evidence. In the absence of such evidence, the committee chose to recommend randomised, comparative research to reduce uncertainty in this area. |
| NHS Solihull CCG | Full<br><br>Short | 67-72<br><br>10 of 22 | <br><br>21-28 | Antioxidant vitamin and mineral supplements:<br>We note that these products were subject to assessment and comment within the body of the guideline, culminating in a statement that "the committee agreed that the current clinical | Thank you for your comment. Although the committee concluded that it had not seen sufficient reliable evidence to make a recommendation in favour of |

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| | | | | evidence was not able to demonstrate a clear treatment benefit of antioxidant vitamin and mineral supplement for people with early AMD and was therefore not sufficient to make a strong recommendation for the use of antioxidant, vitamin and mineral supplements." As a result of this, there is no mention of these products in the section headed Adjunctive therapies.<br><br>The committee were concerned about the safety of the AREDs formula, and requested further research on the AREDS 2 formula. Furthermore, "the committee agreed that it was unlikely to represent good value for money to offer an intervention with an uncertain – but, in any event, limited – effect on people's quality of life. The committee's caution, in this regard, was increased by the large population for which the intervention would potentially be indicated, meaning that the overall resource impact could be significant, even if the cost per person was perceived to be small."<br>On the basis of these comments, we would like to suggest that the summary "the committee agreed that the current clinical evidence was not able to demonstrate a clear treatment benefit of antioxidant vitamin and mineral supplement for people with early AMD…." should lead to a conclusion that prescription of these products should be subject to "do not do" guidance, which should be included in the section on adjunctive therapies. | supplementation, there is clearly clinical expertise in favour of it in practice, and the AREDS trials suggest there may be some degree of benefit. Given this, and in the absence of compelling evidence in either direction, the committee chose not to make a negative recommendation regarding the use of supplementation. Instead, it made a research recommendation encouraging the collection of additional data that could ultimately lead to confident (positive or negative) guidance. |
| NHS Solihull CCG | Short | | | We would welcome a statement on the setting (day-case or out-patients) within which the intraocular injections should be administered | Thank you for your comment. No evidence on this issue was directly reviewed by the guideline committee. However, in advising on the costs that should be assumed for the original health economic analysis, the |

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| | | | | | committee advised that people with late AMD (wet active) are now routinely treated as outpatients, often in specific wet AMD clinic sessions. This is supported by data from Hospital Episode Statistics (provided in Section J.5.3.5 of Appendix J), which suggest that day cases administrations are becoming increasing less common over time. |
| NHS Solihull CCG | Short | 9 of 22 | 3-4 | We would query the grounds on which the statement "bevacizumab may not be prescribed for intraocular use for AMD simply because it is cheaper or more effective than licensed alternative" has been made. The full guideline states a single interpretation of the ethical, legal and regulatory position. David Locke QC has presented an alternative interpretation of the same information, as summarised in an article in the British Medical Journal (BMJ 2014;349:h1377) which does not appear to have been considered by the GDG (or at least, any consideration has not been recorded in the full guideline).<br><br>This definitive statement, based on what appears to be a single opinion without consideration of other views, will have far-reaching effects in terms of cost-effectiveness and allocation of resources. The opportunity cost of this statement means that many thousands of people with ophthalmic or other conditions will remain untreated, resulting in a greater burden of ill-health and a lower return on overall NHS investment. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |

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| NHS Wiltshire CCG | Full | 164 | general | In this summary of the recommendations, it states that no licensed doses of ranibizumab or aflibercept were in the normal cost-effectiveness threshold at list or PAS price. It then goes onto say that as the NICE TAs recommend these 2 (non-cost-effective) drugs, they ought to remove "no treatment" from the cost-effectiveness calculations. It then states that after the removal of the "no treatment" option that "there is very little to choose" between the PRN regimens of the 2 drugs in terms of cost-effectiveness (but doesn't actually state whether they reach the usual NICE threshold- what actually is their ICER in this scenario?). So the clinical guideline group have had to use various manipulations of the health-economic data to find a way to recommend two drugs that the basic new economic data has shown to not be cost-effective.<br>The old NICE TAs for aflibercept & ranibizumab that are currently on the NICE static list need to be reviewed with the updated economic model. TAs that are on the static list are supposed to be reviewed when substantial new evidence comes to light. The new economic data is "substantial evidence" & therefore the TAs need review.<br>In terms of total budget impact for the NHS, the spend on these 2 drugs is amongst the highest individual hospital drug bill for most CCGs.<br>NICE shouldn't continue to recommend non cost-effective drugs when the health economic data clearly shows they are not cost effective. The major issue is that the millions of pounds being spent on these drugs is being diverted from funding other treatments & is not having a big enough impact on quality of life | Thank you for your comments, which have been passed to the technology appraisal programme for consideration. |

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| | | | | or clinical outcomes given the amount of money we are spending on it. The clinical guideline therefore says that for wet AMD patients, they can have a higher cost-effectiveness threshold than any other drug/condition in the NHS.<br>It would be a controversial decision to remove these drugs from being available on the NHS but the manufacturers may well produce a further PAS discount if they are faced with their drugs changing to not being recommended for use in the NHS anymore.<br>So our overall thoughts are that NICE needs to urgently review the TAs for aflibercept & ranibizumab, delay the publication of this clinical guideline whilst that is being done & then re-do the clinical guideline based on the outcome of the review of the 2 technology appraisals.<br>NICE risk losing credibility if they allow continued use of these two non-cost-effective drugs on the NHS. | |
| NHS Wiltshire CCG | Full | 169 | 7-9 | Recommendation 20: appears to be suggesting treating patients with a VA of 6/96 or worse which is not within the NICE TAs & is definitely not cost-effective. | Thank you for your comment. This clinical guideline has adopted recommendations from TA155 and TA294, which cannot be changed. However, the committee was able to make recommends that fall outside the scope of the TA recommendations.<br>Regarding the cost-effectiveness of treating eyes with a VA of 6/96 or worse: the economic model developed for this guideline found that it was never cost-effective versus the equivalent strategy without extending treatment in this way, when all eyes were eligible for treatment, regardless of fellow-eye status. This is because such eyes would frequently be a patient's |

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| | | | | | worse-seeing eye, and improvements in the worse-seeing eye have less of an impact on overall visual function and quality of life.<br>In strategies where treatment was only permitted in better-seeing eyes – where it stands to have a larger impact on overall vision and quality of life – extending treatment this was found to be cost-effective. This is because eyes with VA of 6/96 or worse would only be treated if it was the better-seeing eye, meaning the person would have very low visual function overall, which treatment could potentially improve substantially. For this reason, the committee added the qualifier to their recommendation that treatment for eyes with VA of 6/96 or worse should only be considered if doing so is expected to cause improvement in their overall visual function. |
| Novartis | All | Whole documents | General | Thank you for the opportunity to comment on this draft Clinical Guideline. The guideline recommendations are evidence-based and quite clear. However, we have a number of comments on the guideline documents below which if not addressed will create confusion among clinicians of how to practically implement the recommendations. Once finalised, the guideline recommendations should add considerable value to clinical practice in the field of macular degeneration.<br><br>Our comments fall into five main categories as follows:- | Thank you for your comments. We recognise that you have expanded on each category in separate comments in the rows below. We have therefore provided a thorough response to each expanded comments in the relevant row below (rather than providing one very large response here). |

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| | | | | **1. Quality of the analyses that inform the guideline and key economic model inputs and assumptions**. The analyses that inform the guideline are comprehensive and the overall economic modelling approach appears reasonable. However, we disagree with a number of the model inputs and assumptions with which the model is populated, and hence disagree with the results of the economic modelling of anti-VEGF therapies (see comment 2 and 3 for further details).<br><br>a. Real World Evidence (RWE) was used to inform monitoring visits for PRN in the economic model. However, extensive RCT evidence exists (as identified by the Guideline Commitee) and should inform the base case analysis as the injection and monitoring frequencies are inherently linked.<br>b. Long-term follow up data is derived from the SEVEN UP study (Rofagha *et al.,* 2013), with a scenario analysis using data by Gillies *et al,.* 2015. We believe that the Gillies source is a more appropriate choice for the base case analysis since it more closely reflects current anti-VEGF treatment patterns and is in line with the injection frequency modelled from year 2 onwards. Therefore Gillies *et al.,* 2015 should be preferred in the base case. | |

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| | | | | c. The health economic model appears to be well constructed with few errors. Only two technical errors were identified: firstly, in the calculation of the number of stroke events and the number of patients with a prior stroke, and secondly in the use of life-tables within the model (only the male life-table is being used). Neither of these errors are expected to substantially change the conclusions of the analysis. One error of concern though is that there is no cost of laser delivery associated with PDT. This means the full cost to the NHS for PDT as a treatment option is not captured.<br>d. Overall approach to modelling. The use of a bilateral-eye simulation model and use of a more appropriate approach to transition probabilities than found in some previous models is welcomed.<br>**2. Decision to exclude Treat & Extend (TREX) from the base case analysis.** We disagree with the approach of excluding TREX regimens from the base case economic model analyses. TREX is routinely used in clinical practice and is supported by a wealth of evidence beyond the two studies cited in the guideline, including an additional large RCT in press after the guideline literature searches and after this draft guideline document was | |

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| | | | | released. There are also a number of inaccuracies and conflicting comments on TREX throughout the guideline. All of our comments on this topic have been captured in the following sections;<br>**a. Rationale for exclusion of TREX is inconsistent with other judgements made during development of the guideline**<br>**b. Relevant evidence for TREX has not been considered**<br>**c. Conclusions regarding TREX are inconsistent with the evidence**<br>**d. Concluding arguments for inclusion of TREX in the base case**<br>(see comment 3 details)**3. Prominence of unlicensed bevacizumab throughout the documents.** We fully agree with the positioning of unlicensed bevacizumab in recommendation 21, namely that:<br>*"Bevacizumab is not licensed for intraocular use for AMD. Prescribers should be aware that:*<br>• *bevacizumab can only be prescribed for AMD if a person has a specific need and no other licensed product meets the need;*<br>• *bevacizumab may not be prescribed for intraocular use for AMD simply because it is* | |

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| | | | | *cheaper or more cost effective than a licensed alternative;*<br>• *clinicians should consider relevant professional guidance if prescribing outside a licensed indication;"* Clinical guidelines (long version). May 2017 4.1 Recommendations summary. p.30 lines 25-36.<br>However, given this very clear guidance, which we welcome as a recommendation in the main guideline document, we propose that the main guideline should only focus on analyses for licensed therapies and all bevacizumab analyses should be presented in separate appendices (see comment 4 for detailed comments).<br><br>**4. Minor comments**: A number of more minor comments including:<br>a. General minor comments<br>b. PAS<br>c. Typos<br>d. Missed data (see comment 5).<br>**5. Summary and impact of Novartis suggested changes** (see comment 6)<br>Implementation of the changes to the economic model requested within our response will result in more robust conclusions regarding the cost-effectiveness of licensed anti-VEGF therapies. With these changes incorporated into the | |

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| | | | | model, ICERs (at PAS price) versus sham and PDT for the main ranibizumab regimens used in UK clinical practice (Load+PRN, PRN, TREX, 2 monthly and PRNX) fall in a similar range to that which enabled the positive NICE recommendation in technology appraisal 155. | |
| Novartis | All | Whole documents | General | **Quality of the analyses that inform the guideline**<br><br>The analyses that inform the guideline are thorough. While it is clear every effort has been taken to produce a comprehensive clinical guideline, there are a few issues that need to be addressed to help make the guidelines useful and practical for clinicians to get the most use from all the work that has been put into the development of these documents.The patient-level Markov 'microsimulation' '2-eye' health economic model is thorough and captures the complexity of the disease area. This type of approach is in line with recent economic modelling methodologies published by Novartis (Claxton *et al.,* 2016, Ghosh *et al.,* 2016). However, we disagree with a number of the model inputs and assumptions with which the model is populated, and hence disagree with the results of the economic modelling of anti-VEGF therapies. Full details are provided are provided below. | Thank you for your positive comments regarding the health economic model. We recognise that you have expanded on your model comments below, and have therefore provide responses to each point below. |
| Novartis | All | Whole documents | General | **Key economic model inputs and assumptions**<br><br>We would like to highlight a number of key inputs and modelling assumptions, and make suggestions for improvements; | Thank you for your comments below, which are addressed in turn. |

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| Novartis | All | Whole documents | General | **Errors**<br><br>**Technical error 1: Calculation of the number of stroke events and patients with a prior stroke**<br><br>To identify any unexpected outcome states the mortality rate was set to 100% for all ages, no costs or outcomes should be observed after the first year. In order to test this, the per cycle probability of death was set to 1 on the 'LifeTables' sheet and the model run with 1000 patients. All treatment-related and BCVA health states were empty after the first cycle, as expected, and the values of the death health state were 1 for all Markov traces on the 'Meta-Markov' sheet. However, the values in the 'Stroke events' and 'Stroke %' health states were non-zero for all treatment options associated with a risk of stroke.<br><br>To calculate the number of stroke events in a cycle for the Aflib\|2.0\|1mo_All_norm strategy, the following formula is used:<br><br>$(1 - DC17 - DE17 - SUMIF(\$I\$6:\$AR\$6, 4, DF17:EO17)) * INDEX(rngAE.pStroke, DE\$3)$<br><br>DC17 is the number of patients in the death state, DE17 is the proportion of patients that have previously had a stroke and the SUMIF statement calculates the proportion of patients in treatment-related health state 4, which is patients with one eye | Thank you for highlighting the 2 technical errors in the executable model. These have now been rectified.<br><br>Regarding the cost of laser delivery, we have been unable to identify the £151.50 cost listed in TA155. However, the present model does include a unit cost of £136 associated with the provision of PDT (NHS reference cost code: BX84B [major vitreous retinal procedures]). We are therefore confident that the cost of PDT has not been underestimated to the degree that conclusions regarding its cost-effectiveness are invalid (if at all). |

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| | | | | in year 1 of treatment and one eye in the subsequent years of treatment state. This means the first set of brackets calculates the number of patients at risk of stroke. We believe that this is incorrect and the value in the SUMIF should be looking at patients with no current treatment, so the 4 would be replaced by a 0. The INDEX argument looks up the per-cycle probability of a stroke for the strategy in question.<br><br>The proportion of patients who have previously had a stroke is calculated using the formula:<br><br>$$DE17 * (1 - DC18)/(1 - DC17) + DD17$$<br><br>The first part of the equation calculates the number of patients carried forward from the previous year. DE17 is the proportion of patients who were in the post-stroke state in previous cycle. DC17 and DC18 are the number of patients in the death health state in the previous cycle and the current cycle respectively. Therefore, this part of the equation carries forward the patients previously in this state that have not died. DD17 is the number of patients that have had a stroke in the previous cycle, so these patients are added to the post-stroke state. However, this value is not adjusted for the number of patients that die.<br><br>This results in approximately 0.007 patients in the post-stroke state each cycle and -0.00005 patients having a stroke each | |

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| | | | | cycle. However, if all patients have died then these values should both be zero.<br><br>Additionally, if all patients have died and the values in column DC are 1 then the post-stroke formula would be expected to result in a '#DIV/0!' error, however this is not the case. This is believed to be down to the way values are treated in the VBA code, then pasted into the workbook. In the VBA numbers are treated as doubles, which can lead to some small anomalies when pasted back into the workbook. If the values of 1 are overtyped, then a '#DIV/0!' error does occur.<br><br>These errors result in an over-estimation of the number of patients having a stroke each cycle and the number of patients in the post-stroke state, which in turn will increase costs and reduce QALYs in all strategies associated with a risk of stroke. To correct these errors the calculation of the number of strokes should be done using the formula:<br><br>$(1 - DC17 - DE17 - SUMIF(\$I\$6:\$AR\$6, 0, DF17:EO17)) * INDEX(rngAE.pStroke, DE\$3)$<br><br>The proportion of patients in the post-stroke state should be calculated as: | |

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| | | | | $(DE17 + DD17) * (1 - DC18)/(1 - DC17)$<br><br>It may also be useful to include an error catcher in case of dividing by 0. No correction is suggested for the small errors introduced when pasting from the VBA, as in the normal running of the model this is not expected to impact the results.<br><br>**Technical error 2: Lifetables**<br><br>The model contains separate lifetables for men and women, however, the model only appears to be using the values for men. This is contrary to the model report. To verify that this was the case the probability of death was set to 1 for all ages in the male lifetable, but was left at base case values for women. When the model is rerun all patients are in the death health state after the first cycle. This will lead to a higher mortality rate in the model, underestimating costs and QALYs for all strategies.<br><br>As the VBA code does not contain a marker for sex it is difficult to correct this error. The simplest method would be to add a binary property to the patient class which has a value 0 for men and 1 for women. This could in turn be used to select the correct column in the lifetable for mortality calculations.<br><br>**Data error 1: Laser cost** | |

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| | | | | One error of concern is that there is no cost of laser delivery associated with PDT. Laser is required to activate the administered drug, without activation PDT is ineffective. This means the full cost to the NHS for PDT as a treatment option is not captured. The cost of laser was listed in TA155 (£151.50) therefore we request that the cost of laser is included in the PDT analyses using a current NHS reference cost. | |
| Novartis | All | Whole documents | General | **Relevant evidence for TREX has not been considered**<br>• Multiple references throughout the draft guideline and associated economic appendix (detailed below) are made to "one" randomised trial for ranibizumab TREX. This is incorrect as there are two randomised trials investigating ranibizumab TREX; LUCAS (Berg *et al.*, 2015) and TREX (Wykoff *et al.*, 2015) both of which were included in the draft guideline Network Meta-Analysis (NMA). Appendix G. NMA 2.1.1 table 2, p.11-12. We would like confirmation that the data from TREX regimens is derived from two studies LUCAS (2015) and TREX (2015), as reported in appendix G.<br>• Below is a list of the sections where treat and extend and the 'scarcity' of clinical evidence is incorrectly referred to. We request that all of the statements below be corrected; | Thank you for highlighting the potential confusion caused by the way in which this has been worded. To clarify: one RCT was previously being used to inform the effectiveness of using a treat-and-extend protocol relative to using alternative injection frequencies (e.g. monthly, PRN). The LUCAS study compared 2 treat-and-extend arms, and therefore provided no randomised information regarding the relative effectiveness of treat-and-extend itself. The TREX study compared a treat-and-extent arm with something else, and was therefore incorporated in the evidence synthesis. As per our guideline review protocols, our synthesis of comparative effectiveness evidence was focused on randomised studies, and therefore did not incorporate the non-randomised evidence listed in your comment.<br>The recent TREND study has provided a much more certain estimate of the 1-year relative effectiveness of treat-and-extent dosing. This has been incorporated into our NMAs, as have the 2-year results of the TREX study. All text has been reviewed to ensure this is |

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| | | | | • Draft guidelines. Age-related macular degeneration: diagnosis and management. Clinical guidelines (long version). May 2017;<br>• 10.1.2.1 p.136 lines 12-17. *"Neither 'treat-and-extend' regimens, where treatment intervals can be extended if the clinician feels visual and/or anatomic outcomes will be maintained, nor 'PRN-and-extend' regimens are included in our base-case analysis, owing to their reliance on individual trials with relatively small samples. The limited evidence base means our network meta-analysis predicts both approaches to be superior to routine monthly treatment, which is not consistent with the expected dose–response relationship."* Please include TREX in the base case and remove these sentences. At the very least please remove "individual" and "small" as these are incorrect.<br>• 10.1.2.2.2 p.143 lines 14-16. *"The exception to this is treat-and-extend regimens which, owing to the small clinical evidence base, are evaluated only in a separate scenario analysis."* Please include TREX in the base case and remove this sentence.<br>• 10.2.4 p.165. *"The committee reviewed the scenario analyses in which treat-and-extend and PRN-and-extend regimens had been included in the model. It* | clarified where required. Treat-and-extend regimens are now included our base-case analysis, meaning much of the text that you quote has been removed from the guideline.<br>In light of the new evidence provided by TREND, the committee has revised its research recommendation by specifying that outcomes beyond 1 year are required. The committee has also reduced the priority level for this research (relative to their other research recommendations). |

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| | | | | *understood that effect estimates were based on small, single RCTs, and were therefore subject to considerable uncertainty. Despite this imprecision, the point estimates from these RCTs suggested that both approaches are superior to routine monthly treatment."* Please include TREX in the base case and remove these sentences. As minimum please remove "small, single RCTs" as this is incorrect.<br>• 10.2.4 p.168. *"treat-and-extend in the economic model relied on 1 trial of 60 participants (split 2:1), and that this uncertainty propagates through the model."* Please correct "1 trial of 60 participants".<br>• 10.2.6 p.170 lines 29-33. *"Only 1 trial was identified….. small size of the trial, which recruited only 60 participants."* Please correct "1 trial".<br>• Appendix J: Health economics;<br>o 1. 5.2.3 p.35 lines 1184-1186. *"(TREX and PRNX)….are not included in the base-case due to the scarcity of clinical evidence for them. Each relies on clinical effectiveness evidence from 1 study with, in both cases, a relatively small sample size."* Please include TREX in the base case. Please correct "scarcity" and "1 study". | |

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| | Long | 170 | 10.3.1.1<br>25-26 | ○ 5.2.3 p.37 lines 1218-1219. *"We have not included TREX in our base-case results due to its highly uncertain clinical evidence, reliant on just 1 trial with a small sample size."* Please include TREX in the base case. Please correct "1 trial".<br>○ 5.2.5 p.39. *"'Treat-and-extend' (TREX) regimens and 'treat as needed and extend' (PRNX) regimens are not included in the base-case analysis, due to the reliance of each on individual, small sample trials."* Please include TREX in the base case. Please correct "individual small sample".<br>○ 5.3.2 p.47-48 table 28 *"The reliance of PRNX and TREX clinical evidence on single trials with small samples"* Please correct "single trials".<br>○ 5.5.2 p.87 lines 2366-2368. *"TREX and PRNX regimens are not included in the base-case results, because of their reliance on individual trials with small sample sizes to inform clinical effectiveness and injection frequency (see J.5.2.3)."* Please include TREX in the base case. Please correct "individual trials" and "small samples sizes". | |

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| | | | | ○ 5.6.3 p.124 lines 3039-3040. *"The relative effectiveness and treatment frequency evidence used to inform TREX and PRNX regimens in the model is limited; each relies on an individual, small trial."* Please correct "limited" and "individual, small trial" for TREX.<br>○ 5.6.3 p.124 line 3048 "Recognising that the TREX evidence base is 1 small trial" Please correct "1 small trial".<br>○ 5.6.3 p.125 line 3056. *"Because the relative effectiveness of TREX regimens is based on limited evidence."* Please correct "limited evidence".<br>• Relating to research question 9 "What is the effectiveness and cost effectiveness of 'treat-and-extend' regimen compared with alternative regimens (dosing frequencies)?"<br>• We would like to highlight that ranibizumab TREX has been investigated in an additional large, comparative RCT which was in press after the guideline literature search (Ophthalmology in press, TREND clinicaltrials.gov NCT01948830). The TREND study randomised 650 participants to ranibizumab TREX or ranibizumab monthly (1:1) across sites in 18 countries including the UK. The primary endpoint of the study | |

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| | | | | was non-inferiority of ranibizumab TREX compared to ranibizumab monthly assessed by change in BCVA from baseline to month 12. The study met its primary endpoint, demonstrating that TREX was non-inferior to monthly dosing (LS mean BCVA change from baseline improved by 6.2 ETDRS letters in the T&E group and by 8.1 ETDRS letters in the monthly group, the LS mean difference between the treatment groups was −1.9 letters (95% CI: −3.83, 0.07; P<0.001 for non-inferiority).<br>• This third, randomised, comparative RCT study for TREX should provide a significant evidence base to accompany LUCAS (Berg et al., 2015) and TREX (Wykoff et al., 2015) already included within the guideline NMA and economic analysis. TREND will significantly reduce the uncertainty around the efficacy of the ranibizumab TREX regimen. We believe the more significant effect might be on the NMA for discontinuation; as discussed above, the high discontinuation associated with TREX predicted by the NMA is a cause of the counterintuitive results found within the economic evaluation for TREX regimens. TREND data may be able to resolve this issue.<br>• 5.3.2 p.47 lines 1525-1526. *"The synthesis model was only able to produce year 1 coefficients for PRNX, TREX and treatment frequency, owing to a lack of 2-* | |

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year evidence to inform these relative effects." Please correct this as both LUCAS (Berg et al., 2016) and TREX (Wykoff et al., 2017) have published 2 year data.
<ul>
<li>The Guideline Committee has considered RWE at a number of points throughout the draft guideline where evidence was either not-available or limited (e.g. aflibercept PRNX). We would like to highlight the wealth of RWE (including UK data) which is available and supports the conclusion that TREX is used in routine clinical practice reinforcing the argument that TREX should be included in the base case.</li>
<li>The table below illustrates the extensive non-RCT (including RWE) evidence, in over 1,900 patients, for the effectiveness of the TREX regimen;</li>
</ul>
<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Outcomes</th><th>Topline results</th></tr>
<tr><td colspan="5">Prospective studies</td></tr>
<tr><td>Abedi et al. 2014</td><td>People with CNV due to AMD (n=120 at 12 months and 101</td><td>Ranibizumab Bevacizumab</td><td>% losing <15 letters and change in BCVA</td><td>97.5% and 95% lost <15 letters at 12 and 24 months. +9.5</td></tr>
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| | | | | | at 24 months) | | | and +8 letters at 12 and 24 months | |
| | | | | Toalster *et al.* 2013 | People with CNV due to AMD (n=45) | Ranibizumab | Change in BCVA | +7 letters at month 12 (p=0.008) | |
| | | | | Retrospective | | | | | |
| | | | | Arnold et al 2015 | People with CNV due to AMD (n=1,011) | Ranibizumab Aflibercept Bevacizumab | Change in BCVA | +5.3 letters at 24 months | |
| | | | | Calvo *et al.* 2014 | People with CNV due to AMD (n=30 for PRN and | Ranibizumab PRN and TREX | Change in BCVA of PRN versus TREX | No significant difference in BCVA change between | |

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| | | | | | n=30 for TREX) | | | groups (p>0.05) | |
| | | | | Chen *et al.* 2016 | People with CNV due to AMD (n=79) | Ranibizumab | Change in BCVA after induction and extension phases | +8.4 letters during the induction (p<0.001) with maintenance over TREX phase (p=0.81) | |
| | | | | Gupta *et al.* 2010 | People with CNV due to AMD (n=92) | Ranibizumab | Change in Snellen VA | Significant improvement at 1 year (p<0.001) and 2 year (p=0.002) follow up | |

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| | | | | Hatz & Prünte 2016 | People with CNV due to AMD (n=70 for PRN and n=70 for TREX) | Ranibizumab PRN and TREX | Change in BCVA of PRN versus TREX | +0.18 for TREX versus +0.07 for PRN at month 12 (p=0.001) | |
| | | | | Mrejen *et al.* 2015 | People with CNV due to AMD (n=185) | Ranibizumab Aflibercept Bevacizumab | Change in BCVA | −0.1245 logMAR at 18 months, −0.1061, −0.0896, and −0.0782 logMAR at 3, 4, and 5 years | |
| | | | | Oubraham *et al.* 2011 | People with CNV due to | Ranibizumab | Change in BCVA of PRN | +10.8 letters for TREX | |

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| | | | | | AMD (n=52 for PRN and n=38 for TREX) | | versus TREX | vs. +2.3 for PRN at month 12 (p=0.036) | |
| | | | | Rayess *et al.* 2014 | People with CNV due to AMD (n=189) | Ranibizumab Bevacizumab | Change in BCVA | +11.6 letters at year 1, +10.7 at year 2 and +13.6 at year 3 | |
| | | | | Vardarinos *et al.* 2017 | People with CNV due to AMD (n=54 people at 12 months and n=45 people | Ranibizumab | Change in BCVA at 12 and 24 months | +8.3 letters at month 12 (p<0.001) and +5.2 letters at month 24 (p=0.007) | |

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| | | | | at 24 months) | |

References;

Abedi F, Wickremasinghe S, Islam AF et al (2014) Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years Retina 34(8)1531-8

Arnold JJ, Campain A, Barthelmes D (2015) Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration Ophthalmology 122(6) 1212-9

Berg K, Hadzalic E, Gjertsen I 2016 Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results Ophthalmology 123(1)51-9
Calvo P, Wang Y, Ferreras A (2014) Treat and Extend Versus Treat and Observe Regimens in Wet Age related Macular Degeneration Patients Treated with Ranibizumab: 3-year Surveillance Period Clin & Exper Ophthalmology 5(1) e1-5

Chen YN, Powell AM, Mao A (2016) Retrospective review of Lucentis "treat and extend" patterns and outcomes in age-related macular degeneration Retina 36(2) 272-278

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| | | | | Gupta OP, Shienbaum G, Patel AH et al (2010) A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact Ophthalmology 117(11) 2134-40<br><br>Hatz K, Prünte C (2016) Treat and Extend versus Pro Re Nata regimens of ranibizumab in neovascular age-related macular degeneration: a comparative 12 Month study Acta Ophthalmol 95(1) e67–e72<br><br>Mrejen S, Jung JJ, Chen C et al (2015) Long-Term Visual Outcomes for a Treat and Extend Anti-Vascular Endothelial Growth Factor Regimen in Eyes with Neovascular Age-Related Macular Degeneration J Clin Med 4(7) 1380-1402<br><br>Oubraham H, Cohen SY, Samimi S et al (2011) Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration Retina 31(1) 26-30<br><br>Rayess N, Houston SK 3rd, Gupta OP (2014) Treatment outcomes after 3 years in neovascular age-related macular degeneration using a treat-and-extend regimen Am J Ophthalmol 159(1) 3-8.e1<br><br>Toalster N, Russell M, Ng P (2013) A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration Retina 33(7)1351-8 | |

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| | | | | Vardarinos A, Gupta N, Janjua R et al (2017) 24-month clinical outcomes of a treat-and-extend regimen with ranibizumab for wet age-related macular degeneration in a real life setting BMC Ophthalmol 17(1) doi: 10.1186/s12886-017-0451-1<br><br>Wykoff C, Ou W, Brown D 2017 Randomized Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: 2-Year Results of the TREX-AMD Study Ophthalmology Retina 1(4)314-321 | |
| Novartis | All | Whole documents | General | **Conclusions regarding TREX are inconsistent with the evidence.**<br>There are a number of misleading and contradicting comments regarding treat and extend (TREX) in the draft guideline and associated economic appendix (detailed below), all of which require correction. The guideline wording suggests that the TREX regimen is less effective and also less intensive, however data within the draft guideline contradicts this. In addition discontinuation rates for TREX have been misintrepeted from the trial data (Wykoff *et al.*2015).<br>Relative clinical effectiveness<br><br>• Appendix G p.20 figure 3 shows that the point estimate for BCVA with TREX is at least as good as monthly and PRN. Table 5 p.18 appendix G demonstrates that TREX has 1.3 letters (-6.7, 9.2) more than monthly. Also in | Thank you for highlighting potential inconsistencies in the discussion regarding TREX regimens. The model has been revised and now makes use of the additional evidence regarding TREX regimens. TREX regimens are also now included in the base-case model. |

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| | | | | Appendix J: Health economics 5.3.7 p.82 table 45, TREX appears to have similar BCVA gains to monthly ranibizumab (1.238 mean difference in letters year 1). These examples from the guideline highlight that the effectiveness of TREX is similar to monthly, therefore condradicting the statement above that "the TREX regimen is less effective".<br>Relative intensity (frequency of injections)<br>• Appendix J p. 59-60 table 35 presents the mean number of treatments per year, TREX is not less intensive than any other regimen (except monthly treatment).<br>List below of conflicting comments throughout NICE documents;<br>• Draft guidelines. Age-related macular degeneration: diagnosis and management. Clinical guidelines (long version). May 2017;<br>- 10.1.2.2.2 P.138 lines 40-42. *"Treat-and-extend regimens provide the least benefit among anti-VEGF 40 therapies, and PRNX regimens provide the most."*<br>• Appendix J: Health economics;<br>- 5.5.2 p.87 lines 2370-2372. *"TREX regimens are estimated to be conspicuously less effective than other discontinuous-* | |

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| | Long<br><br>Appendix G | 165<br><br>72 | 10.2.4<br><br>Table 39 | *treatment regimens. These regimens are therefore included in scenario analyses."*<br>- 5.6.3 p.124 lines 3040-3044. *"This led to our network meta-analysis predicting PRNX to appear conspicuously effective – even more so than regular monthly injections. Similarly, TREX appears conspicuously less effective compared with other discontinuous regimens, with a high rate of treatment discontinuation. For these reasons, we have included PRNX and TREX in scenario analyses only."*<br>- 5.6.3 p.124 lines 3050-3052. *"TREX regimens are the lowest-intesnsity anti-VEGF regimens included in this analysis, but are also the least effective. They are extendedly dominated or dominated by the regimens shown."* 5.6.3 p.125 lines 3056-3058 *"Because the relative effectiveness of TREX regimens is based on limited evidence, a scenario analysis was performed whereby their effectiveness is equal to that of monthly regimens." "A scenario analysis was performed whereby their effectiveness is equal to that of* | |

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| | | | | *monthly regimens. This is likely to present a highly optimistic view of TREX, which is a discontinuous treatment regimen, particularly as it makes the cost–utility frontier consist entirely of TREX regimens."* Appendix J: Health economics 5.6.3 p.125 lines 3056-3060.<br>• We seek clarification in the guideline and the cost effectiveness analyses as the above statements contradict the NMA, which reveals TREX regimens to be *more* clinically effective than most other strategies (with the exception of PRNX) in *'the most critical synthesis for the health economic model'.*<br>Discontinuation rate<br>• The finding in the economic model that TREX is dominated by other strategies is driven by an high rate of discontinuation predicted by the NMA.<br>Within the NMA the probability of discontinuation at year 1 for TREX was derived from two studies, LUCAS (Berg et al. 2015) and TREX (Wykoff et al. 2015). Table 39 suggests that 6/40 patients in the T&E arm of the TREX study discontinued, we would like to highlight that this in fact should be 3/40. This is evident from the year 2 publication of the TREX study (Wykoff et al. 2017) which states "Of the 57 patients (95%) completing month 12, 50 (88%) completed month 24, with 7 patients withdrawing because of death (n = 1), family deaths (n = 1), | |

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| | | | | personal illness (n = 1), relocation (n = 1), and loss to follow up (n = 3)". Clarification from the lead author, Dr Charles Wykoff (personal communication) confirmed that 3 patients did not attend their month 12 visit however they continued in the study and returned for study visits in year 2. Furthermore inclusion of the large, comparative RCT data from TREND, which has a lower discontinuation rate of 10.2% will reduce the overall discontuation rate. This will be more in line with ranibizumab discontinuation data across all indications. | |
| Novartis | All | Whole documents | General | **Concluding arguments for inclusion of TREX in the base case**<br>• It is inappropriate to exclude TREX regimens from the base case, when they are robust enough to be included within a product's Summary of Product Characteristics following regulatory assessment.<br>• TREX is used in routine clinical practice in the UK as evident by this UK RWE; Vardarinos *et al.* (2017); Yang *et al.* (2017). We believe it is more robust to include TREX dosing within the base case analysis.<br>• The guideline committee also agrees Treat and extend (TREX) is commonly used in practice;<br>- "Treat-and-extend regimens are authorised by the SPCs of both ranibizumab and aflibercept, and the guideline committee advised that they are commonly used in practice." Draft guidelines Age- | Thank you for your comments regarding TREX, which we hope have been suitably addressed in our previous responses. |

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| | | | | related macular degeneration: diagnosis and management. Clinical guidelines (long version). May 2017 10.2.6 p.170 lines 28-29.<br>• We would add that the TREX regimen has an extensive evidence base (both RCT and non-RCT) which has demonstrated significant clinical benefit to patients. Uncertainty alone is not sufficient justification for excluding a relevant treatment regimen for which RCT evidence exists. Probabilistic sensitivity analysis will characterise the uncertainty associated with small sample sizes. We do not believe it is consistent to include these clinical studies within the NMA but exclude the TREX regimens from the base-case economic evaluation.<br>• Similarly, treatment regimens are included within the economic evaluation for which no evidence exists (e.g. aflibercept PRNX). Therefore excluding the TREX regimen from the economic evaluation because the amount of evidence is low and inconsistent with this position.<br>• Reference;<br>Yang Y, Downey L, Mehta H *et al.* (2017) Resource Use and Real-World Outcomes for Ranibizumab Treat and Extend for | |

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| | | | | Neovascular Age-Related Macular Degeneration in the UK: Interim Results from TERRA. Ophthalmol Ther 6(1):175-186.<br><br>Vardarinos A, Gupta N, Janjua R et al (2017) 24-month clinical outcomes of a treat-and-extend regimen with ranibizumab for wet age-related macular degeneration in a real life setting BMC Ophthalmol 17(1) doi: 10.1186/s12886-017-0451-1. | |
| Novartis | All | Whole documents | General | **Minor comments**<br><br>A number of more minor comments, including comments on typos and data omissions, are provided for completeness which we hope are of value. | Thank you for your comments, which have been addressed in the relevant rows below. |
| Novartis | All | Whole documents | General | **PAS**<br>• In all sections relating to list price it is not always clear that a confidential simple disount is available to the NHS via the Patient Access Scheme (PAS) for ranibizumab.<br>• Please could all the below tables/figures presenting CE analyses for ranibizumab and/or aflibercept state that list prices are used (with a clear footnote to say that a lower confidential PAS price is available to the NHS).<br><br>• List of sections in table below where the list price is used and it's not clear it's not the PAS price;<br><br>Document Page Section Line/Table<br>Long 134 10.1.2.1 21-24<br>Long 138 10.1.2.2.2 38-50 | Thank you for your comment. We have added additional text, particularly to table and figure titles, to highlight where analyses used list prices. We have also added further detail to the PAS price results section of Appendix J. |

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| | | | | Long 139 10.1.2.2.2 1-23 & table 41<br>Long 140 10.1.2.2.2 1-35<br>Long 141 10.1.2.2.2 Table 42, lines 3-12<br>Long 142 10.1.2.2.2 Figure 2, lines 1-12, table 43<br>Long 143 10.1.2.2.2 Lines 1-9; 11-22, figure 3<br>Long 144 10.1.2.2.2 Lines 1-9; 12-23, table 44<br>Long 145 10.1.2.2.2 Figure 4, lines 1-18<br>Long 153 10.1.5.1 Lines 11-45<br>Long 154 10.1.5.1 Lines 1-16<br>Long 157 10.2.2.1 Lines 9-20<br>Long 158 10.2.2.2 Lines 1-38<br>Long 160 10.2.3.2.2 Lines 8-21<br>Long 163-166 10.2.4 -<br>Appendix J 100-103 J.5.6.2 Table 47<br>Appendix J 105 J.5.6.2 Table 48<br>Appendix J 105 J.5.6.2 Figure 17<br>Appendix J 107 J.5.6.2 Table 49<br>Appendix J 106 J.5.6.2 Figure 18<br>Appendix J 107 J.5.6.2 Figure 19<br>Appendix J 108 J.5.6.2 Figure 20<br>Appendix J 109 J.5.6.2 Table 50<br>Appendix J 109 J.5.6.2 Figure 21<br>Appendix J 111 J.5.6.2 Figure 22 and 23<br>Appendix J 112 J.5.6.2 Figure 24 and 25<br>Appendix J 113 J.5.6.2 Table 51<br>Appendix J 114 J.5.6.2 Table 52<br>Appendix J 114-115 J.5.6.2 Table 53<br>Appendix J 116 J.5.6.2 Table 54 | |

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| | | | | Appendix J 117 J.5.6.2 Table 55<br>Appendix J 117-118 J.5.6.2 Table 56<br>Appendix J 119 J.5.6.3 Figure 26<br>Appendix J 120 J.5.6.3 Figure 27<br>Appendix J 121 J.5.6.3 Figure 28<br>Appendix J 122 J.5.6.3 Figure 29<br>Appendix J 123 J.5.6.3 Figure 30<br>Appendix J 124 J.5.6.3 Figure 31<br>Appendix J 124-125 J.5.6.4 Table 57<br>Appendix J 125 J.5.6.4 Table 58<br>Appendix J 125-126 J.5.6.4 Table 59<br>Appendix J 126 J.5.6.4 Figure 32<br>Appendix J 127 J.5.6.4 Table 60 and 61<br>Appendix J 128 J.5.6.4 Table 62 and 63<br>Appendix J 129 J.5.6.4 Table 64 and 65<br>Appendix J 130 J.5.6.4 Table 66 and 67<br>Appendix J 130-131 J.5.6.4 Table 68<br>Appendix J 131 J.5.6.4 Table 69<br>Appendix J 132 J.5.6.4 Table 70 and 71<br>Appendix J 133 J.5.6.4 Table 72 and 73<br>Appendix J 134 J.5.6.4 Table 74<br>Appendix J 135 J.5.6.4 Table 75, 76 and 77<br>Appendix J 136 J.5.6.4 Table 78 and 79<br>Appendix J 137 J.5.6.4 Table 80<br>Appendix J 138 J.5.6.4 Table 81 and 82<br>Appendix J 149 J.5.8 Table 85 | |

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| Novartis | All | Whole documents | General | **Missed data**<br><br>We would like to highlight fixed bi-monthly RCT evidence has been published for ranibizumab since the literature search conducted by the Guideline Committee. Feltgen N, Bertelmann T, Bretag M et al 2017 Efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with neovascular age-related macular degeneration: results from the RABIMO trial Graefes Arch Clin Exp Ophthalmol. 255(5):923-934 | Thank you for highlighting this additional evidence, which is now captured in our evidence synthesis and economic model in a scenario analysis. |
| Novartis | All | Whole documents | General | **Summary and impact of Novartis suggested changes**<br><br>• We request that the economic model inputs are updated to include RCT evidence for PRN monitoring visits, ranibizumab RCT evidence for Load+PRN injection numbers and long-term data from Gillies *et al* 2015. We also request that TREX is included in the base case along with the additional RCT evidence (TREND and second year data for TREX and LUCAS). Finally we propose that bevacizumab is removed from the base case and all analyses including bevacizumab are reported in a separate appendix.<br><br>Implementation of the changes to the economic model requested within our response will result in more robust conclusions regarding the cost-effectiveness of licensed anti-VEGF therapies. With these changes incorporated into the model, ICERs (at PAS price) versus sham and PDT for the main | Thank you for your comments. Please find responses to each of your comments above. Changes made to the economic model have not substantially changed its results or conclusions. |

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| | | | | ranibizumab regimens used in UK clinical practice (Load+PRN, PRN, TREX, 2 monthly and PRNX) fall in a similar range to that which enabled the positive NICE recommendation in technology appraisal 155. | |
| Novartis | Appendix J | 94-98 | 5.6.1 2556 Figures 12, 13 and 14 | **<u>Typos and formatting</u>**<br>Formatting is not correct here. Figure 12 appears three times, before figure 13 (appears also three times) and figure 14. They are not labelled and there is a mistake on line 2556. "*In*"<br>• "*reverse"* should be 'reversed'.<br>• "*intesnsity*" should be 'intensity'. | Thank you for highlighting formatting and typing errors, which have now been rectified. |
| | Appendix J | 16 | 462 | • "*UK"* should be 'Australian' as Gillies et al. (2015) is a real world Australian study. | |
| | Appendix J | 124 | 5.6.3 3050 | *"Changes"* should be 'change'. | |
| | Appendix J | 56 | 5.3.1 1836-1837 | | |
| | Appendix J | 55 | 5.3.3 1785 | | |

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| Novartis | Appendix J<br><br>Appendix J<br><br>Appendix J | 133<br><br>88-89<br><br>72-76 | 5.6 table 72<br><br>5.5.2 2425-2458<br><br>5.3.8 table 45 | **<u>Long term follow up data</u>**<br><br>Gilles *et al.* (2015) should be used instead of SEVEN UP (Rofagha *et al.* 2013) in the base case as it is a much closer representation of current UK clinical practice. This is based on the following arguments;<br><br>• Gillies *et al.* (2015) is a more recent representation of anti-VEGF treatment that is able to take into account the growing clinical experience of appropriate and optimal treatment regimens. Gilles *et al.* (2015) included patients who started treatment more recently, between Jan 2007 and Jan 2010. However SEVEN UP (Rofagha *et al.*, 2013) included patients who started treatment much earlier, between March 2003 and Sept 2004. Although Gillies *et al.* (2015) is used in the scenario analysis, we think it is more relevant to current UK clinical practice and should be used in the base case.<br>• SEVEN UP (Rofagha *et al.* 2013) clearly presents under dosing from the beginning of the third year of treatment onwards. This underdosing in a large part explains the VA decline seen in SEVEN UP. The SEVEN UP study's participants received a mean of ≈2 anti-VEGF injections annually between exit from the HORIZON extension and the end of the SEVEN UP study. Authors from SEVEN | Thank you for your comment, which has highlighted an inconsistency with the data used to model long-term VA outcomes and injection frequencies in the model. We have now revised the model to rectify this.<br>We note that your comment suggests using Gillies et al. (2015) to inform long-term outcomes. We have opted to use the third-year data from the ARMD database, reported graphically by Tufail et al. (2014). The VA decline in the third year of treatment with ranibizumab PRN is 2.5 letters, compared with the previous value of 3.7 letters per year (Rofagha et al. 2013) and 0.7 letters per year (Gillies et al. 2015). These annual letter declines were presented to the guideline committee, who advised that the Gillies value seemed to underestimate VA decline compared with clinical practice. The ARMD data is recent, like the Gillies study, but the ARMD registry is larger and based in the UK, and is therefore more likely to accurately reflect current NHS practice.<br>As before, our reference VA decline for ranibizumab PRN (now 2.5 letters per year) is allowed to vary for each regimen, based on the relative treatment effects observed in the second year of treatment (from our NMA).<br>VA decline in year 3 from Tufail et al. (2014) is assumed to continue beyond year 3, as the decline during the third year is approximately linear. |

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| | Appendix J | 133 | 3207-3218 Table 72 | UP highlight the underdosing seen within their study; *"Such low treatment frequencies may reflect the contemporaneous management during those years and may have contributed to the decline in mean visual acuity."* Moreover a subgroup of patients who received ≥11 anti-VEGF injections had a significantly better mean gain in vision, ($p<0.05$) reinforcing that clinical outcomes are linked with injection frequency.<br>• When compared to SEVEN UP RWE the NICE model shows higher injection numbers. RWE from the UK (Tufail *et al.*, 2014), demonstrated 3.7 injections were given annually in years 2 and 3. The NICE model uses between 3.51 - 11.01 injections annually for continuous regimens, and 4.96 - 7.74 injections annually for discontinuous regimens from year 2 onwards. Therefore SEVEN UP does not represent UK clinical practice. Gillies *et al.* (2015) demonstrated 5 injections annually in years 2-5 and is more representative of UK clinical practice and therefore should be used in the base case.<br>• Authors from Gillies *et al.* (2015) concur with this conclusion; *"There are several potential reasons why our results may have been better than in the SEVEN UP and the UK studies. Although it is possible that a treat-and-extend approach, such as seems to have been favored by the investigators in this study, is superior to a* | A further change to the model, to ensure clinical and resource use inputs are consistent, was made to the number of injections required beyond year 3. Previously, the number of injections required in year 2 (derived from RCT evidence) was carried forward for each regimen. However, this was inconsistent with using a reference long-term VA decline from the SEVEN-UP study. Now, with a reference long-term VA decline from Tufail et al. (2014), the reference number of injections per year has been set to 3.7 for ranibizumab PRN (as reported in the ARMD report). Because the average VA decline for other regimens is allowed to deviate from this based on 2nd-year relative effects, the number of injections per year beyond year 2 is also allowed to vary by regimen. We have assumed that the proportional difference in injections required between each regimen and ranibizumab PRN in year 2 is maintained into year 3 and beyond. For example, if a regimen has been estimated to require 30% more injections than ranibizumab PRN in year 2, then it will require 4.81 injections per year from year 3 onwards (i.e. 3.7 * 130%).<br>The number of injections required in year 3 is assumed to remain constant in ever year on treatment thereafter. This is supported by the Gillies et al. study, which shows injection requirement to remain stable for 7 years. |

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| | | | | *PRN approach that was used by the UK study, we believe it is more likely due to the increased number of injections given in the present study compared with the other 2."* Gillies *et al.* (2015)<br>As already stated with the economic appendix, including Gilies *et al* 2015 in the base case results in *"larger QALY gains, because it takes longer for VA to decline following the initial 2-year treatment effects (Table 73)".* | Using the Gillies et al. data to inform long-term model outcomes is still included as a scenario analysis. In this scenario, the reference mean VA decline is 0.7 letters per year, as before. However, now, the reference number of injections also changes to reflect the data source, to 4.9 per year.<br>Using the Rofagha et al. data to inform long-term model outcomes has been retained as a scenario analysis. In this scenario, the previous reference mean VA decline of 3.7 letters per year takes effect. However, now, the reference number of injections also changes to reflect the data source, to 2.0 per year. |
| Novartis | Appendix J | 36 | 5.2.3 table 23 | **<u>Decision to exclude treat and extend (TREX) from the base case analysis.</u>**<br><br>We do not agree with the rationale for exclusion of treat and extend (TREX) from the base case. Our evidence for this is detailed below under the following subheadings;<br><br>a. **Rationale for exclusion of TREX is inconsistent with other judgements made during development of the guideline:** Other regimens are included despite no evidence so it seems illogical to exclude TREX on the basis of limited evidence.<br>b. **Relevant evidence for TREX has not been considered**: The Guideline Committee has concluded the available TREX data is limited but we believe that | Your comments regarding treat-and-extend dosing have been responded to in the rows below. |

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| | | | | substantive evidence has been overlooked in reaching this conclusion.<br>**Conclusions regarding TREX are inconsistent with the evidence:** There are several conflicting comments about the relative effectiveness and intensity of TREX which are not supported by the Committee's own analyses. | |
| Novartis | Appendix J | 36 | 5.2.3 1189-1193 | **<u>Rationale for exclusion of TREX is inconsistent with other judgements made during development of the guideline</u>**<br>• The Guideline Committee has included a number of regimens within the base case which 'are not used in practice, and in some cases have not been explored in clinical trials'. This runs counter to the reason for excluding TREX from the base case analysis.<br>• *"We recognise that a number of regimens in Table 23 are not used in practice, and in some cases have not been explored in clinical trials (e.g. aflibercept PRNX, ranibizumab 2-monthly). However, our method of estimating relative effectiveness has made it possible to simulate a world in which such regimens are available, thus allowing us to include them in the model."*<br>TREX should be included within the base case. | Thank you for your comment. While some regimens have not been explored in clinical trials, our NMA methodology means that when they are separated into their constituent parts they may still be well informed by the network. For example, there is no comparative evidence on continuous, 2-monthly ranibizumab – but there is evidence on aflibercept and there is evidence on the extent to which extending treatment intervals beyond 1 month affects outcomes. Both of these components of '2-monthly ranibizumab' are well-connected within the network, therefore we can produce a reasonable estimate of its relative effectiveness.<br>In the case of PRNX, this is very weakly connected to the network by just 1 small study. Therefore in estimating the effectiveness of, say, ranibizumab PRNX, substantial evidence exists within the network for the agent, ranibizumab, but the PRNX component remains highly uncertain, reliant on the single study. The point estimates suggested that PRNX was, on average, more effective than regular monthly treatment, |

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| | | | | | which subverts the expected dose–response relationship and was felt by the guideline committee to be clinically implausible. The estimate is highly uncertain, however, with the conspicuously positive point estimate consistent with sampling error. Due to this uncertainty, including PRNX in the base case was judged to be inappropriate and potentially misleading.<br>The same comment previously applied equally to TREX regimens, however in light of the new evidence listed below – in particular the TREND study – it has become possible to include TREX regimens in the revised base-case analysis. |
| Novartis | Appendix J | 36 | 5.2.3 1203-1205 | The guideline committee advised there are circumstances where bevacizumab is currently considered in the NHS. These will be limited in nature, with all/most use in indications where NICE guidance does not exist for the licensed treatments. These guidelines cover the treatment of AMD and there are two licensed treatments available for these patients, both with positive NICE guidance. Therefore, we believe it is fully justifiable to remove bevacizumab from the base case, with analyses only being presented in the scenario analyses. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use |

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| | | | | | of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use.<br>The inclusion of bevacizumab-based regimens in the base case of our evaluation is consistent with the scope for this guideline, which stated that 'bevacizumab will be included in the evaluations carried out to develop the guideline'. Analyses omitting bevacizumab from the decision space are also provided. |
| Novartis | Appendix J | 62 | 5.3.5<br>1980-<br>1994 | **Real World Evidence (RWE) was used to inform monitoring visits for PRN in the economic model. However, extensive RCT evidence exists (as identified by the guideline) and should inform the base case analysis.**<br>• It is unclear why RCT evidence has not been included in the base case analysis for PRN monitoring visits, when RCT data has been used for the injection number. From SALUTE the mean clinic visits for year 1 were 12.7 and 10.1 with 6.6 and 6.0 injections for PRN and PRNX respectively. In contrast RWE (Tufail *et al.* 2014) shows a mean number of clinic visits of 9.2 with 5.7 injections associated with PRNX.<br>• PRN entails monthly monitoring, as demonstrated in SALUTE, anything less than monthly monitoring will likely result in fewer injections therefore the only robust | Thank you for highlighting this potential inconsistency in how PRN and PRNX monitoring had been included in the model. In light of this, we have revised the analysis to use the SALUTE data for the *total number of visits* in a year. The number of injections required per year is subtracted from this total, for each PRN and PRNX regimen, to give the total number of *monitoring-only* visits per year required for each PRN and PRNX regimen. The *total number of visits* from SALUTE is used in year 1 and year 2 of treatment.<br>We have also revised the inputs used to inform the base-case model in the long-term (year 3 onwards). These changes are detailed in the comment below. In short, the model now consistently uses the ARMD data (Tufail et al. 2014) beyond year 2. To make PRN and PRNX monitoring consistent with this approach, from year 3 onwards the *total number of visits* per year is informed by the ARMD point estimate in year 3 (8.2 visits). The number of injections required is subtracted |

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<tr><td></td><td></td><td></td><td></td><td>approach is to use the monitoring data in conjunction with the injection frequency data from SALUTE.<br>• While we understand the concept of your approach to use RWE for the monitoring visit frequency i.e. adding 2 additional monitoring visits to the UK AMD database to compensate for the difference observed between SALUTE and the RWE, this approach would be better served in a sensitivity analysis as it is not the most methodologically robust approach.<br>Including RCT monitoring data from SALUTE in the base case would result in a very modest change in the cost for ranibizumab PRN strategies.</td><td>from this total, for each PRN and PRNX regimen, to give the total number of monitoring-only visits per year, from year 3 of treatment and thereafter.</td></tr>
<tr><td>Novartis</td><td>Full & Appendix J</td><td>All</td><td>General</td><td>• Bevacizumab has undue prominence in the guideline analyses and is shown in the majority of the tables (40% of all tables, 33% of all figures in the full clinical guideline and 72% of all tables, 26% of all figures in appendix J). Separate analysis without bevacizumab would greatly enhance the clarity of the guideline.<br>• List of sections in table below where bevacizumab has undue prominence;<br><table><tr><th>Document</th><th>Page</th><th>Section</th><th>Line/Table</th></tr><tr><td>Long</td><td>30</td><td>4.1</td><td>25-36</td></tr><tr><td>Long</td><td>134</td><td>10.1.2.1</td><td>16-26</td></tr><tr><td>Long</td><td>136</td><td>10.1.2.1</td><td>5</td></tr></table></td><td>Thank you for your comment. The inclusion of bevacizumab-based regimens in the base case of our evaluation is consistent with the scope for this guideline, which stated that 'bevacizumab will be included in the evaluations carried out to develop the guideline'. Analyses omitting bevacizumab from the decision space are also provided.</td></tr>
</table>

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| | | | | Long 138 10.1.2.2.2 44-47<br>Long 164 10.2.4 -<br>Long 169 10.2.4 10-20<br>Appendix J 99-100 5.6.2 2632-2646<br>Appendix J 105 5.6.2 Table 48<br>Appendix J 127 5.6.4 Table 60<br>Appendix J 140 5.7.1 3379-3404 | |
| Novartis | Long<br><br>Appendix J<br><br><br>Appendix J | 135<br><br>141<br><br><br>142 | 10.1.2.2.1 17-28<br><br>5.7.2 3446-3454<br><br>5.7.3 3495-3503 | **Overall approach to modelling**<br>The approach to the economic evaluation marks a departure from many previous analyses. The use of simulation methods allows the characterisation of the effects of changes in visual acuity across both eyes, and therefore a more appropriate attribution of outcomes and costs when compared to 'single-eye' models. The use of such simulation models echoes the results of previous studies, sponsored by Novartis, which have found patient-level simulations to be appropriate tools for decision-making in AMD and ophthalmology more generally (Claxton *et al.* 2017).<br>We do note, however, that the model structure employed, based on the population distribution of patients across health states, does not allow for as granular attribution of costs and outcomes | Thank you for your positive comments regarding the model. We recognise that simulation modelling approaches have been utilised in the literature. While patient-level simulation modelling has its benefits, the Markov microsimulation approach retains more transparency, particularly in the calculation of costs and QALYs, and it is important that a model of this size is as accessible as possible.<br>As pointed out, the ability of a patient-level simulation model to capture patient-level heterogeneity has been advanced as a benefit of the approach. However, for this reason, it also imposes additional data requirements on the simulation, which may undermine or overwhelm any benefit. For example, we note that, in Claxton et al.'s simulation homogeneous rates of acuity change were assumed and, in the case of 2-year–5-year extrapolation, an assumption of constant BCVA for |

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| | | | | (in particular, health-related quality of life) as the approach adopted by Claxton *et al.* (2017), which was based on mean changes in BCVA at the individual-level. Nor does the model characterise heterogeneity across the population, which is traditionally seen as a key advantage of simulation models (for example, all patients are assumed to be of the same age).<br><br>Nevertheless, the use of a bilateral-eye simulation model and use of a more appropriate approach to transition probabilities than found in some previous models is to be welcomed. | all simulated eyes was made. We argue that the microsimulation approach takes advantage of the benefits of the simulation approach while avoiding the necessity for additional assumptions and unfeasible data requirements. |
| Novartis | Long<br><br>Appendix J<br><br>Appendix J | 170<br><br>37<br><br>108 | 10.2.6<br>28-29<br><br>5.2.3<br>1217-1220<br><br>5.6.2 | • Aflibercept has a treat and extend license from the second year only (in year one the license states three consecutive doses followed by one injection every two months). This is not clear in both examples below and we request it is updated;<br>- "*Treat-and-extend regimens are authorised by the SPCs of both ranibizumab and aflibercept, and the guideline committee advised that they are commonly used in practice."*<br>- "*TREX is listed on the labels of aflibercept and ranibizumab."*<br>• The SmPC wording for aflibercept is below. EMC (2017) Available at: https://www.medicines.org.uk/emc/medicine/27224 Date last accessed 26/07/2017. | Thank you for highlighting this potential inconsistency. Aflibercept TREX included in the model – which applies a TREX protocol from day 1 of treatment – has now been removed from model analyses that limit strategies to SPC-based treatment protocols. |

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| | | | | *"Posology wet AMD The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres. Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with Eylea, and based on visual and/or anatomic outcomes, the treatment interval may be extended, such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly."* | |
| Novartis | Long | 196 | 10.4.1 | **General**<br>• Option regarding patients' preference of regimen. Not substantiated with evidence. *"Patients may prefer to have a treatment regimen that has fewer injections (for example, aflibercept is normally provided on a bi-monthly schedule)."* Please remove the example.<br>A bevacizumab trial (Barikian 2015) is used to inform the ranibizumab PRN injection number however a more scientifically robust approach would have been to include a ranibizumab trial e.g. IVAN (Chakravarthy *et al.* 2012) / HARBOUR (Busbee *et al.* 2013). Including ranibizumab RCT data to inform the injection number in the base case would result in a very modest change in the cost and QALYs for ranibizumab Load+PRN. | Thank you for your comment. Injection frequencies have been revised in conjunction with our revisions to the long-term (year 3+) model inputs.<br>The Barikian study was only used to inform the expected effect of having a loading phase compared with starting a 'truly' PRN regimen (i.e. treatment on an as-needed basis from day 0) in year 1 of treatment. This was to avoid the potential for a 'load+PRN' regimen requiring fewer injections than a 'true PRN' regimen. However, we agree that using the RCT evidence for studies with a loading phase followed by PRN would be valid here, and have therefore used these pooled sources to inform year 1 ranibizumab loading + PRN injections. The number of injections for bevacizumab PRN in year 1 remains unchanged, |

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| | | | | | informed by CATT and the Barikian study for 'true' PRN, and then +0.2 injections for loading+PRN.<br>These changes, as suggested in your comment, do not significantly affect the conclusions drawn from the model. |
| Novartis | Long | 30 | 4.1<br>25-36 | **<u>Prominence of unlicensed bevacizumab throughout the documents</u>**<br>• We fully agree with the positioning of unlicensed bevacizumab in recommendation 21, namely that:<br>*"21. Bevacizumab is not licensed for intraocular use for AMD. Prescribers should be aware that:*<br>• *bevacizumab can only be prescribed for AMD if a person has a specific need and no other licensed product meets the need;*<br>• *bevacizumab may not be prescribed for intraocular use for AMD simply because it is cheaper or more cost effective than a licensed alternative;*<br>• *clinicians should consider relevant professional guidance if prescribing outside a licensed indication;"*<br>• However, given this very clear guidance, which we welcome as a recommendation in the main guideline document, we propose that the main guideline should | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |

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| | Long | 167 | 10.2.4 | only focus on licensed therapies and all bevacizumab analyses should be presented in separate appendices.<br>• Unlicensed bevacizumab is mentioned frequently throughout the text in all sections and appears with priority over licensed therapies. For example, we suggest the recommendation not to recommend unlicensed bevacizumab (currently recommendation 21) is moved down to sit after the current recommendation 35 (i.e. after all of the recommendations that relate to the use of licensed therapies). Additionally moving all the bevacizumab analyses to a separate appendix would help avoid diluting the usefulness of the guidelines for routine clinical practice in the UK.<br><br>We note in this respect that the committee would like to "future-proof" the guidance in case bevacizumab has a change in its regulatory position. However, the current structure of the guidelines makes it difficult to find the relevant information for the current situation where ranibizumab and aflibercept are licensed and have NICE guidance and could lead to unintentional misunderstanding/confusion. | |
| Optical Confederation and Local Optical | Short | General | | As organisations which represent optometrists and dispensing opticians who are by far the most numerous primary care eye health professionals, we welcome the NICE Clinical Guidelines on macular degeneration. However, we are very disappointed about the general lack of acknowledgement of the current & | Thank you for your comment. The committee comprised representation from a range of relevant stakeholders including optometrists. The role of optometrists was discussed and their importance acknowledged in the guideline. The committee also |

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| Committee Support Unit | | | | potential role of optometrists and dispensing opticians in the entire consultation.<br><br>The regulations (and NHS England) are clear that General Ophthalmic Services (GOS) are only for the testing of sight (including opportunistic case finding, treatment or referral) and should not be used for monitoring established eye health conditions.<br><br>Instead, extended primary care services should be commissioned for these purposes in line with local needs (including improved access and convenience for patients). The contractual framework for this has been in place since 2006.<br><br>NHS England Local Eye Health Networks (LEHN), the LOC Support Unit (LOCSU), Local optical Committees (LOCs) can work with commissioners to arrange such services ideally at NHS regional level for maximum efficiency. | benefited from evidence presented from expert witnesses from the Association of British Dispensing Opticians; see section 8.1.1.<br>Very little evidence was identified regarding the optimal configuration of primary eyecare services, as they relate to AMD. However, at its post-consultation meeting, the committee agreed to add a new research recommendation – What is the diagnostic accuracy of OCT offered in primary care? This recommendation seeks to encourage research into one way in which the role of community eyecare services in the AMD pathway may expand. |
| Optical Confederation and Local Optical Committee Support Unit | Short | General | | Optical practices, optometrists and dispensing opticians, as the most numerous of those included in the definition of primary eye care professionals, need to be connected to the NHS IT infrastructure. If this is in place, optical practices will provide the much-needed additional clinical capacity to meet this growing patient demographic more effectively. Currently the technological isolation of optical practices prevents the true two way exchange of information stifling potentially new ways of working. | Thank you for your comments which were noted by the committee. However, the structure and resources of community eyecare services generally was beyond the scope of this guideline. |

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| Optical Confederation and Local Optical Committee Support Unit | Short | 3 | 4 | We note that small "hard" drusen (less than 63um) is now only classified as a variation of normal under the revised international classification. Clear guidance on this is urgently needed to avoid confusion among patients with one practitioner explaining that hard drusen are "normal" and another who informs the patient of early AMD. Such differences could lead to unnecessary complaints to the General Optical Council (GOC) creating an unnecessary additional burden for all parties. The Optical Confederation will work with the College of Optometrists and education providers to ensure practitioners are aware of the change and reflect that appropriately in their practise and patient communications. | Thank you for your comment. We agree with this, and hope our classification is clear. It is consistent with other classification systems in this regard. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 5 | 11 | Whilst we are naturally supportive of any aims to increase understanding and support for patients, this section does not accurately reflect the role of primary care. Patients could and should be directed towards appropriate optical practices for advice and support. As noted above however this extended primary care service should be commissioned separately from GOS sight testing in England. Scotland and Wales have national schemes for services that fall outside of GOS, England is sadly trailing far behind. | Thank you for your comments which were noted by the committee. However, the structure and resources of community eyecare services generally was beyond the scope of this guideline. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 6 | 11 | Community optical practices are by far the largest providers of NHS eye care. As such they are the most logical location for patients to access information, ask questions and discuss concerns. As above this needs to be commissioned separately from GOS in line with local needs. | Thank you for your comments which were noted by the committee. However, the structure and resources of community eyecare services generally was beyond the scope of this guideline |

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| Optical Confederation and Local Optical Committee Support Unit | Short | 7 | 2,3,4 | We have concerns over the term "offer ophthalmoscopy" as this is backward step. Further, the term 'ophthalmoscopy' is inconsistent with the later sections on examining patients where slit lamp biomicroscopic fundus examination is recommended.<br><br>Slit lamp biomicroscopic fundus examinations are already routinely provided by optometrists in optical practices and form a fundamental part of the clear majority of referrals to secondary care which come via this route. This recommendation appears to not understand or be unaware of this and the role optometrists currently play which is of great concern if the needs of AMD patients are to be met. | Thank you for your comment. The wording of recommendation 1.4.1 has been revised to recommend the use of 'fundus examination' rather than ophthalmoscopy. It was not the committee's intention to suggest that ophthalmoscopy should be preferred to slit lamp biomicroscopy; rather, it wanted to emphasise that the important thing, in the first instance, is that the fundus is visualised using whatever means are available. It acknowledged that, in most cases (i.e. those that present in community optometry settings), this will mean using slit lamp biomicroscopy. Therefore, 'fundus examination' was agreed as a better generic term. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 7 | 6,7,8,9 | As above this draft appears not to understand the role of optical practices or GOS. The recommended diagnosis and triaging of patients falls outside of the remit of GOS.<br><br>An increasing number of optical practices now offer Optical Coherence Tomography (OCT) privately but could equally do so for the NHS to give a definitive AMD diagnosis and classification. This service could be commissioned locally ideally through a primary eyecare company (PEC) to ensure consistent standards, clinical governance and hospital clinic liaison. | Thank you for your comment. The structure and resources of community eyecare services generally was beyond the scope of this guideline. However, at its post-consultation meeting, the committee agreed to add a new research recommendation – What is the diagnostic accuracy of OCT offered in primary care? This recommendation seeks to encourage research into one way in which the role of community eyecare services in the AMD pathway may expand. |
| Optical Confederation and Local Optical | Short | 7 | 22,23 | The benefits of offering this service in primary care (although not via GOS) are increased capacity to meet growing need, better access and earlier diagnosis for patients, avoidance of unnecessary referrals, better differential diagnosis and more | Thank you for your comment. |

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| Committee Support Unit | | | | appropriate and timely referral and monitoring of other macula conditions. | |
| Optical Confederation and Local Optical Committee Support Unit | Short | 8 | 6,7,8,9,10,11 | We believe that local pathways lead to confusion, adding risk and cost. This is especially the case for locum clinicians of all disciplines who only occasionally work in a given geographical area and whose work is made more difficult than it should be. It is time for a national AMD referral protocol, with clear procedures to avoid placing patients and clinicians of all disciplines at risk. | Thank you for your comment. The committee noted your comments however it did not agree that it was feasible to specify a single pathway that could be applied in all local healthcare settings. No evidence was identified in the service provision questions of this guideline that could inform its specification in an evidence-based way. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 8 | 21,22,23,24,25 | We are concerned by the omission of optometrists and potentially dispensing opticians from the list of suitably trained professionals. There are already optometrists providing intraocular injections. This section should either add all professionals who may be involved or remove the examples and simply state "suitably trained healthcare professionals". | Thank you for your comment. This recommendation has been amended as suggested to include optometrists in the list of suitably trained professionals. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 12 | 1,2,3 | This recommendation rejects hospital monitoring, but is silent on monitoring in primary care. Monitoring could and should be provided in optical practices as part of extended primary care services. | Thank you for your comment. No specific evidence was identified on how monitoring in primary care services should be organised, and therefore the committee agreed it would not be appropriate to make recommendations on this topic. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 12 | 6.7.8 | As above we urge NICE to recognise that monitoring could and should be provided by optical practices as part of an extended primary care service. Also there is an anomalous reference to 1.8.5 which does not appear to exist. | Thank you for your comment. The structure and resources of community eyecare services generally was beyond the scope of this guideline, and therefore it was not possible for the committee to make recommendations on this topic. |

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| | | | | | Thank you for highlighting the anomalous reference; we have corrected this. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 12 | 9,10 | We are disappointed to see that given the immense financial and capacity strain caused by the monitoring of AMD a recommendation has not been made to deliver NHS monitoring within suitably equipped optical practices. | Thank you for your comment. No specific evidence as identified on how monitoring in primary care services should be organised, and therefore the committee agreed it would not be appropriate to make recommendations on this topic. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 12 | 14,15 | Optical practices will most likely see the majority of patients with visual concerns, either directly or via referral from a GP. Yet, without an extended primary care service in place, some of these patients will not be able to be seen for an NHS sight test (GOS) and will need to be re-referred to a more expensive and less convenient hospital service. | Thank you for your comment. The structure and resources of community eyecare services generally was beyond the scope of this guideline, and therefore it was not possible for the committee to make recommendations on this topic. |
| Optical Confederation and Local Optical Committee Support Unit | Short | 12 | 24,25 | This could be provided in optical practices with suitable equipment. If IT connectivity is in place, safe remote monitoring of wet AMD will be possible from suitable practices. This will increase capacity in hospital clinics and improve access for patients. | Thank you for your comment. This guideline reviewed evidence on different organisational models for ongoing treatment and follow up for people with diagnosed late AMD (wet active) (see chapter 8.1). However, no evidence was found on the safety and efficiency of remote monitoring in community optical practices. |
| Roche Products | Full – General comment | | | **Research landscape**<br><br>We propose to add information on the research landscape and potential future therapies in AMD.<br>We would advise the guideline is updated when new evidence from ongoing research trials becomes available that may impact on the future treatment and care for patients with AMD. | Thank you for your comment. The NICE surveillance team periodically identify and review any new evidence in the field, and will recommend an update to the guideline if necessary. |

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| Roche Products | Full | 9 / 243 | 27, 28, 29 / top box | We recommend to avoid using the terms 'very slowly', 'gradual change', 'usually takes a number of years' and 'tends to progress slowly' when describing GA and suggest that utilising these descriptive terms may not accurately reflect the variation in disease progression – we suggest to describe GA as an irreversible disease with heterogeneous progression rates.<br>● There is recent and growing evidence that GA does not always progress slowly and different phenotypes of disease progress at different rates (see for example: Holz. F. G. *et al.* Am J Ophthalmol. 2007 Mar;143(3):463-72 and Monés J, Biarnés M. Br J Ophthalmol 2017;0:1–5).<br>● With foveal involvement patients can experience a more rapid deterioration in vision (Sunness J.S. *et al.* Ophthalmology 1999 Sep;106(9):1768-79) | Thank you for your comment. The committee acknowledged that the progression of geographic atrophy (as with all forms of AMD) can be highly heterogeneous, and this has been clarified in the text cited. However, they also agreed that the text did reasonably describe the way GA "usually" progresses, as is specified in the wording. |
| Roche Products | Full (Short) | 169 (short - page 9) | 18, 19, 20 (short - lines 7, 8, 9) | **Safety profile of bevacizumab**<br><br>Also full guideline, page 161 'Trade off' section, in particular this comment 'the safety profiles of all 3 anti-VEGF therapies can be considered to be comparable'<br><br>We have additional comments relating to the guideline discussions of the off-licence use of bevacizumab (Avastin©) for intraocular use;<br>● Avastin is not developed and manufactured according to the quality standards for drugs to be injected into the | Thank you for your comments. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers |

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| | | | | eye. These quality standards are different from those required for drugs that are given as an intravenous (IV) infusion. Avastin is licensed as a concentrate solution for IV infusion. It is not approved for intravitreal injection. EU health authorities approved an update of Avastin's labelling including specific warnings related to its use in the eye. The warnings refer to systemic adverse events and eye disorders, including that non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors. We suggest consulting the Avastin SmPC for further information.<br>● Although to the best of our knowledge there is no single comparison trial that has been scaled or powered to detect rare individual adverse event differences, several published meta-analyses have shown an association between Avastin and higher rates of certain systemic adverse events. We would also draw attention to the comparative AE rates seen in the CATT data (Ophthalmology. 2012 Jul;119(7):1388-98). We would suggest the committee consider this information in the context of the guideline development,<br>● We also recommend that the guideline considers that clinical evidence for bevacizumab has been generated using the originator product. Health authority regulators will not consider extrapolation of this data for bevacizumab biosimilar candidates as it is off-licence, and therefore any guideline recommendation about | to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use.<br>The evidence reviewed by the committee included a scenario analysis in which the likelihood of endophthalmitis associated with bevacizumab in the original model was increased to an implausibly high level (20% per year). It saw that this had no material effect on the net balance of benefits and harms between the different agents (see appendix J.5.6.4). Therefore, it concluded that the evidence was robust to any uncertainty, in this area. |

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| | | | | bevacizumab cannot be assumed to apply to these products. We would refer to NICE guidance on biosimilar medicines stating that biologic medicines should be prescribed by brand, and adverse events should be reported by brand name and batch number. | |
| Roche Products | Short (and full) | 12 | 2-8 | **Monitoring for Geographic Atrophy**<br><br>*Other relevant sections in full guideline: page 32, lines 3-9 and page 203, lines 2-8*<br><br>We are concerned the following recommendations regarding monitoring for patients with GA may lead to variation in standards of care for patients across the country:<br>▪ do not routinely monitor people with early AMD or late AMD (dry) through hospital eye services<br>▪ advise people with late AMD (dry), or people who have been discharged from hospital services to 1) self-monitor their AMD and 2) consult their healthcare professional if their vision changes as soon as possible.<br><br>Our suggestions are as follows;<br><br>1. We would advise that the guideline to emphasises the importance of an annual eye health check in the primary care setting, this is particularly important in the | Thank you for your comments. A bullet-point recommending advice on sight-tests has been added to 1.7.2.<br>The committee agreed that, as there are no effective therapies available for geographic atrophy, it would not be an effective use of ophthalmologist time to provide secondary care services for the classification and monitoring of late AMD (dry). What is important is that people with diagnoses in this category receive access to appropriate support services, and it is emphasised in 1.4.5 that this may be a reason to refer people to secondary care. |

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| | | | | monitoring of patients with early or intermediate AMD (per ICD-11 beta draft proposal).<br><br>2. We would advise that patients with a confirmed diagnosis of GA within HES (even if lesions are under 175µm, i.e. these patients are currently in the 'high risk early' group in the proposed classification system but all GA would be in the advanced disease classification in the ICD-11 beta draft proposals) are subsequently monitored annually (either in the primary care setting or HES). This will arguably enable better quality care by improving access to support services for this group of patients such as low vision services or those provided through Patient Advisory Groups (e.g. counselling).<br>○ *See 'trade off between benefits and harms' section, page 202, line 9.* We would caution against the general advice of promoting patients with GA to self-monitor as patients with AMD, particularly with GA, are elderly and may attribute visual functional loss to ageing or may not notice visual functional changes quickly, especially if they have unilateral disease or co-morbidities such as cataract / glaucoma.<br>– The consequences may be lack of prompt access to support services in the event of visual deterioration as a result of progression of GA, or in the event of exudative / neovascular AMD, | |

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| | | | | delayed identification and implementation of appropriate management.<br>– In the full guideline we note that page 236, lines 24-33 provide further support to the importance of regular HCP monitoring.<br><br>3. *General comment on document and also see page 211, Section 11.3.* We would suggest the committee consider whether another section is needed in the guideline making recommendations relating to monitoring strategies and tools for people with GA. However, if the committee feel there is an absence of sufficient evidence to make recommendations, we suggest consideration is given to inclusion of this information in a future guideline update and could utilise the following data sources;<br>○ results from **Research recommendations B, C and expanded Research recommendations 5 and 6**, suggested above.<br>results from ongoing research within the geographic atrophy diease area | |
| Roche Products | Short (and full) | 3, 4 (full - page 28) | 2, 3, 4 (full - lines 2, 3) | **Classification and description of AMD**<br><br>We would like to draw attention to elements of the classification system used within the guideline; we suggest review of the ICD- | Thank you for your comment. In regards to your comment regarding the new classification system and geographic atrophy. There have been recent advances in our understanding of this sub-type or feature of AMD, including consensus recommendations on imaging |

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| | | | | 11 beta draft update proposal and recommend close alignment of the new NICE classification with this: http://apps.who.int/classifications/icd11/browse/f/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f2100480156 Notes: 1) the ICD-11 beta draft proposal is currently in consultation phase, and 2) the proposed ICD-11 classification also closely aligns with the new ICD-10-CM classification utilised in the United States (updated end 2016).<br><br>We would also draw attention to the Ryan Initiative for Macular Research Committee classification system (Ferris F.L. *et al*. Ophthalmology 2013;120:844 – 851) which closely aligns with the above-mentioned ICD-11 beta draft.<br><br>In addition, we make the following points in concordance with this recommendation;<br>● We note that in the new classification system, geographic atrophy (GA) with lesions < 175µm is classified as 'early AMD (high risk)' and believe that incorporating GA within an 'early category' could inaccurately represent the potential severity and impact of this disease. We advise all GA is categorised as advanced AMD (with foveal involvement or without foveal involvement) as per the ICD-11 beta draft proposal.<br>● We would suggest that the term 'late' is replaced with the term 'advanced' AMD as per the ICD-11 beta draft proposal. | modalities used in researching it (not relevant to this classification). We have dropped the specific term Geographic for small areas of atrophy which include areas of incomplete loss of retinal/RPE layers. The term Geographic Atrophy now appears only in the Late AMD (dry) category, although it is recognised it can occur in other categories, such as Late AMD (wet active) but these will be the dominant category. |

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| | | | | ● We suggest to segment out other phenotypes described in the 'late AMD (dry)' category more clearly from GA (i.e. confluent drusen, advanced pigmentary changes and adult vitelliform lesion). These could be included into an intermediate stage disease category, as per the ICD-11 beta draft proposal.<br>● Regarding the 'atrophy' in the 'late AMD (wet inactive)' category we advise the ICD-11 beta draft proposal is followed, which classifies all atrophy into advanced AMD - GA.<br>● *Also see: full guideline page 31, line 45; page 196 'factors for stopping treatment'; page 198 line 7 and short guideline page 11, line 8.* We are concerned about the disease phenotypes within the late AMD (wet inactive) category, particularly with regard to the advice provided to stop treatment for patients with these phenotypes. These could co-exist with active disease also, but we cannot see this specifically mentioned as a separate point.<br>○ We would make reference to the treatment cessation and discontinuation section in the RCOphth AMD Guidelines 2013 - www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf (section 9.7, pages 81-83), noting that the guidance only states to consider temporary treatment discontinuation if there is no disease | |

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| | | | | activity, and that these signs are not specifically mentioned in the guidance as indications to discontinue treatment permanently.<br>○ We suggest it could be clarified within the new guideline to note that the presence of these phenotypes may not always mean that disease is inactive.<br><br>We would suggest that if the classification system is changed then all relevant sections in the document are amended to reflect this and consistency is applied throughout *(for example in full document -'Context' section, lines 10, 11, 12)* | |
| Roche Products | Short (and full) | 7 | 8, 9, 13-18 | **Referral and treatment pathways for Geographic Atrophy**<br><br>*Other relevant sections in the full guideline: page 29, lines 31-37; page 107, section 'early AMD and late AMD (dry)'; page 109, lines 4-10*<br><br>We are concerned about the following recommendations regarding referral and treatment pathways for patients with GA considering they may lead to variation in standards of care for patients across the country:<br>▪ not to refer people with early AMD to hospital eye services (making this point with reference to previous comments that 'early AMD' in the new classification system also encompasses patients with GA) | Thank you for your comments.<br>(1) The committee agreed that, as there are currently no effective therapies available for geographic atrophy, it would not be an effective use of ophthalmologist time to provide secondary care services for the classification and monitoring of late AMD (dry). What is important is that people with diagnoses in this category receive access to appropriate support services, and it is emphasised in 1.4.5 that this may be a reason to refer people to secondary care.<br>(2) For similar reasons, the committee were unconvinced that research into techniques to classify geographic atrophy should be considered a priority. Fundus autofluorescence was a technology of interest in review questions concerning the diagnosis of |

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| | | | | ▪ only refer people with late AMD (dry) to hospital eye services 1) for certification of sight impairment, or 2) if this is how people access low-vision services in the local pathway, or 3) if they develop new visual symptoms that may suggest late AMD (wet active).<br><br>Our suggestions are as follows;<br><br>1. We would strongly advise any patient with a suspected diagnosis of GA seen within the primary care setting (even if lesions are under 175µm, i.e. these patients are currently in the 'high risk early' group in the proposed classification system but all GA would be in the advanced disease classification in the ICD-11 beta draft proposals) be referred to hospital eye services (HES) for confirmation of diagnosis.<br>○ We would propose a **research recommendation (A)** to understand the optimal time and pathway for referral to HES of this group of patients related to outcomes and suggest consideration of referral via a direct pathway, distinct from the neovascular / exudative AMD pathway.<br>○ *See also full, page 94, lines 12, 13:* We would suggest to also include GA here to acknowledge that Optometrists will usually be the first HCPs seeing patients with GA and will | geographic atrophy and late AMD (wet active); however, very limited data meeting the eligibility criteria of the reviews were found. The 'evidence review' section of the relevant chapter (7.2.1) has been revised to make this clearer.<br>(3) The effectiveness of support services for people with visual impairment was assessed using a review that included 'functional capacity, participation, independence and ability to carry out activities of daily living' as an outcome. This was an important component of the evidence reviewed by the committee.<br>(4) The committee did not agree that a research recommendation regarding service pathways for people with geographic atrophy should be prioritised, at this stage, as the absence of effective therapies for the condition means the priority should be to ensure that people have access to appropriate support services. The committee believes that its recommendations should help to optimise and standardise practice, in this regard. |

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| | | | | need to make the most appropriate referral / follow up decisions.<br><br>2. We would suggest that the guideline incorporate information about diagnostic imaging to assist in classification and monitoring of patients with GA. We would refer the panel to the recently published paper from the Classification of Atrophy Consensus Meetings (Holz F. J. *et al*. Ophthalmology. 2017 Apr;124(4):464-478) outlining imaging assessments recommended in AMD clinical trials.<br>○ We would suggest consideration be given to the incorporation of Fundus Autofluorescence Imaging alongside OCT in Standard of Care assessment of GA patients<br>○ We also suggest a **research recommendation (B)** to understand which diagnostic imaging should be used in the primary care setting and also in HES in the 1) diagnosis and 2) monitoring - of patients with high risk early ( / intermediate in ICD-11 proposal) AMD, and GA to help evaluate the effectiveness of support strategies.<br><br>3. *See also: full, page 121, line 23, box 1.* We advise the guideline to provide, if possible, education on additional functional tests and patient reported outcome measures (PROMs) that could be used for patients with GA to help | |

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| | | | | evaluate the effectiveness of support strategies. Even without foveal involvement, patients with GA will still experience functional deficits and BCVA testing does not adequately represent the degree of visual functional impairment (Sunness J. S. *et al.* Ophthalmology. 1997 October; 104(10): 1677–1691).<br>○ We suggest that further evidence for functional testing provided from ongoing GA research trials should be taken into consideration and the guideline be amended as appropriate (e.g. low luminance visual acuity, reading speed, microperimetry and patient reported outcome measures such as the functional reading independence index which can be accessed from MAPI Research Trust - PROinformation@mapi-trust.org). Please see: Sadda S. R. *et al*. RETINA 36:1806–1822, 2016 for context.<br>○ We would also suggest a **research recommendation (C)** to understand which functional tests and PROMs should be used in the primary care setting and in HES in the 1) diagnosis and 2) monitoring of patients with high risk early ( / intermediate in ICD-11 proposal) AMD, and GA to help evaluate the effectiveness of support strategies. | |

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| | | | | 4. *See also: full, page 109, lines 24-31 and page 110, lines 1-18*<br>○ **Research recommendation 5**: We would suggest this could be expanded to include GA as well as 'suspected late AMD (wet active)'. It will also be critical to understand the future role of digital technology in helping support future diagnostic accuracy of GA to ensure the correct patients are identified and referred to HES from the primary care setting - this will become increasingly important also with the upskilling of Optometrists and their increasing use of technologies such as OCT machines.<br>○ **Research recommendation 6**: We would suggest to either add to this or add another research recommendation to include patients with GA. There is a need to understand how future service pathways should be set up to provide the best patient care. We would advise to include other visual functional and QoL metrics (see point 3 above). | |
| Royal College of General Practitioners | General | | | The Role of the Gp is mentioned only briefly in 4 places in the document on pages 71,94,96 and 106.<br><br>GPs can play a critical role in identification and timely referral in patients with wet AMD, facilitating smoking cessation, advising | Thank you for your comment. The committee agreed the appropriate focus for the guideline was on the services that should be provided to people, rather than who should provide each of those services, which is a matter for local service organisation and contracting. |

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| | | | | on diet rich in dark green leafy vegetables and enabling them to access support services for the visually impaired. In addition there is a significant role in offering emotional support and treating any associated depression. The role is summarised well in an article by Dr Horton and Dr Gully in January 2017 Prescriber http://www.prescriber.co.uk/article/prevention-treatment-age-related-macular-degeneration/.<br><br>Prevention and treatment of age-related macular degeneration www.prescriber.co.uk<br><br>Age-related macular degeneration (AMD) is a common cause of visual loss in older people and GPs play a critical role in identification and timely referral.<br><br>They also highlight the rapid access Wet AMD form developed by the Royal College of Ophthalmologists for optometrists and GPs. www.rcophth.ac.uk/wp-content/uploads/2015/04/2010-SCI-048-AMD-Electronic-Referral-Form-edited.pdf. This includes useful reminder photos of fundoscopy appearances.<br><br>This large NICE document would enhanced with specific sections on the role of GPs and optometrists which would help make it accessible to primary care. | |
| Royal College of | Full | Sections 7.1 and | general | **(1) diagnostic tests to detect early AMD and late dry AMD:** suggest fundus auto-fluorescence should be considered as a | Thank you for your comments. Fundus autofluorescence was a technology of interest in review |

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| Ophthalmologists | short | 7.2 pages 75-93<br><br>1.4.8 and 1.4.9 pages 7-8 | | potentially useful diagnostic test to include in the review, as it detects and quantifies atrophy of the retinal pigment epithelium.<br><br>**(2) Choice of reference standard to diagnose wet active AMD**<br>The reference standard should be the best test currently available, and is the standard against which the index test is compared. It need not be the test used routinely in practice (although it can be).<br><br>It is unclear why the committee used two different reference standards to diagnose wet AMD. In section 7.1. the reference standard used was fluorescein angiography, FFA. However, in section 7.2 the reference standard was OCT (and FFA was considered to be an index test). It is unclear why a different reference standard has been used. The RCOphth suggests the reference standard for diagnosing wet AMD should be FFA (as used in Section 7.1) and not OCT. | questions concerning the diagnosis of geographic atrophy and late AMD (wet active); however, very limited data meeting the eligibility criteria of the reviews were found. The 'evidence review' section of the relevant chapter (7.2.1) has been revised to make this clearer.<br>In 7.2, as in 7.1, FFA was the reference standard against which included studies assessed diagnostic accuracy for the detection of late AMD (wet active). We have revised section 7.2.1 to make this clearer. |
| Royal Free London NHS Foundation Trust | Full | General | General | We thank the panel for their hard work putting these updated guidelines together. There are two areas where we feel the guidance could be improved. | Thank you for your comment, and your acknowledgement of our work in the development of the guideline. |
| Royal Free London NHS Foundation Trust | Full | General | General | The first concern relates to patients with better than 6/12 (70 LogMAR letters) vision being denied access to NICE recommended licensed anti-VEGF treatment. The UK AMD | Thank you for your comments. The committee considered stakeholder comments and revised health economic modelling of relevance to the upper acuity threshold for initiating anti-VEGF treatment at its post-consultation meeting. It noted that the revised model |

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| | | | | EMR Users Group evaluated the efficacy of initiating treatment with ranibizumab for neovascular AMD in eyes with baseline VA better than 6/12 (>70 LogMAR letters) in routine clinical practice in the UK National Health Service. Some of the commissioning groups in the UK had provided funding to treat patients with better than 6/12 baseline VA. This is to allow patients to maintain driving level vision and independence. Anonymised structured data were collected from 14 UK centres. The primary outcome was the mean VA at year 1, 2 and 3. A total of 754 of 11,135 patients had baseline VA better than 6/12 and at least 1-year of follow-up. All eyes with baseline VA better than 6/12 maintained superior mean VA than the eyes with baseline VA between 6/12 to 6/24 at all time-points for at least 2 years (globally adjusted p-values <0.001 in year 1 and 2). The authors reported that the significantly better visual outcome in patients who were treated with good baseline VA had implications for future policy regarding funding treatment for wet AMD (Lee et al., 2015). | suggested that, compared with restricting antiangiogenic therapy to the range recommended in TA155 and TA294, offering treatment to eyes with acuity greater than 6/12 invariably provides benefits at a cost that would conventionally be considered an effective use of resources. However, the committee understood that, unless the agent used was either bevacizumab or very low-intensity ranibizumab, extending treatment was only cost effective compared with something that was, in itself, not cost effective. Because the analysis had convincingly shown that there are many strategies that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation explicitly mandating such an approach. However, the committee noted that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used. |

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| | | | | Data can also be evaluated from other countries where arbitrary baseline VA restrictions are not applied. Five year real-world outcomes of intravitreal ranibizumab for wet AMD in 549 eyes from the FRB! database mainly set in Australia, stratified by baseline VA are illustrated in Figure 4 (Gillies et al., 2015). Eyes with better baseline VA maintain good vision for longer although there is less scope for improvement in VA because of a ceiling effect.<br><br>Frieden, T.R., 2017. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med 377, 465-475.<br>Gillies, M.C., Campain, A., Barthelmes, D., Simpson, J.M., Arnold, J.J., Guymer, R.H., McAllister, I.L., Essex, R.W., Morlet, N., Hunyor, A.P., Fight Retinal Blindness Study, G., 2015. Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 122, 1837-1845.<br>Kim, L.N., Mehta, H., Barthelmes, D., Nguyen, V., Gillies, M.C., 2016. Metaanalysis of Real-World Outcomes of Intravitreal Ranibizumab for the Treatment of Neovascular Age-Related Macular Degeneration. Retina 36, 1418-1431.<br>Lee, A.Y., Lee, C.S., Butt, T., Xing, W., Johnston, R.L., Chakravarthy, U., Egan, C., Akerele, T., McKibbin, M., Downey, | |

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| | | | | L., Natha, S., Bailey, C., Khan, R., Antcliff, R., Varma, A., Kumar, V., Tsaloumas, M., Mandal, K., Liew, G., Keane, P.A., Sim, D., Bunce, C., Tufail, A., Group, U.A.E.U., 2015. UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. Br J Ophthalmol 99, 1045-1050. | |
| Royal Free London NHS Foundation Trust | Full | General | General | The second concern relates to treat-and-extend (T&E) regimens in real-world practice. Real-world evidence has identified countries like Australia and USA where treat-and-extend is established have achieved better long-term visual outcomes than PRN regimens which used to be more common in the UK. This is likely because it is difficult to achieve the frequency of follow-up visits (every 4 weeks) as mandated in clinical trials of PRN regimens in the real-world. Also, with each recurrence vision can be irreversibly lost. T&E is more proactive and reduces the number of clinic visits compared with PRN approaches.<br><br>A meta-analysis of global real-world outcomes of over 13,000 eyes receiving ranibizumab for neovascular AMD identified treat-and-extend regimens were associated with better vision outcomes versus PRN regimens, albeit with more injections; the mean number of yearly injections (over the three years) was 4.7 for PRN versus 6.9 for T&E. After 3 years, the meta-analysis identified a mean loss of 1.9 letters (95% CI: -9.8-6.0; n=11,714) from baseline for the PRN regimen, compared with a mean gain of 5.4 letters (95% CI: -4.1-14.9; n=1,298) for the T&E regimen, | Thank you for your comments. Because additional evidence on treat-and-extend regimens has become available (as highlighted by other stakeholders), the original economic model has been revised and now makes use of this evidence. TREX regimens are also now included in the base-case model results.<br>The collection of randomised evidence that is now available suggests that TREX regimens are similarly effective to PRN regimens at 1 year, and may be somewhat less effective after 2 years' follow-up (though this latter finding is subject to considerable uncertainty).<br>Considering a collection of uncontrolled case series on its merits leads to unfavourable conclusions for such evidence. While it is possible that the relative effectiveness of different treatment regimens differs in experimental and observational contexts, a wide variety of other factors (including selection biases, cohort effects, publication biases) could account for differences between PRN case series and TREX case series. We consider that it would pose a greater risk to patient wellbeing to treat such evidence uncritically. |

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| | | | | with both groups having similar mean baseline visual acuity.(Kim et al., 2016).<br><br>A recent paper in the New England Journal of Medicine by the former head of the CDC advises (Frieden, 2017) titled "Evidence for Health Decision Making - Beyond Randomized, Controlled Trials" advises that all evidence be considered on its merits. Real-world evidence can be complementary to randomised control evidence – our patients may well be harmed if it is ignored.<br><br>Frieden, T.R., 2017. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med 377, 465-475.<br>Gillies, M.C., Campain, A., Barthelmes, D., Simpson, J.M., Arnold, J.J., Guymer, R.H., McAllister, I.L., Essex, R.W., Morlet, N., Hunyor, A.P., Fight Retinal Blindness Study, G., 2015. Long-Term Outcomes of Treatment of Neovascular Age-Related Macular Degeneration: Data from an Observational Study. Ophthalmology 122, 1837-1845.<br>Kim, L.N., Mehta, H., Barthelmes, D., Nguyen, V., Gillies, M.C., 2016. Metaanalysis of Real-World Outcomes of Intravitreal Ranibizumab for the Treatment of Neovascular Age-Related Macular Degeneration. Retina 36, 1418-1431.<br>Lee, A.Y., Lee, C.S., Butt, T., Xing, W., Johnston, R.L., Chakravarthy, U., Egan, C., Akerele, T., McKibbin, M., Downey, L., Natha, S., Bailey, C., Khan, R., Antcliff, R., Varma, A., Kumar, V., Tsaloumas, M., Mandal, K., Liew, G., Keane, P.A., | |

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| | | | | Sim, D., Bunce, C., Tufail, A., Group, U.A.E.U., 2015. UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12. Br J Ophthalmol 99, 1045-1050. | |
| Royal Holloway, University of London | Full in each case | 231 | 'Other consider - ations' | Other points missed from the recommendations.<br><br>-No mention of the role GPs play in providing information and support? Evidence for this is provided in Mitchell et al 2002 (cited for other reasons in the draft guidelines) and Boxell et al 2017.<br>- No mention of visual hallucinations (CBS) and the impact of not receiving information on this. Information on this is provided by Boxell et al (2017) cited above.<br><br>General points<br>It is difficult to work out which publications have provided which evidence. Surely it would be easier for the guideline developers to keep track of the evidence and its sources if they cited the evidence throughout? It would certainly be easier for those of us reviewing the guidelines. It is not always possible to recognise evidence we ourselves have provided (see point above re p225).<br><br>It is unfortunate that the guidelines 'are primarily concerned with barriers and facilitators to adherence of appointment and | Thank you for your comment. The committee agreed it would be helpful to add 'the possibility of developing visual hallucinations associated with retinal dysfunction (Charles Bonnet syndrome)' to the list of topics that should be discussed with people with AMD (1.2.2) |

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| | | | | treatment' (p231) when there is much evidence to suggest that clinicians are all too frequently not providing the information that patients need and in this omission, are failing to adhere to the guidelines of the Royal College of Ophthalmologists (2009 and later). It is encouraging that the guideline developers recognised that 'patients felt a lack of confidence not only on how to make straightforward decision(s) themselves, but also when and where to report any vision changes'. We have found in the course of our research that it is far from 'straightforward' for patients to make a decision about when and how to seek help because they have not been given the information they need (Boxell et al 2017 BMJ Open. Full reference given above). | |
| Royal Holloway, University of London | Full | | | We published the following paper recently which has not been captured by the present guidelines and provides useful evidence for many of the issues covered (eg Section 7 on diagnosis, Section 11 on monitoring and Section 12.2: Informational needs of people with suspected or confirmed AMD and their family members/carers<br>Pg 232) and some not covered (see our final comments below). The full reference for the paper is:<br>Boxell, E.M., Amoaku, W.M. & Bradley, C. (2017). Healthcare experiences of patients with age-related macular degeneration: have things improved? Cross-sectional survey responses of Macular Society members in 2013 compared with 1999. *BMJ Open. 7.* | Thank you for your comment. Unfortunately, this paper was published after the cut-off search dates for inclusion in the guideline, and therefore has not been included within the evidence base.<br>We have passed this reference to the NICE surveillance team, both so it can be used to inform when future updates of the guideline may become necessary, and so that it can be included as evidence when any such future updates may be conducted. |
| Royal Holloway, | Full | 200 | | Further evidence to support the recommendation to inform patients about self-monitoring comes from a study which found that patients with AMD who were not told at the time of | Thank you for your comment. Unfortunately, this paper was published after the cut-off search dates for |

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| University of London | | | | diagnosis about what to do if they notice a sudden deterioration in vision, were more likely to be registered as sight impaired later on (Boxell, Amoaku & Bradley, 2017). | inclusion in the guideline, and therefore has not been included within the evidence base.<br>We have passed this reference to the NICE surveillance team, both so it can be used to inform when future updates of the guideline may become necessary, and so that it can be included as evidence when any such future updates may be conducted. |
| Royal Holloway, University of London | Full | 225 | 37 | If this evidence is from Mitchell et al 2002 we think it may not be described accurately. Patients reported reasons for satisfaction/dissatisfaction which is not the same as reporting 'obstacles' to treatment which suggests that the source of dissatisfaction prevented them from having treatment but there was no evidence for treatment not being followed through with in this paper. | Thank you for your comment. We have updated the wording to refer specifically to dissatisfaction rather than obstacles, as we agree these may not be measuring the same thing. |
| Royal Holloway, University of London | Full | 232 | | The section on 'Informational needs of people with suspected or confirmed AMD and their family members/ carers' could usefully include the recent paper by Boxell, Amoaku & Bradley (2017) called, 'Healthcare experiences of patients with age-related macular degeneration: have things improved? Cross-sectional survey responses of Macular Society members in 2013 compared with 1999' (published in BMJ Open by Boxell et al 2017).<br>Line 5, page 233, states that the reviewed evidence only included people who were being treated for AMD. It is not clear why this criterion was set and would exclude some important evidence which suggests that lack of information provision is associated with subsequent registration as severely visually impaired/visually impaired. | Thank you for your comment. Unfortunately, this paper was published after the cut-off search dates for inclusion in the guideline, and therefore has not been included within the evidence base.<br>We have passed this reference to the NICE surveillance team, both so it can be used to inform when future updates of the guideline may become necessary, and so that it can be included as evidence when any such future updates may be conducted. |

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| | | | | An additional criterion was that evidence included in this section was qualitative only (see page 237, line 28). However patient experiences on this topic are represented in the recently published quantitative study by Boxell, Amoaku & Bradley (2017) cited above. | |
| Royal Holloway, University of London | Full | 237-8 | | Under 'Evidence to recommendations' table, the section on 'Trade-off between benefits and harms' states that committee reported that optometrists were reluctant to stock information on AMD. The Boxell et al., (2017) paper found that 45% of respondents to the Macular Society 2013 survey had been diagnosed by an optometrist. Many people are diagnosed by an optometrist and not seen in an eye clinic unless they are receiving treatment. Therefore it is particularly important that information is given to patients by optometrists and concerning if optometrists are reluctant to provide information on AMD. It is not clear if these concerns have been resolved since optometrists were permitted to make a diagnosis of AMD or whether they continue to have concerns about providing information. Participants in our research have reported that optometrists diagnosing cases of dry AMD no longer refer patients to ophthalmologists so it would seem that concerns that the final diagnosis may differ from that which the optometrist provided are historical and no longer apply. | Thank you for your comment. Unfortunately, this paper was published after the cut-off search dates for inclusion in the guideline, and therefore has not been included within the evidence base.<br>We have passed this reference to the NICE surveillance team, both so it can be used to inform when future updates of the guideline may become necessary, and so that it can be included as evidence when any such future updates may be conducted. |
| Royal Holloway, University of London | Full | 32 | 5 - 6 | Recommendation states that people with late AMD (dry), or people who have been discharged from hospital services to: self-monitor their AMD, and consult their healthcare professional if their vision changes as soon as possible. All patients with AMD, including those who have been seen by an optometrist or | Thank you for your comment. The committee agreed that the recommendation that people should be advised to 'consult their eye-care professional as soon as possible if their vision changes' (1.7.2) constitutes clear advice on what patients should do if their vision |

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| | | | | who have early stage AMD, would benefit from being told what to do if their vision deteriorates. Our recently published paper found that many patients are not being given this information at diagnosis (Boxell, Amoaku & Bradley, 2017). Those who weren't told at diagnosis about what to do if their vision deteriorates were more likely to report being registered as sight impaired later on (at the time of survey completion) (Boxell, Amoaku & Bradley, 2017).<br>The recommendation number 39 (line 12/13) states that self-monitoring should be discussed with patients and thus goes some way to address the above issue. Recommendation 37 and 39 could be re-worded so they are not conflicting and to make clear when urgent action is needed. | changes. Additional detail is provided in 1.7.5 regarding symptoms to be vigilant for in people who are self-monitoring their condition.<br>The committee noted your comments with regard to possible conflicting statements in recommendations 37 and 39 however they did not agree that the wording of the recommendations presented any contradiction. Recommendation 37 is intended to advise people with AMD of the actions they should take following discharge. This now also includes continued attendance at routine sight tests with a community optometrist. Recommendation 39 is in place to ensure that all people with AMD are provided sufficient detail regarding the self-monitoring strategies available to them. |
| Royal Holloway, University of London | Full | 32 | 38 | Recommendation 47 focuses on information and support for people with AMD. The reviewed evidence to support these recommendations could usefully include our recently published paper which focuses on information and support provision in the diagnostic consultation (Boxell, Amoaku & Bradley, 2017). Information and contacts for support groups are provided in the Macular Society 'Guide to AMD' booklet. This leaflet could be given in diagnostic consultations as a resource for patients and carers to take away and read. | Thank you for your comment. Unfortunately, this paper was published after the cut-off search dates for inclusion in the guideline, and therefore has not been included within the evidence base.<br>We have passed this reference to the NICE surveillance team, both so it can be used to inform when future updates of the guideline may become necessary, and so that it can be included as evidence when any such future updates may be conducted. |
| Royal National | Short | General | General | **RNIB recommend a specific provision in this guideline for people with AMD to feedback on their experience of treatment and care**. | Thank you for your comment. This general principle, which NICE supports, is contained in the NICE |

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| Institute of Blind People | | | | 78 per cent of the people we spoke to said that they had not been asked about their level of satisfaction regarding their treatment and 81 per cent had not completed any patient satisfaction questionnaires. Some people said they would have welcomed the opportunity to say they were happy with the service they received while others felt that some aspects of their treatment could be improved – this mainly related to the lack of information provision from the hospital. Individual issues included delayed appointments, health professionals being 'cold' in their delivery of information and no continuity of consultants. | guideline on Patient experience in adult NHS services, to which we refer at the beginning of the guideline. |
| Royal National Institute of Blind People | Short | General | General | RNIB carried out a survey of 153 AMD patients recruited from RNIB's support base and beyond to inform the response to this Clinical Guideline draft to ensure patient voice and experience is represented in our response.<br><br>The rapid survey was carried out in the consultation period to capture patient responses to the content of the draft guidance. Our findings from this survey will be referred to throughout where relevant. Bases vary and are provided.<br><br>**Profile of respondents**<br>First diagnosis of AMD (base: 150):<br>• 10 per cent less than a year ago (n=15)<br>• 16 per cent one to two years ago (n=25)<br>• 33 per cent three to five years ago (n=50)<br>• 17 per cent six to ten years ago (n=25) | Thank you for providing information from your support base. |

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| | | | | • 25 per cent less than a year ago (n=38)<br><br>Type of AMD:<br>• Wet AMD: 38 per cent (n=57)<br>• Dry AMD: 41 per cent (n=63)<br>• Wet and Dry AMD: 21 per cent (n=32)<br><br>Gender (base: 150):<br>• 64 per cent male (n=98)<br>• 35 per female (n=53)<br>• One respondent declined to respond<br><br>Age (base: 150):<br>• No respondents aged between 18-24 or 25-34<br>• 1 per cent aged between 35-44 (n=2)<br>• 3 per cent aged between 45-54 (n=4)<br>• 7 per cent aged between 55-64 (n=10)<br>• 17 per cent aged between 65-74 (n=25)<br>• 44 per cent aged between 75-84 (n=66)<br>• 27 per cent aged between 85-94 (n=40)<br>• 1 per cent aged 95 and over (n=2).<br>• One respondent declined to respond<br><br>Location (base: 150):<br>• The majority of respondents were from England (92 per cent; n=138) with the majority of respondents from the | |

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| | | | | South East (22 per cent; n=33) and the North West (24 per cent; n=36)<br>• 8 per cent from Wales (n=12)<br>• 2 per cent declined to respond (n=3)<br><br>Living with another eye condition (base: 153):<br>• 52 per cent of respondents reported living with another eye condition(s) (n=78) | |
| Royal National Institute of Blind People | Short | 5 | 6,8-9 | **1.2.1 RNIB supports the provision of information to patients in a format that is accessible to them**. This is now a requirement covered by the NHS Accessible Information Standard (2016).<br><br>Just over a quarter of respondents (26 percent) reported that they had not been given information about their condition or treatment tailored to their needs.<br><br>When asked whether the risks of different treatments were explained to them in a way they could understand, 21 per cent of the people we spoke to said this was not explained in a way they could understand.<br><br>**RNIB recommends the NHS Accessible Information Standard be explicitly included and highlighted in section 1.2.1 with particular note of the requirement to undertake a** | Thank you for your comments, and endorsement of the recommendation.<br>In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |

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| | | | | **patient assessment to identify, capture and record the person's accessibility requirements.**<br><br>**RNIB recommends that sections 6.4.2 and 6.4.3 of the Accessible Information Standard Implementation Guide be highlighted, with mention of the need to use plain language.** | |
| Royal National Institute of Blind People | Short | 5 | 1-10 | **1.2.1 RNIB supports information being tailored to the individual's needs.**<br><br>A fifth of respondents (20 percent [base 152]) we spoke to said that the formant they've received information in during their treatment did not suit their needs. Some respondents wanted information in a different format to that which they had received. In particular, some wanted audio format as they couldn't read the text they were provided with.<br><br>23 per cent [base 152] of respondents reported that they were not aware that they could request written information in an accessible format.<br><br>RNIB's 'My Voice' survey revealed that 37 percent of registered blind and partially sighted people with AMD said that in the preceding 12 months they had never received information from health care providers in an accessible format (My Voice, RNIB, 2015, http://www.rnib.org.uk/sites/default/files/My%20Voice%20 | Thank you for your comments, and endorsement of the recommendation.<br>In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |

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| | | | | 2015%20-%20Full%20report%20-%20Accessible%20PDF_0.pdf).<br><br>**RNIB supports the NHS Accessible Information Standard which requires that patients are explicitly asked and made aware that information is available in an accessible format that meets their needs. RNIB recommends the following inclusion of wording in line 6:**<br><br>**Tailored to meet the person's needs, for example, in an accessible format. Discuss with the person their needs and inform them of all formats available to them as outlined in the NHS Accessible Information Standard.** | |
| Royal National Institute of Blind People | Short | 5 | 4 | **1.2.1 RNIB supports the provision of information on an ongoing basis and relevant to the stage of the person's condition.**<br><br>Visual function, registration status and support needs change over time and so people should be given multiple opportunities to receive information and support for their visual impairment (Hodge et al 2015). Additionally, lack of information throughout a person's AMD journey can cause feelings of stress, anxiety and fear (Mitchell et al 2002, Burton, Shaw and Gibson 2013, Burton et al 2013).<br><br>Currently not all patients are receiving information on an ongoing basis. 31 per cent of the people we spoke to told us that | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |

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| | | | | they have not been given access to information at all points of their AMD journey.<br><br>Information provision on an ongoing basis would ensure that it is appropriate to the individual at the specific stage of their journey and help to avoid a negative experience for patients. | |
| Royal National Institute of Blind People | Short | 5 | 7 | **1.2.1 RNIB supports the provision of information for people with AMD to be delivered in a caring and sensitive fashion**.<br><br>A fifth of the respondents (20 per cent) that we spoke to reported that the information they had received had not been given to them in a caring or sensitive way.<br><br>We asked patients what they would feed back to eye care services about their experiences of treatment. Individuals commented on health professionals being 'cold' in their delivery of information.<br><br>Being diagnosed with a sight threatening condition can be distressing and patients should receive information about their condition, treatment and prognosis in a way that minimises anxiety. | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |
| Royal National Institute of Blind People | Short | 5 | 11-28 | **RNIB supports the opportunity for people to discuss AMD including the range of topics covered in 1.2.2** | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |

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| | | | | Literature shows that there is a lack of understanding among AMD patients about their condition and it's progression (Stanford et al 2009, Burton Shaw and Gibson 2013). 29 percent of people that we spoke to reported feeling that they they'd not been given enough time to discuss any questions and or concerns with a health professional.<br><br>Significant numbers of people we spoke to reported that they did not receive the information detailed in section 1.2.2<br><br>In our survey we asked participants if they had received the information outlined in section 1.2.2. Below we outline the percentages of respondents that did **not** receive the information specified.<br><br>• 19 per cent - what AMD is and how common it is<br>• 23 per cent - the different types of AMD<br>• 44 per cent - causes of AMD<br>• 7 per cent - advice about stopping smoking<br>• 43 per cent - other lifestyle advice<br>• 42 per cent - how AMD may progress and possible complications<br>• 44 per cent - different tests and investigations<br>• 43 per cent - different treatment options, including possible benefits and risks<br>• 45 per cent - who to contact for practical and emotional support<br>• 27 per cent - injections and dealing with fear of them | At its post-consultation meeting, the committee reviewed the list of items your respondents would have liked to have known more about however they agreed that these items were adequately covered in the topics listed in 1.2.2. |

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| | | | | • 9 per cent - where their appointments would take place<br>• 22 per cent - which health professionals would be responsible for their care<br>• 32 per cent - expected waiting times for consultations, investigations and treatments<br>• 35 per cent - potential benefits of certification and registration<br>• 25 per cent - when, where and how to seek help with changes to their vision<br>• 38 per cent - signposting to other sources of support and information<br><br>When asked if there was any information about their AMD they would have liked or would have been helpful 137 respondents commented. They wanted to know more about:<br><br>• How AMD progresses and how to monitor it<br>• Injections and treatment options<br>• The risks involved<br>• Benefits of certification<br>• Who to speak to about emotional support<br>• They type of AMD they have.<br><br>Literature shows that patients are often forced to rely on the judgements of healthcare professionals because of their own lack of knowledge. Patients often accept healthcare professional's decisions because they are viewed as experts (Goyder et al 2009). Providing clear information as outlined in | |

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| | | | | the guideline will contribute to patient understanding enabling them to more fully be involved in shared decision making regarding their treatment (also relevant to section 1.5.18).<br><br>The guidance on information in section 1.2.2 will support patients to be more active in decisions relating to their care as well as ensure that there is greater equity of care in terms of distribution of information to patients. | |
| Royal National Institute of Blind People | Short | 5 | 11-28 | **RNIB recommends the addition of information about Charles Bonnet Syndrome in the information offered to patients in section 1.2.2.**<br><br>Up top half of all people with macular degeneration suffer or will experience visual hallucinations(https://www.macularsociety.org/visual-hallucinations). The Royal College of Ophthalmology AMD guideline states that "people see different images, from simple patterns of straight lines to detailed pictures of people or buildings. These can be disturbing, and may not be voluntarily mentioned by patients to friends, family or the medical profession as sufferers may be concerned that they might be developing a serious mental illness. The anxiety is more damaging than the hallucinations themselves. Patients should be alerted to the possibility of CBS which typically improves by 18 months but can last many years. The Macular Society is familiar with the condition and can talk to patients and provide a leaflet. It is recommended that clinicians educate all relevant | Thank you for your comment. The committee agreed it would be helpful to add 'the possibility of developing visual hallucinations associated with retinal dysfunction (Charles Bonnet syndrome)' to the list of topics that should be discussed with people with AMD (1.2.2) |

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| | | | | clinic staff about CBS, including receptionists and technicians" (https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf (P94))<br><br>Information should be provided to people with AMD to raise awareness and assure people that the hallucinations are a common feature of AMD and are not a sign of mental illness. | |
| Royal National Institute of Blind People | Short | 6 | 1-10 | **RNIB supports 1.2.3 the provision of information in accessible formats for people to take away from their first appointment and whenever they request it including the topics listed.**<br><br>While some people with AMD receive the information outlined in section 1.2.3 not all patients do. Our survey revealed that the following percentages of respondents did **not** receive the information outlined in section 1.2.3<br><br>• 37 per cent - timescales for treatment<br>• 13 per cent - who to contact if appointments need to be altered<br>• 17 per cent - what to do and where to go if their vision gets worse<br>• 36 per cent - parking at the hospital and transport to the hospital<br>• 28 per cent local and national support groups | Thank you for your comments, and endorsement of the recommendation.<br>In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |

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| | | | | As previously mentioned all information should be accessible to the individual as per the Accessible Information Standard (2016). | |
| Royal National Institute of Blind People | Short | 6 | 11-13 | **RNIB supports healthcare professionals giving time to discuss the person's concerns and questions about their diagnosis, treatment and prospects for vision.**<br><br>29 per cent of the people we spoke to said that they did not feel that they had enough time to discuss any questions or concerns about their condition.<br><br>Additionally 28 per cent of people we spoke to said that they didn't feel they had the right information to make a decision about which treatment option was right for them. Some of these respondents said that they did not feel that they had a choice in terms of treatment options and that the information was not provided to help them to make a decision.<br><br>Clear guidance set out in 1.2.4 will ensure that there is greater equity of care in terms of time for discussion and distribution of information to patients. This will be beneficial for patients supporting them to make decisions about their treatment and care. | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |

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| Royal National Institute of Blind People | Short | 6 | 14-16 | **RNIB supports the promotion of peer support groups for people with AMD including those beginning intravitreal injections as outlined in section 1.2.5**<br><br>Research shows that significant numbers of patients experience anxiety relating to anti-VEGF treatment for AMD regardless of the number of injections received (Senra, Balaskas, Mahmoodie and Aslam, 2017).<br><br>A significant number of people we spoke to said they found it useful/would find it useful to speak to someone about how they felt about their diagnosis, treatment, the impact of AMD on their sight and day to day life.<br><br>38 per cent of the people we spoke to said that they would have found it useful to talk to someone about how they are feeling about their AMD diagnosis. People cited various options for support including family and friends but also Eye Clinic Liaison Officers, doctors and charities.<br><br>52 per cent of the people that we spoke to said they found it useful/would have found it useful to speak to someone about how they felt about how their sight would be affected by AMD. | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |

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| | | | | Again various options of support were mentioned but some of the respondents said that they did not know where to go for additional help or not having anyone in their life to offer this kind of support.<br><br>47 per cent of respondents said they found it useful/would find it useful to talk to someone about how they felt about having AMD treatment.<br><br>50 per cent of people we spoke to said they found it useful/it would be useful to talk to someone about how they felt about the impact of AMD on their day to day life. | |
| Royal National Institute of Blind People | Short | 7 | 8-9 | RNIB is concerned that there is no protocol for monitoring people with asymptomatic AMD is specified in Section 1.4.3.<br><br>**RNIB recommends that individuals with asymptomatic AMD are monitored every 6 – 12 months and issued an Amsler chart and information for self-monitoring.** | Thank you for your comment. Amsler grids were amongst the technologies for which evidence was sought in our review question on self-monitoring strategies (chapter 11.2); however, no evidence meeting the eligibility criteria was identified. The committee made a research recommendation to assess 'the effectiveness and cost-effectiveness of self-monitoring strategies in improving the long-term visual, functional and quality of life outcomes of people with early, indeterminate or late AMD (dry)'. |

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| Royal National Institute of Blind People | Short | 8 | 3-5 | 1.4.10 RNIB is concerned that the referral period of 21 days for patients with late AMD (wet active) is too long and risks the sight of the individual. The RCO Age-Related Macular Degeneration: Guidelines for Management (2013) states that a person with wet AMD should have "immediate rapid access to retinal specialists with expertise in the management of exudative AMD for all patients should be available, irrespective of geographic location. Patients should be seen by a specialist with medical retinal expertise within one week of diagnosis, and, there should be no more than one week between evaluation and treatment." https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf<br><br>This urgency suggests that a period of 21 days will risk sight.<br><br>**RNIB recommends that wording in section 1.4.10 should be amended to read**<br><br>**For eyes with confirmed late AMD (wet active) for which antiangiogenic treatment is recommended (see Section 1.5), offer treatment as soon as possible (within 1 week of referral to the hospital eye service).** | Thank you for your comment. Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |
| Royal National Institute of Blind People | Short | 11 | 12-13 | **RNIB supports section 1.5.18 – ensuring the active involvement of patients in all decisions about stopping or switching of treatment.** | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |

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| | | | | 29 per cent of the people we spoke to (when relevant to their situation) said that they did not feel actively involved in decision making about stopping or switching their treatment. Some of this group said that they had not been consulted and were just told of the change to their treatment.<br><br>28 per cent of patients we spoke to said that they did not have the right information to make a decision about which treatment option was right for them.<br><br>RNIB believes that patients should be actively involved in decision making around their care; the provision of information as well as opportunity for discussion are vital to making this happen. As previously noted literature shows that patients are often forced to rely on the judgements of healthcare professionals because of their own lack of knowledge, pointing to the importance of the information provided in section 1.2.2. | |
| Royal National Institute of Blind People | Short | 11 | 18-27 | **RNIB support section 1.6.2, 1.6.3, 1.6.4 and 1.6.5, and note that these sections of guidance could be carried out effectively by an Eye Clinic Liaison Officer (ECLO).**<br><br>In addition to practical support, ECLOs offer the opportunity for patients to discuss the impact of their diagnosis, treatment and management of their condition. As previously outlined, a significant number of people we spoke to said they found it useful/would find it useful to speak to someone about how they felt about their diagnosis, treatment, the impact of AMD on their | Thank you for your comment, and for providing this information. The committee specifically discussed the role of ECLOs within the section of the guideline on patient information. Quoting from section 12.2.3 of the full guideline:<br>"The committee agreed that the information also needed to be matched to the stage of disease progression and should be provided at multiple points during the disease course. It discussed who would be best placed to impart this information and, from |

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| | | | | sight and day to day life. However, the majority of people we spoke to (64 per cent) had not been referred to an ECLO in relation to their AMD. The minority that had been referred to an ECLO commented on how helpful this had been.<br><br>RNIB investigated the impact of Eye Clinic Liaison Officers (ECLO impact tool: UK wide findings 2015-2016), finding that this provision increased emotional well-being as well as increasing patient understanding of the support available to them outside of the eye clinic. Additionally people who received support from an ECLO reported that as a result they felt reassured and more optimistic about the future.<br><br>Below are results from the above report available here: www.rnib.org.uk/ECLO-impact-tool<br><br>• After visiting an ECLO, people's understanding of the support available outside of the eye clinic rose from **23 per cent** to **91 per cent**<br>• **75 per cent** of respondents reported their emotional well-being had increased as a result of seeing an ECLO<br>• **85 per cent** of respondents reported feeling either much more or more reassured after contact with an ECLO<br>• **70 per cent** of respondents either strongly agreed or agreed that they felt more optimistic about the future, due to the support of an ECLO This figure stayed relatively stable at **69 per cent** when asked 3 months later in the follow up survey | committee members' experience, agreed that an ECLO (eye clinic liaison officer) would be a good choice, if available. However, due to the lack of AMD-specific evidence in the literature on the benefits of ECLOs, the committee was unable to recommend this directly."<br>Following stakeholder feedback, the committee were keen to stress their agreement of the importance of ECLOs, but agreed there remained insufficient evidence to make a specific recommendation around this issue. |

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| | | | | Additional independent research led by the Welsh Institute for Health and Social Care (Llwellyn et al 2017) outlinines the positive impact of ECLO services. The research report states "ECLOs help those patients experiencing sight loss with the greatest needs. Evidence shows they appear to maintain their health-related quality of life over time. They provide a wide range of welltargeted, well-appreciated services".<br>The report can be found here: Filling the gap where patients used to fall: evaluating the role and impact of eye clinic liaison officers and other vision support workers across the United Kingdom<br><br>**RNIB recommend in the inclusion of referral to an ECLO where available in both section 1.2 and 1.6 of the guideline.** | |
| Royal National Institute of Blind People | Short | 11 | 22-23 | **RNIB supports section 1.6.3, referral of people with AMD to low vision services.**<br><br>The majority of people we spoke to who had been referred to low vision services mentioned how helpful the low vision clinic had been in administering aids and giving them support.<br><br>Independent research by the Office for Public Management (Sin et al 2017) shows that good vision rehabilitation not only has a positive impact on beneficiaries but can also avoid substantial health and social care costs. Local health and social care services can avoid incurring over £3million annually. Research report can be found at www.rnib.org.uk/rehabcostavoidance | Thank you for your comment. A recommendation has been added to emphasise the importance of certification: 'Offer certification of visual impairment to all patients as soon as they become eligible, even if they are still receiving active treatment.' (1.6.4)<br>The reasoning for the weaker form of recommendation adopted in 1.6.3 is explained in section 9.2.3: 'Having reviewed the included evidence, the committee agreed that the evidence was not sufficiently robust to make a strong recommendation for low vision services. However based on committee members' experience of the benefits of the support provided, and the evidence available from non-AMD populations (Binns et al., |

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| | | | | **RNIB recommend that the wording of section 1.6.3 should be changed to ensure that where AMD is causing visual impairment all patients are given the opportunity to access low vision services. Patients should also be made aware that they have the option for vision rehabilitation (which does not need to be group based) and where appropriate considered for CVI:**<br><br>**1.6.3 Offer people with AMD causing visual impairment a referral to low vision services and rehabilitation**. **Where appropriate issue CVI.** | 2012), it agreed to recommend that the provision of such services should be considered for people with AMD when they experience vision problems. Due to the conflict between the committee's understanding of the benefits of low-vision services and the lack of any high-quality evidence to substantiate this, the committee agreed that more research would be useful to understand the impact of improving low-vision services specifically on people with AMD and made a research recommendation to this effect.' |
| Royal National Institute of Blind People | Short | 11 | 18-27 | **RNIB recommend the inclusion of advice on visual standards for driving in Section 1.6.**<br><br>The RCO has published guidance on Vision Standards for Driving (https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013_PROF_216_Vision_Standards_for_Driving_April_2013.pdf) outlining the duty of care of Ophthalmologists towards patients to give information if driving is threatened.<br><br>"Ophthalmologists should be aware that sight problems often affect safe driving and the issue of driving should be considered in every consultation with a patient. The main onus is for drivers to self-report, but the ophthalmologist must be aware of when | Thank you for this suggestion. The committee agreed it would be helpful to add 'vision standards for driving' to the list of topics that should be discussed with people with AMD (1.2.2) |

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| | | | | driving may threatened and should be familiar with the relevant chapter in the 'At a glance guide' so that appropriate information can be given to the patient. " (P4)<br><br>"When it is likely that a patient is outside the required standard then they should be asked if they drive, and appropriate advice given in an empathetic but clear manner" (P5)<br><br>Patients receiving NICE approved treatments for AMD will have reached the visual acuity threshold for these treatments (VA 6/12 to 6/96). Current DVLA standards place the minimum VA (with glasses) for driving at 6/12 (https://www.gov.uk/driving-eyesight-rules) meaning those receiving treatment for AMD more likely not to meet the standards for driving.<br><br>29 per cent of the people that we spoke to said they had not been given information or advice about driving.<br><br>**RNIB recommend the inclusion of the following wording:**<br><br>**Consider giving appropriate advice with regard to driving to people with AMD taking into account visual acuity and visual field.** | |
| Royal National Institute of Blind People | Short | 12 | 2-3 | **RNIB support section 1.7.1, however recommend that the service for routine monitoring for people with early or late AMD be specified.** | Thank you for your comment. The committee agreed that the recommendation that people should be advised to 'consult their eye-care professional as soon as possible if their vision changes' (1.7.2) constitutes clear |

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| | | | | | advice on what patients should do if their vision changes. Additional detail is provided in 1.7.5 regarding symptoms to be vigilant for in people who are self-monitoring their condition.<br><br>Other than these points, the committee agreed that the evidence did not enable them to make specific points about how routine monitoring should be organised for these individuals. |
| Royal National Institute of Blind People | Short | 12 | 7 | **RNIB support section 1.7.2, and recommend that 'healthcare professional' be specified.** RNIB believe that it is not advisable for people with early or late AMD to approach their GP about changes in their sight as this will slow down the referral process. RNIB recommend that 'healthcare professional' be specified as 'Optometrist'. | Thank you for your comment. As it may sometimes be appropriate for a patient to consult their GP (if they have been closely involved in their eye-care) and some other patients may have direct access to secondary care professionals, it was agreed that a better form of words would be that people consult their eye-care professional. |
| Royal National Institute of Blind People | Short | 12 | 12-13 | **RNIB support section 1.7.4 and recommend that people with AMD are offered appropriate tried and tested resources to ensure that patients know how to monitor their vision.**<br><br>46 per cent of the people we spoke to said they had not been given any advice or guidance about self-monitoring their condition pointing to current gaps in information provision. | Thank you for your endorsement of the recommendation. We hope that our guidance will help to optimise and standardise practice in this area. |
| Royal National | Short | 12 | 14-15 | **RNIB support section 1.7.4, and recommend that 'healthcare professional' be specified.** RNIB believe that it is not advisable for people with AMD to approach their GP about | Thank you for your comment. As it may sometimes be appropriate for a patient to consult their GP (if they have been closely involved in their eye-care) and some |

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| Institute of Blind People | | | | changes in their sight as this will slow down the referral process. RNIB recommend that 'healthcare professional' be specified as 'Optometrist'. | other patients may have direct access to secondary care professionals, it was agreed that a better form of words would be that people consult their eye-care professional. |
| Salar Surgical Ltd. | Full | 34-35 | | There are a number of devices, including SP.eye™, which have the potential to reduce the discomfort associated with intravitreal injections. Given the large and increasing numbers of these procedures being performed, we believe that a research recommendation on assessing the impact of alternatives to bare needle injections on patient-relevant outcomes would be valuable. | Thank you for your comment. Issues around bare needle versus alternative injection techniques were not within the scope of this guideline, and therefore it was not possible to make recommendations on this topic. |
| Salar Surgical Ltd. | Short | 5 | 19 | We agree that opportunities should be provided to discuss AMD with the person but in relation to treatment options we believe that it is important to include the additional topic of choice of injection, whether bare needle injection or an alternative.<br><br>People being treated for late AMD (wet active) reported that injections are a barrier to management and treatment, with 'scared about receiving an injection' being one reason for difficulty attending every appointment.[1] Discussing and providing alternatives to bare needle injections may reduce barriers to treatment and improve adherence.<br><br>SP.eye™ is an example of an intravitreal injection system which provides an alternative to bare needle injections. SP.eye™ is intended for use as an aid for intravitreal injection with provision for sharps safety. It may be used for any medication licensed for trans pars plana injection into the eye using a 30 gauge needle. | Thank you for your comment. Issues around bare needle versus alternative injection techniques were not within the scope of this guideline, and therefore it was not possible to make recommendations on this topic. |

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| | | | | Before injection the needle tip is not exposed and after injection the needle tip may be locked safe and disposed of in a suitable sharps bin.<br><br>Varano M. et al. Clin Ophthalmol. 2015; 9: 2243–2250. | |
| Salar Surgical Ltd. | Short | 6 | 11-13 | We agree that enough time should be allowed to discuss the person's concerns and questions about their diagnosis, treatment and prospects for their vision. When discussing the person's concerns and questions with regard to treatment, we believe that it is important to ensure that the patient is involved in the decision on choice of injection, whether bare needle injection or an alternative.<br><br>People being treated for late AMD (wet active) reported that injections are a barrier to management and treatment, with 'scared about receiving an injection' being one reason for difficulty attending every appointment.[1] Discussing and providing alternatives to bare needle injections may reduce barriers to treatment and improve adherence.<br><br>SP.eye™ is an example of an intravitreal injection system which provides an alternative to bare needle injections. SP.eye™ is intended for use as an aid for intravitreal injection with provision for sharps safety. It may be used for any medication licensed for trans pars plana injection into the eye using a 30 gauge needle. Before injection the needle tip is not exposed and after injection the needle tip may be locked safe and disposed of in a suitable sharps bin. | Thank you for your comment. Issues around bare needle versus alternative injection techniques were not within the scope of this guideline, and therefore it was not possible to make recommendations on this topic. |

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| | | | | Varano M. et al. Clin Ophthalmol. 2015; 9: 2243–2250. | |
| Salar Surgical Ltd. | Short | 8 | 21-25 | We agree with the recommendation to ensure intraocular injections are given by suitably trained healthcare professionals. However, we believe that it is essential that the recommendation also includes the use of safer sharps in the delivery of intraocular injections.<br><br>Needlestick injuries (NSI's) may result in the transmission of an infection from blood-borne pathogens such as, hepatitis B, hepatitis C and HIV.[1] Even when a serious infection is not transmitted, the emotional impact of NSI's can cause untold psychological harm.[2] The financial costs relating to NSI's have been estimated (in 2008) as £500,000 per NHS trust per annum.[2] In a US survey on intravitreal injections, 8% of physicians reported suffering at least one NSI.[3]<br><br>Regulations issued by the Health and Safety Executive (HSE) in 2013 require that '(t)he employer must substitute traditional, unprotected medical sharps with a 'safer sharp' where it reasonably practicable to do so.'[4] This followed from EU Council Directive 2010/32/EU - prevention from sharp injuries in the hospital and healthcare sector.[1] Prior to the HSE regulations, the use of sharps safety devices was recommended in CG139 Healthcare-associated infections: prevention and control in primary and community care: '1.1.4.5 Use sharps safety devices if a risk assessment has indicated that they will provide safer systems of working for healthcare workers, carers and patients.'[5] | Thank you for your comment. Issues around bare needle versus alternative injection techniques were not within the scope of this guideline, and therefore it was not possible to make recommendations on this topic. |

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| | | | | RCN Guidance advises use of 'needle devices using innovative designs to limit the risk of injury.'[6]<br><br>SP.eye™ is an example of a suitable safer sharp device. SP.eye™ is intended for use as an aid for intravitreal injection with provision for sharps safety. It may be used for any medication licensed for trans pars plana injection into the eye using a 30 gauge needle. SP.eye™ combines both passive and active sharps safety to minimise the risk of injury to staff and patients. Before injection the needle tip is not exposed (passive safety) and after injection the needle tip may be locked safe (active safety) and disposed of in a suitable sharps bin.<br><br>1. EU Council Directive 2010/32/EU - prevention from sharp injuries in the hospital and healthcare sector. 10th May 2010.<br>2. Royal College of Nursing (2008) Needlestick injury in 2008: results from a survey of RCN members, London: RCN. Publication code 003 304.<br>3. Shah et al (2014) Assessment of the risk of needlestick injuries associated with intravitreal injections, Retina;34(4):781-4.<br>4. Health and Safety Executive (2013). Health and Safety (Sharp Instruments in Healthcare) Regulations 2013.<br>5. NICE Clinical Guideline 139. Healthcare-associated infections: prevention and control in primary and community care.<br>Royal College of Nursing (2013) Sharps Safety. Publication code: 004 135. ISBN: 978-1-908782-91-5 | |

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| Sunderland CCG – on behalf of the Northern CCG Forum | Full | 30 | 25-36 | We are concerned that this recommendation implies that there are legal, regulatory and professional barriers to the use of bevacizumab for the treatment of AMD. We do not accept that this is the case and can see no compelling legal analysis to support the case that these barriers exist. The guideline committee have concluded that bevacizumab is as safe and effective as ranibizumab and aflibercept, as evidenced by clinical trial data. If the points in this section are included in the final guidance, it will result in the NHS being compelled to unnecessarily spend millions of pounsds on drugs that have no additional clinical or safety benefit over bevacizumab.<br>We therefore invite NICE to reconsider the wording in these draft Guidelines because the suggestion that there are barriers to offering patients a choice between bevacizumab, ranibizumab and aflibercept does not appear to us to be legally correct.<br><br>Line 34 states that there is 'no clinically significant differences in effectiveness and safety between aflibercept, ranibizumab and | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |

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| | | | | bevacizumab seen in the trials considered by the guideline committee'<br>However, guidance then appears to encourage NHS bodies to commission the more expensive drugs, ranibizumab and aflibercept, even though there is no clinical justification for requiring NHS commissioning bodies to incur the additional costs.<br><br>Line 29 states '… bevacizumab may not be prescribed for intraocular use for AMD simply because it is cheaper or more cost effective than a licensed alternative'<br>and line 27; '… bevacizumab can only be prescribed for AMD if a person has a specific need and no other licensed product meets the need'.<br><br>We note that NICE have offered no explanation as to why it is suggested that there are legal and regulatory barriers to clinicians treating patients with bevacizumab if the patient | |

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| | | | | makes an informed choice to be treated with bevacizumab as opposed to being treated with ranibizumab or afilbercept.<br>The advice appears to replicate arguments in a letter written by the former Minister, Mr George Freeman MP, on 23 March 2015, to Mr Steve Hulme of NHS South Derbyshire CCG which sought to equate the position of NHS hospitals with the position of pharmaceutical companies under the EU Directive 2001/83/EU, and suggested that NHS Hospitals could only use unlicensed drugs under the "specials" regime where no licensed alternative exists.<br>We consider that legal position is erroneous because it is not correct to equate the position of NHS hospitals with the position of pharmaceutical companies. EU laws apply to the manufacture and distribution of pharmaceutical products. However, the EU has no competence with respect to the internal operation of the NHS under article 168(7) of the Treaty for the Functioning of the European Union. The Court of Justice has made it clear in *R (ABPI) v MHRA* that the EU rules on the | |

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| | | | | marketing and distribution of pharmaceutical products have no role within a state healthcare system as a result of article 168(7).<br><br>Line 10 states, " bevacizumab is not licensed for intraocular use for AMD."<br>We consider that bevacizumab is a licensed drug. NHS pharmacies at Moorfields and the Royal Liverpool Hospitals have been sub-dividing bevacizumab into vials for ophthalmic use for a considerable period of time and, as far as we are aware, providing the drugs lawfully in this form to both NHS and non-NHS bodies. There is no suggestion that these pharmacies have been acting unlawfully in doing so. In any event, we consider that it is plain that this is lawful activity under section 10 of the Medicines Act 1968.<br><br>Thus we invite NICE to accept that:<br>a. the manufacture of vials of bevacizumab for ophthalmic use is lawful; and | |

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| | | | | b. the supply of these vials to NHS Foundation Trusts is lawful.<br><br>We accept that offering NHS patients the possibility of being treated with bevacizumab for AMD involves prescribing the drug outside the terms of its marketing authorisation. It is thus an 'off label' prescription. However, it is wholly unclear how it could be argued that that this is the provision of an "unlicensed drug" because bevacizumab is a drug with a marketing authorisation (albeit it cannot be marketed for this particular use).<br>The use of bevacizumab for AMD patients happens regularly in the private sector and in many places within the NHS (saving considerable sums which are available to benefit other patients). Further, there are numerous other examples of occasions on which drugs with a marketing authorisation are prescribed for medical conditions which differ from those for which the drug can be marketed (and in quantities which are different from those set out in a marketing authorisation). We consider that the use of bevacizumab as one option for AMD patients does | |

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| | | | | not represent any real difference from many other clinical uses where drugs are used outside the terms of their marketing authorisation.<br>Thus we cannot accept that the draft NICE Guidance correctly states the law in suggesting that there is a legal barrier to such uses.<br>There are, as far as we are aware, no legal restrictions preventing clinicians prescribing bevacizumab 'off label' when treating non-NHS patients. Further we do not accept that there is any hard legal basis for suggesting that different rules apply to the NHS to those that apply when patients are treated outside the NHS. It therefore seems to us that the draft Guidance is legally erroneous in suggesting that there are hard restrictions on NHS clinicians which do not apply to clinicians working in the private sector.<br><br>We thus invite NICE to accept that NHS clinicians will be acting lawfully in giving patients the informed choice of being treated with a range of drugs for AMD. We also invite NICE to amend | |

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| | | | | its Guidance to remove any suggestion that it is unlawful per se to offer patients an informed choice of being treated with aflibercept or bevacizumab as opposed to being treated with ranibizumab.<br><br>Line 16 states, "Clinicians should consider relevant professional guidance if prescribing outside relevant professional guidance if prescribing outside a licensed indication."<br><br>We accept that GMC Guidance supports prescribing licensed drugs in preference to off-label prescribing but does not prevent doctors giving patients a choice of on-label and off-label prescribing, where there are good reasons to do so. We believe that the opportunity costs provided by switching to the cheaper drug are more than sufficient justification for offering patients this choice. Nonetheless, we accept that there is a theoretical possibility that a doctor may be the subject of a GMC complaint for offering the patient a choice between the three drugs. | |

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| | | | | However we do not accept that there is any serious possibility that a doctor could be considered to have his or her practice impaired as a result of acting in accordance with the policy of commissioners and their own local professional bodies who support the policy.<br><br>The reality is that doctors in the UK have prescribed bevacizumab for AMD patients outside the NHS for many years and, on occasions, within the NHS. We are not aware of any doctor ever being brought before the GMC to answer a complaint that an AMD patient should not have been given the choice between bevacizumab and ranibizumab or aflibercept. Whilst these issues are not straightforward, we are confident that there are no proper grounds for putting a doctor's registration under threat because a patient has been offered the chance to benefit other NHS patients by being prescribed a cheaper 'off-label' drug in preference to an expensive licensed alternative, especially given that the draft guidance has | |

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| | | | | confirmed that there is no difference in safety and effectiveness between the drugs in question.<br><br>**Summary**<br>We do not accept that there are hard legal, regulatory or professional bars to offering patients a choice between bevacizumab, ranibizumab and aflibercept, as suggested by this section of the guidance. We have seen no compelling legal analysis to support the case that they exist. If the points in this section remain unchanged in the final guidance, it will result in the NHS being compelled to unnecessarily spend millions of pounds on drugs that have no additional clinical benefit over bevacizumab.<br>Whilst there are concerns that the NHS should support the UK pharmaceutical industry, in this case the ultimate intellectual property right holders of bevacizumab and ranibizumab is a single US company.<br>We thus invite NICE to review this section of the draft Guidance and seek legal advice before publishing any final Guidance. | |

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| | | | | The existence of hard legal bars also seems to us to be misguided not only as a matter of law but also to be inconsistent with the long established pharmacy practices adopted by NHS pharmacies at Moorfields and the Royal Liverpool Hospitals, and pharmacy practices adopted in relation to other drugs. We therefore invite NICE to reconsider the wording in these draft Guidelines because the suggestion that there are hard legal bars to offering patients a choice between bevacizumab, ranibizumab and aflibercept does not appear to us to be legally correct. | |
| The Clinical Council for Eye Health Commissioning | Full | General | General | The Clinical Council for Eye Health Commissioning welcomes the development of a NICE guideline on age-related macular degeneration (AMD).<br><br>AMD is a very common eye condition and the number of people affected is very likely to increase due to an ageing population. | Thank you for your comment, and recognising the value of the guideline. |

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| The Clinical Council for Eye Health Commissioning | Full | General | General | Given the escalating NHS resources and volume of activity involved in managing patients with AMD, we note the omission of outcomes of their management within this Guideline which would serve to provide further assurance to support the investment in these services (commissioning and provision of care) and to demonstrate their impact for a population at Sustainability and Transformation Partnership level.<br><br>Reported outcomes should be also included in discussion with patients and the information material provided to them - given that benefits of treatment are implied within the Guideline and in the recommendations for patient information.<br><br>We would propose that NICE considers recommending some outcomes or audit standards that would support implementation of this Guideline; or at least consider referring directly to related NICE Guidance and Pathways that are potential sources for these.<br>Additionally we would propose that NICE considers developing quality standards around this Guideline that address processes for timeliness of treatment and failsafe arrangements. | Thank you for your comment. These comments have been passed to both the NICE pathways and quality standards teams for consideration. |
| The Clinical Council for Eye Health Commissioning | Short | 8 | 7 | We welcome the recommendation 1.4.11 of commissioners and providers to agree a clear local pathway for people with AMD.<br><br>We would like to suggest that this recommended local pathway also cover feedback and replies to referrals as it will help improving the relevance and the quality of referral letters, which | Thank you for your comment. The committee agree this was an important issue, but also that the evidence available did not allow them to make specific recommendations around feedback to referrers. |

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| | | | | will support the implementation of NHS England RightCare principles ensuring people access the right care, in the right place at the right time.<br><br>We suggest amending the recommendation 1.4.11 as follows:<br><br>"Commissioners and providers should agree a clear local pathway for people with AMD, which should cover:<br>• referral from primary to secondary care, with direct referral preferred<br>• discharge from secondary to primary care, covering ongoing 10 management and re-referral when necessary<br>• **feedback to the primary referring practitioner**." | |
| The Royal College of Ophthalmologists | Both versions | General | | We would like to emphasise the increasing role of multimodal imaging in the mangagement of AMD which is downplayed in this document. Increasingly autofluorescence, OCT-A and multimodal imaging is used to properly diagnose patients for example some cases of GA may in fact be late on set Stargadts or LORD and so AF and a multi model approach to imaging is needed. MacTel can also be confused. | Thank you for your comment. The assessment of multimodal imaging has challenges as regards defining objective multi-criteria decision-rules and appropriate reference standards, although we agree that research on such approaches may prove valuable. We have recommended that a multimodal protocol should be used as the reference standard in future research on OCT-A.<br>Autofluorescence was not included as a technology of interest for the review question on monitoring (11.3). It was one of the tools for which data were sought with regard to accuracy in a diagnostic setting (7.2); however, very limited evidence was identified. |

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| The Royal College of Ophthalmologists | Both versions | General | | The method of giving intravitreal injection, setting, procedure etc is not mentioned and should be. The Royal College of Ophthalmologists has previously published guidelines on this. | Thank you for your comment however these issues were not within the scope of this guideline and we are therefore unable to provide guidance in this area. |
| The Royal College of Ophthalmologists | Full | 28 | 3 (table) | Indeterminate is a new term, it is inappropriate. The distinction should be made by multimodal imaging to identify AMD mimics from non-AMD. There is nothing indeterminate about AMD. There are exudative macular lesions which are not AMD and ophthalmologists are able to differentiate these conditions from neovascular AMD. With the advent of OCT A and high resolution FA and ICG with OCT ophthalmologists can make these distinctions. | Thank you for your comment. Part of this confusion has arisen because stakeholders interpreted the indeterminate to refer to whether a patient has AMD or not. In fact the patient has AMD but their category of Late AMD is indeterminate. This has been altered to Late AMD (indeterminate) to clarify. The first clinical description has also been altered to clarify.<br>The type of AMD in this category is recognised by clinicians but not present in other classification systems. Other terms were considered, but none were judged to be entirely suitable. Intermediate AMD is used in other classification systems for other sub-types, and implies progression to other, more advanced categories. Late AMD (indeterminate) does not necessarily progress to Late AMD (wet active) although it is at risk of doing so. |
| The Royal College of Ophthalmologists | Full | 28 | 3 (table) | Atrophy. Evidence supports the view that depigmentation and GA are not distinguishable easily if diam is < 175. Retain this cut off. There appears to be some confusion regarding depigmentation and its distinction from GA. GA is a term that was used previously to distinguish an area of retina on clinical examination that appeared devoid of cellular components (photoreceptors/RPE and choriocapillaris). Now with multimodal imaging ophthalmologists can see incomplete | Thank you for your comment. There have been recent advances in our understanding of this sub-type or feature of AMD, including consensus recommendations on imaging modalities used in researching it (not relevant to this classification). We have dropped the specific term Geographic for small areas of atrophy which include areas of incomplete loss of retinal/RPE layers. The term Geographic Atrophy now appears only |

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| | | | | atrophy in some layers giving rise to the depigmentation and fully developed GA where outer retina and RPE are lost and this is seen when the diameter of the lesion exceeds 150 microns and thus the 175 micron which the WARMGS classification suggested seems reasonable. Anything less than 175 should not be termed GA | in the Late AMD (dry) category, although it is recognised it can occur in other categories, such as Late AMD (wet active) but these will be the dominant category. |
| The Royal College of Ophthalmologists | Full | 46 | 3 Table 13: AMD classification | Evidence for use of PDT as combination for PCV is strong and growing stronger therefore the treatment algorithm is out of date. | Thank you for your comment. The committee discussed your comments however it did not share this interpretation of the evidence, and agreed that it could not make an evidence-based recommendation in favour of PDT as an adjunct to anti-VEGF for eyes with PCV. Although it noted that there is some evidence of improvement in surrogate measures of disease activity, no benefit for patients has been demonstrated. In particular, Everest 1 showed no significant differences in visual acuity between people receiving PDT+anti-VEGF or ant-VEGF alone. Indeed, in the meta-analysis combining all types of late AMD (wet active), a significantly **lower** proportion of people randomised to combination therapy achieved a gain of 15 letters or more in BCVA, and there was no evidence that results were significantly different in the PCV-only stratum (see appendix H.6.3.1). In addition, other stakeholders for this guideline have highlighted a large RCT for which a full publication is currently in press (PLANET; see ID267); preliminary data from this trial further reinforce |

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| | | | | | the absence of acuity gains with combination therapy, compared with anti-VEGF monotherapy, in PCV. |
| The Royal College of Ophthalmologists | Full<br><br><br><br>short | Section 7.2 pages 80 -93<br><br>1.4.8 and 1.4.9 pages 7-8 | general | There is an attempt to validate the selection of OCT as reference standard to diagnose wet AMD in section 7.2.4., **Page 89: "the committee noted at the largest, most recent, UK-based study co compare OCT with FFA (Wilde et al, 2015) found no false-negative diagnosis at all (a sensitivity of 100%) but was subject to a false positive rate of around 1-in-5 (specificity of 81%). The committee agree that these findings provided good validation of the current common practice of using OCT as a non-invasive first-line investigation, to rule out cases that do not have late AMD (wet active), in identify those that require FFA to confirm a positive diagnosis".** However: there is no mention of high risk of bias of the paper by Wilde et al.; this study is retrospective, and excluded 346 of 822 (42%) potential participants and thus not generalisable. There was no detailed explanation of reasons of exclusion (i.e., whether it was due to OCT or FFA or both tests). In addition, the reported sensitivity was not 100% because for one participant with wet AMD the OCT was interpreted as negative (page 606) and only after knowing the result of the FFA the OCT test was re-classified. | Thank you for your comment. OCT was not used as the reference standard for this question; rather, OCT was compared against a reference standard of FFA. This was ambiguous in our draft for consultation, but has now been clarified in chapter 7.2.1.<br>The issues with the Wilde study were considered as part of the guideline development process, and let to a downgrading of the quality of the evidence associated with that study. However, the committee noted that overall 4 studies were identified looking at the comparison of OCT and FFA, and these provided consistent evidence that OCT has good sensitivity and specificity (93.5% and 89.2% respectively, in the pooled analysis).<br>The error in describing the study as having 100% specificity has now been corrected. |
| The Royal College of Ophthalmologists | Full | Section 7.2 pages 80 -93 | general | **(3) Section 7.2.4. Evidence to recommendation section. Pages 90-92, Considerations of health benefits and resource use:**<br>**"The committee considered that the modelled cohort in the included CUA had some characteristics that are not** | Thank you for your comment While it is true that people with poor baseline BCVA will have low quality of life compared with people whose BCVA exceeds 6/24, they remain an important group of patients, within the VA range for treatment specified by TA155 and TA294. |

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| | short | 1.4.8 and 1.4.9 pages 7-8 | | **representative of the group's clinical experience. In particular the committee considered 6/24 as an upper bound for presenting VA as an unrealistic assumption, given that many patients will present with greater loss of vision".** Incorporating people with very poor visual acuity would mean that only a small QALY difference would be possible and thus the least costly strategy would be selected in the CUA (a cost-minimisation approach)<br><br>**"The assumption that 10% of patients will receive FFA was also considered too conservative and… it was agreed that this would underestimate the total cost of FFA"**<br>Higher uncertain results of other diagnostic tests would reduce their relative cost-effectiveness. This was tested in sensitivity analysis with the unclear results from the Ophthalmologist or nurse assessments rising to 50% ad no unclear test results from OCT. While Ophthalmologist or nurse led assessment were less cost-effective, OCT only based diagnosis was still being dominated by FFA-based diagnosis.<br><br>**"The committee also considered that the cost of treatment in the model did not reflect the patient access scheme pricing for ranibizumab, and that the model could have considered other treatment options in a scenario analysis"**<br>The committee seems to ignore the scenario analysis conducted with details provided in page 71, including a cost for anti-VEGF therapy of £50. "Scenario analysis was conducted in order to | The committee agreed that a proportion of patients with late AMD (wet active) can be expected to present with BCVA below 6/24, making the modelled population less representative of expected NHS practice. Data obtained from 2 NHS Trusts to inform baseline VA of presenting eyes in the economic model conducted for this guideline show that more than half of unilaterally treated eyes possess BCVA of 55 EDTRS letters or less at baseline.<br>Regarding the proportion of ophthalmologist assessments that returns an uncertain result, the committee agreed that the parameter was uncertain having been derived from expert opinion. Though the sensitivity analyses described do not change the model's conclusions relative to OCT, it was deemed to be 1 of a number of parameters / assumptions that may favour FFA, compounding to decrease their certainty in the overall model results.<br>Regarding the cost of treatment, the committee agreed that the scenario analysis was still unlikely to reflect current NHS practice. Thank you for highlighting that the second part of the sentence is incorrect, however, and this has been amended.<br>Regarding the improved diagnostic accuracy of state-of-the-art technology, while it is true that the committee graded the OCT-A evidence as poor quality, clinical expertise within the committee agreed that OCT-A is likely to more accurate in practice, based on clinical |

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| | | | | explore the conditions under which an OCT only strategy would become cost-effective…"<br><br>**"The parameterised diagnostic accuracy of OCT was also considered to be a likely underestimate of the current state-of-the-art as image resolution has improved considerably since the studies in the authors' systematic review were published"**<br>It is unclear how much the diagnostic decisions can be improved with improved technology. E.g., recent studies reporting diagnostic performance of OCT-A for wet active AMD have been considered to be of poor quality by the committee.<br><br>**"On examining the diagnostic accuracy parameters, the committee agreed it was a weakness of the model that a systematic review was undertaken to establish sensitivity and specificity ranges for OCT, but that the 'Ophthalmologist' diagnostic strategy, which includes OCT, is based entirely on expert opinion. There are evidently correlations between strategies that share a common diagnostic tool and his is not accounted for in the model. Given the assumption of perfect information for FFA, and an expert opinion based parameterisation of the 'Ophthalmology' strategy, the committee felt that the model could be systematically biased away from OCT."**<br>We agree that correlations would have an impact in the probabilistic analysis. However, the bias would be in favour of OCT only strategies. If positive correlations were allowed for, | experience. This discussion is detailed in 'Trade-off between benefits and harms', in section 7.2.4 of the full guideline. The committee agreed that a good quality comparative study is required to definitively quantify the accuracy of OCT-A, rather than relying on the existing poor quality evidence. The committee therefore made a recommendation for further research for this.<br>Regarding the diagnostic accuracy of ophthalmologist strategies, while applying a correlation structure might not bias against OCT-only strategies, the committee agreed that the other issues raised – perfect FFA accuracy and expert opinion parameterisation of 'ophthalmologist' accuracy – were the 2 that might bias results against OCT-only. This distinction has been made clearer in the document.<br>Regarding potential differences in QoL associated with OCT and FFA, the committee agreed that the increased invasiveness of FFA, requiring a dye injection, and with the potential for injection-related anxiety and complications, it is not implausible to associate a disutility with FFA appointments compared with OCT appointments. This discussion is detailed in the in the 'Trade-off between benefits and harms' section of 7.2.4. While the committee agreed that the expected impact on the average patient in terms of QALYs lost may be small, overall incremental QALYs are themselves small (e.g. OCT & Nurse vs. FFA & Nurse: -0.008). As such, an appointment-related disutility scenario, such as the |

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| | | | | higher (lower) sensitivity and specificity from the possible range would favour results for ophthalmologist or nurse strategies each time a high (low) value was sampled for OCT only.<br><br>**"The committee also agreed that important differences between the invasiveness of FFA and OCT had not been accounted for in the model"**<br>We do not think FFA has a significant impact in QoL. | one included in our economic evaluation associated with intraocular anti-VEGF injections, may well be influential for the cost-effectiveness of FFA compared with other strategies. |
| The Royal College of Ophthalmologists | Overall comment | | general | Overall the RCOphth supports this guideline and agrees the recommendations will have a positive impact in delivering care for people with AMD.<br><br>It would be useful to have Figures with algorithms to describe decision making and patients' pathways<br><br>For wet active AMD: the impact of repeated intraocular injections of antiagiogenic therapies and frequent visits to hospital eye services in quality of life (QoL) have not been considered. Quantification of "disutilities" associated with repeated intraocular injections of anti-angiogenic therapies and hospital visits would perhaps be a useful research recommendation. | Thank you for your comments. An interactive depiction of the patient pathway – showing interaction with technology appraisals and other NICE guidance – will be provided in the NICE Pathway for macular degeneration on publication of this guideline.<br>Although no empirical quantification of disutility associated with intraocular injections was possible, the committee estimated a value for this, and it was incorporated in the original health economic model simulating the repeated administration of antiangiogenic therapy (see 'Adverse events' under appendix J.5.3.7). |
| The Royal College of Ophthalmologists | Short | 4 | Definitions in table | Adult vitelliform lesion is a confusing term. Adult vitelliform dystrophy is a different condition from AMD. This term should not be used. Indeterminate AMD – see comment below. | Thank you for your comment. There is potential to confuse Adult vitelliform macular dystrophy with an age-related vitelliform lesion as part of AMD. We have therefore dropped the descriptor "Adult". |

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| The Royal College of Ophthalmologists | Short | 7 | Section 1.4.2 | Subtle features such as sub-retinal fluid, intra-retinal fluid other pathology eg vitreomacular traction can all be missed by slit-lamp examination alone. It is not clear why OCT is being excluded as a diagnostic test. It is the practice of almost all medical retinal specialists to use OCT imaging in clinical practice for AMD including early or late dry AMD. Increasingly high street optometrists have this technology too so it should not be recommended to just use slit lamp examination when OCT is so useful and widely available. | Thank you for your comment The committee agreed that, where available, OCT may reasonably play a role in primary eye-care settings. However, it had no particular evidence as to the benefits and harms of OCT in that setting, so it did not consider it appropriate to make an explicit recommendation in favour of its use. Instead, a research recommendation has been made, seeking evidence on the diagnostic accuracy of OCT offered in primary care. |
| The Royal College of Ophthalmologists | Short | 7 | Section 1.4.5 | Dry AMD patients should also be referred to hospital so they can participate in clinical trials which are becoming increasingly widely available. | Thank you for this suggestion; an additional bullet-point has been added to 1.4.5 specifying that participation in research is another reason for referring people with late AMD (dry) to hospital eye services. |
| The Royal College of Ophthalmologists | Short | 8 | 14-16 | It would be useful to specify the type of anti-VEGF that is currently recommended, i.e., "offer ranibizumab or aflibercept" | Thank you for your comment. The committee agreed that the choice of anti-VEGF agent is a matter for individual clinicians, as guided by good prescribing practice. |
| The Royal College of Ophthalmologists | Short | 8 | Section 1.5.2 | This section contradicts previous NICE guidance that treatment should not be given if visual acuity is worse than 6/96. Do you mean use bevacizumab in this scenario where NICE states not to use ranibizumab or aflibercept. Please clarify as the current statement is contradictory and ambiguous. | Thank you for your comment. The committee agreed that no contradiction is present here, and the recommendations are unambiguous: anti-VEGF should be offered for eyes presenting with acuity between 6/12 and 6/96 and may be considered under the limited circumstances specified in 1.5.2 for eyes with acuity worse than 6/96. |
| The Royal College of | Short | 8 | 1.5.3 | It says injections can be given by a practitioner with experience of injections. Clearly this should be qualified by appropriately trained and should be under the supervision of a qualified | Thank you for your comment. The committee agreed with this suggestion, and added the following qualification to recommendation 1.5.4: 'If the injection is |

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| Ophthalmologists | | | | medical practitioner. Our patients are often elderly and could have a reaction or collapse so there needs to be suitable support available, secondly often such practitioners are also making decisions and they need to have ready access to appropriate advice and support. | delivered by someone who is not medically qualified, ensure that cover is in place to manage any ophthalmological or medical complications.' The recommendation already stipulates that the professional giving the injection should be suitably trained. |
| The Royal College of Ophthalmologists | Short | 8 | 26 | The statement "Bevacizumab is not licensed for intraocular use for AMD" is factually correct. The 2014 RCOphth public statement on Bevacizumab concluded with "There is clear evidence that, despite the lack of a licence, Avastin is a safe and effective drug for the treatment of neovascular AMD. The College would therefore welcome an urgent review of this issue by the United Kingdom Health Regulatory Bodies to consider how this unusual situation can be remedied". https://www.rcophth.ac.uk/2014/12/use-of-avastin-bevacizumab-in-age-related-macular-degeneration-2/<br>This remains our position. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |
| The Royal College of | Short | 9 | 10-13 | Treatment via intravitreal injections are cost effective from 6/12-6/96. There are clear benefits shown in the following paper that treating patients with AMD with VA better than 6/12. | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. |

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| Ophthalmologists | | | | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431059/.<br><br>Why is only Ranibizumab recommended? NICE did show benefits for Bevacizumab in VA better than 6/12 which is where there are benefits for CCG's and the NHS as a whole.<br><br>It is estimated that about a third of new patients could be treated if treatment started at better than 6/12. Every patient will lose vision and hit the 6/12 mark the recommendation to delay treatment until vision has reduced to this level means patients will lose sight unnecessarily. Starting treatment at an earlier stage would significantly reduce costs (in the order of millions of pounds) to the whole NHS system as these patients' vision would then be maintained at a higher level.<br><br>Bevacizumab is as efficacious as Ranibizumab. There are two studies which confirm this (CATT and IVAN). These studies were mentioned in the RCOphth letter to the GMC in 2015.<br><br>There is no direct RCT head to head comparison of Bevacizumab to Aflibercept. However, it can be extrapolated that as aflibercept = Ranibizumab then they are likely to be equally efficacious. The RCOphth calls for clinicians to be able to use their judgement to prescribe Bevacizumab for patients with VA better than 6/12 when appropriate. | These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use. |

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| | | | | To provide the most clinically and cost effective care to patients, clinicians should have access to Bevacizumab as a first line treatment with the ability to switch to another drug (licenced) at their clinical discretion.<br><br>Clinicians should also have access to Bevacizumab if there is a limited response to aflibercept and Ranibizumab. We accept there is no RCT data to support this, but in line with the above evidence this would be a pragmatic and cost effective approach. Clinicians should be able to use all tools in their armoury. This would be supported by GMC as failure of the other two drugs essentially means that clinicians have run out of licensed alternatives.<br>Clinicians should also have access to bevacizumab where a licenced drug is not available eg Wet AMD with visual acuity better than 6/12 or worse than 6/96 or where the choroidal neovascularization falls outside current NICE guidance eg peripapillary or extra-foveal. | |
| The Royal College of Ophthalmologists | Short | 9, line 10 to page 10, line 19 | 1.5.5-1.5.8 | This section perhaps inadvertently seems to favour ranibizumab over aflibercept for treatment of wet AMD. We recommend it is rephrased.<br>The recommendation for ranibizumab is clearly stated (1.5.5), but the recommendation for aflibercept is only stated after recommending that pegaptanib shouldn't be used (1.5.6 & 1.5.7), and only in terms of a reference that is should be used in accordance with the recommendations for ranibizumab in NICE technology appraisal guidance 155. | Thank you for your comment. These recommendations have been incorporated from the relevant technology appraisals (TA155 and TA294) and cannot be altered. |

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| | | | | We think the positive recommendation to use aflibercept should immediately follow that for ranibizumab, and clearly state the criteria for use as is done in the second part of 1.5.5 for ranibizumab ("the best-corrected visual acuity is between 6/12 and 6/96 ...."). <br><br> Failure to make these changes might lead to the suggestion that ranibizumab is favoured over aflibercept | |
| The Royal College of Ophthalmologists | Short | 11 | 1-5 | **1.5.14. Switching antiangiogenic therapy**. It would be useful to specify that the comment regarding switching antiangiogenic therapy refers to ranibizumab and aflibercept. | Thank you for your comment. The committee agreed that the choice of anti-VEGF agent is a matter for individual clinicians, as guided by good prescribing practice. |
| The Royal College of Ophthalmologists | Short | 12-13 | 2-12 | The monitoring recommendation should include the need to ensure timely bookings and chase DNAs and cancellations is often used to ensure safe regular delivery of treatment in active disease. | Thank you for your comment. The committee agreed these comments represented important issues of good practice throughout the NHS, but were not specific issues around AMD that would be appropriate to mention in a clinical guideline. |
| The Royal College of Ophthalmologists | Short | 13 | Section 1.7.9 | Autofluorescent imaging is also a very useful test to investigate a decline in visual acuity. It is much more sensitive than a colour photograph in detecting for example progression of foveal atrophy. This imaging modality should be included here and also in general in the guidelines. | Thank you for your comment. Autofluorescence was not included as a technology of interest for the review question on monitoring (11.3). It was one of the tools for which data were sought with regard to accuracy in a diagnostic setting (7.2); however, very limited evidence was identified. |
| The Royal College of Ophthalmologists | short | Section 1.4.11 | 7-11 | The recommendation should be explicit about the need for a clear urgent referral pathway and include an associated requirement to educate and support those in primary care to identify suitable patients and be able to use that pathway. | Thank you for your comment. As only very limited evidence was available for the committee to review on this topic, it was unable to make detailed, specific |

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| | | | | | recommendations. However, the committee recognised that a clear local pathway was imperative. |
| Thomas Pocklington Trust | Short | 5 | 20 | We are pleased that recommendation 1.2.2 suggests that healthcare professionals provide opportunities to discuss AMD with the person who has been diagnosed and stipulates that these discussions cover 'who to contact for practical and emotional support'. Eye Clinic Liaison Officers (ECLOs) play a vital role in providing the support people need to understand their diagnosis, deal with their sight loss and maintain their independence. RNIB's 2015-16 UK-wide ECLO impact tool reported that 86% of 752 respondents felt that seeing an ECLO had given them the practical support needed to help live with their sight loss. Of the 344 respondents who completed the follow-up questionnaire, 75% reported that their emotional well-being had increased as a result of seeing an ECLO. Eye departments with an ECLO should therefore signpost every person diagnosed with AMD to the service. Although it is alluded to, please could you specifically mention 'signposting individuals to the ECLO service' under recommendation 1.2.2. | Thank you for your comment. As stated in 12.2.3, the committee 'discussed who would be best placed to impart this information and, from committee members' experience, agreed that an ECLO (eye clinic liaison officer) would be a good choice, if available. However, due to the lack of AMD-specific evidence in the literature on the benefits of ECLOs, the committee was unable to recommend this directly.' |
| Thomas Pocklington Trust | Short | 5 | 24-25 | Th One of the potential benefits of certification and registration is access to vision rehabilitation assessments. Vision rehabilitation provides training and advice to people with sight loss to maximise independence. Local authorities are required to provide vision rehabilitation under the Care Act. The 2016 'See, Plan and Provide' report from the RNIB revealed that 49% of blind and partially sighted people in contact with their local authority | Thank you for this suggestion. Recommendation 1.2.2 has been revised to specify that people with AMD should be advised about 'the benefits and entitlements available through certification and registration when sight impaired or severely sight impaired'. |

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| | | | | do not go on to receive an assessment for vision rehabilitation support. Healthcare professionals should be informing people with AMD about their entitlement to receive vision rehabilitation from their local authority, to help ensure that they have access to this vital support. Although it is alluded to, please could you specifically mention 'informing individuals about vision rehabilitation entitlements' under recommendation 1.2.2. | |
| Thomas Pocklington Trust | Short | 5 | All lines in section 1.2.2 (11-28) | Healthcare professionals should be aware of the Driver and Vehicle Licensing Agency (DVLA) minimum eyesight standards for licensed drivers. Where a person with AMD does not meet the minimum standards, healthcare professionals should signpost them to further information and advise them on notifying the DVLA. Please can 'information and advice on minimum eyesight standards and driving' be included as a topic under recommendation 1.2.2. | Thank you for this suggestion. The committee agreed it would be helpful to add 'vision standards for driving' to the list of topics that should be discussed with people with AMD (1.2.2) |
| Thomas Pocklington Trust | Short | 5-6 | All lines in section 1.2 (1-28;1-16) | It is important people understand their AMD diagnosis and treatment regimen and we welcome this inclusion in the guidance. This understanding can reduce the risk of any future 'did not attends' (DNAs) for follow up appointments. Timely provision of treatment is imperative for people with Wet AMD, as it can prevent permanent damage to the macula. A recent study conducted by the Royal College of Ophthalmologists found that up to 22 patients a month in England experience sight loss as a result of hospital-initiated appointment delays. | Thank you for your comment, and recognition the value of the guideline |

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| | | | | The full study reported that AMD was the second most prevalent eye condition (23%) amongst the 169 patients who experienced preventable loss of vision. | |
| Thomas Pocklington Trust | Short | 6 | 1-2 | The language in this recommendation implies that after the first appointment, accessible information should only be made available upon request. All organisations providing NHS care are legally required to follow the Accessible Information Standard, which sets out that people with communication needs should receive accessible information and communication support when accessing services. In line with the Standard, people with AMD should be asked their preferred format during initial contact and receive any/all future correspondence regarding their diagnosis and treatment in this format. Additional communication needs, such as a learning disability, should also be considered when providing healthcare information. Please can the language in recommendation 1.2.3 be amended to reflect these two points. | Thank you for your comment. In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |
| Thomas Pocklington Trust | Short | 6 | 14-16 | Where possible health professionals should provide explicit guidance as to where people can receive peer support, such as the details of their local Macular Society support group or other peer support groups. | Thank you for your comment. The committee agreed that, as networks vary across the country, it is difficult to provide specific advice on this point, though the examples specified are reasonable. |
| Thomas Pocklington Trust | Short | 7-8 | 1-26;1-5 | Recommendation 1.4 focuses solely on the diagnosis and referral of AMD in cases where the condition is already suspected. It omits from providing guidance around the improvement of diagnosing AMD more generally. We would recommend that, in order to improve the rate of early diagnosis and reduce the risk of people developing AMD: | Thank you for your comment. Screening for AMD – and optimising the detection of visual impairment more generally – was beyond the scope of this guideline and therefore the committee were unable to make recommendations in this area. |

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| | | | | • The importance of sight tests in screening for AMD is promoted for people over defined threshold ages / those with a family history of the condition.<br>• The risk factors associated with AMD (listed in recommendation 1.3) are promoted, particularly amongst those at high risk of developing the condition, through public awareness campaigns. | Thank you for your comment. 'Preventing sight loss' will be considered by NICE at a future topic selection review. |
| Thomas Pocklington Trust | Short | 8 | 3-5 | The Royal College of Ophthalmologists guidelines recommend that people with Wet AMD should be seen by a specialist with medical retinal expertise within one week of diagnosis and there should be no more than one week between evaluation and treatment. Given that Wet AMD can develop rapidly, causing serious changes to central vision within a matter of days or weeks, prompt delivery of treatment is vital. A recent 12 month study conducted by the Royal College of Ophthalmologists reported that AMD was the second most prevalent eye condition (23%) amongst the 169 patients who experienced preventable loss of vision due to hospital-initiated delays. Please can the Royal College of Ophthalmologists guidance be incorporated into recommendation 1.4.10. | Thank you for your comment. Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |
| Thomas Pocklington Trust | Short | 8 | 6-11 | Any local pathway that commissioners agree for people with AMD should include referral to local authority social care for a vision rehabilitation assessment. The assessment should result in a vision rehabilitation plan tailored to the needs of the individual, maximising independence and confidence. Local | Thank you for your comment. In as much as these consideration bear on all forms of visual impairment, they are beyond the scope of this guideline. However, recommendations have been added to ensure that people with AMD are advised of 'the benefits and |

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| | | | | authorities and the NHS also benefit from effective vision rehabilitation as it can reduce the risk of falls and other conditions, such as depression. The RNIB has recently launched research showing the economic value of vision rehabilitation which shows significant cost avoidance. The local pathway should include how and when referrals to local authority social care are made. Where available, an Eye Clinic Liaison Officer (ECLO) should be involved in the referral process. | entitlements available through certification and registration when sight impaired or severely sight impaired' and to emphasise that all eligible patients should be offered 'certification of visual impairment… soon as they become eligible, even if they are still receiving active treatment.' |
| Thomas Pocklington Trust | Short | 11 | 19-21 | The NICE guideline on depression in adults with a chronic health problem was last updated in November 2015 and therefore does not take the Accessible Information Standard into account. It states that, "When working with patients with depression and a chronic physical health problem…ensure that comprehensive written information is available in the appropriate language and in audio format if possible". Please can you acknowledge that the detail around communication within the NICE guideline is out of date and is superseded by the more recent Accessible Information Standard. Thomas Pocklington Trust's research into access to psychological therapies for people with sight loss and depression has identified the need for extensive training for professionals who support people with sight loss, to improve recognition of depression and enhance a facilitated pathway to psychological treatments. | Thank you for your comment. In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |
| Thomas Pocklington Trust | Short | 11 | 22-23 | Low vision services are not consistently available across England. Please could you acknowledge the recent Low Vision, Habilitation and Rehabilitation Framework published in 2017 from the Clinical Council for Eye Health Commissioning, which | Thank you for your comment. The committee is aware of disparity in low service provision in England. We hope that this guideline will help to standardise provision. |

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| | | | | calls for more joined up commissioning to ensure better access and consistency of services. | |
| Thomas Pocklington Trust | Short | 12 | 8 | Refers to recommendation 1.8.5, which does not exist within the short version document. | Thank you; this has been corrected. |
| Vision 2020 | Full | 69 | 6.2.4 | Evidence for cost effectiveness of antioxidant vitamin and mineral supplements<br><br>The Macular Society has funded a study to assess the cost effectiveness of antioxidant vitamin and mineral supplements which is to be published on 24 August 2017 in the British Journal of Ophthalmology:<br><br>The age-related macular degeneration study supplements are cost-effective for use. A dominant health economic intervention modelled using real-world outcomes<br>Lee AY, Butt T, Chew E, Agron E, Clemons T, Egan C, Lee CS, Tufail A<br><br>The conclusions of the study are that a model based on AREDS clinical trial data & real-world data is likely to be a realistic reflection of the health gains and resource use of anti-VEGF for neovascular AMD in the UK NHS. Initiating AREDS supplements in AREDS category 4 with neovascular AMD who present opportunistically is both cost saving (through reduced need for anti-VEGF therapy) and more effective than no supplements and should therefore be considered in public health policy. | Thank you for your comment. This evidence was presented to the committee at the post-consultation meeting. The study concludes that the supplement may be a cost-effective use resources; however, it did not resolve the committee's uncertainty regarding the AREDS data.<br>The committee agreed that, if an effect of the magnitude reported in the AREDS1 post-hoc subgroup could be expected in practice, supplementation would be very likely to be cost effective. This has recently been demonstrated by a cost–utility analysis conducted by Lee *et al.* (2017), which evaluated the AREDS supplement based on AREDS1 trial data. This UK study concludes that the supplement may be a cost-effective use resources; however, it did not resolve the committee's uncertainty regarding the AREDS1 data, described in the 'Trade-off between benefits and harms' section of 6.2.4 in the full guideline. The absence of robust evidence therefore makes it impossible to judge whether the supplementation from AREDS1 would indeed be cost-effective. |

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| | | | 6.2.6<br>4 | VISION 2020 UK would like to refer NICE to this publication and note the ongoing consultation by NHS England on guidance to CCGs on items which should not be routinely prescribed in primary care. The draft guidance includes lutein and antioxidants for AMD and the Macular Society will be responding to this consultation.<br><br>**Research recommendation**<br><br>VISION 2020 UK supports the Macular Society research recommendation on AREDS:<br><br>What is the effectiveness of antioxidant and zinc supplements on AMD disease progression for people with early AMD at high risk of progression in the context an RCT? | In view of the large population for which supplementation would be indicated, and the extended length of time for which people would need to take the supplements, the committee was also bound to consider the potential resource impact of a positive recommendation. It noted its responsibility, as set out in *Developing NICE guidelines*, that, 'In general, the Committee will want to be increasingly certain of the cost effectiveness of a recommendation as the cost of implementation increases. Therefore, the Committee may require more robust evidence on the effectiveness and cost effectiveness of recommendations that are expected to have a substantial impact on resources' (7.2). In this case, any evidence of effectiveness and cost effectiveness is highly uncertain, and the committee agreed that they were unable to make any recommendation that would impose significant additional costs on the NHS.<br>Accordingly, the committee recommended that additional research was necessary to confirm or refute the post-hoc findings from AREDS1. |
| Vision 2020 | Full | 106 | | Referral and treatment pathways<br><br>We question the maximum of 7 days from initial presentation to referral implied by 'urgent' in Recommendation 9 on referral to hospital services of people with suspected late AMD (wet active). We would like to see evidence to support the statement | Thank you for your comment. Following discussion of stakeholder feedback, the committee agreed that the time from suspicion of late AMD (wet active) to referral should be defined as 1 working day, with an additional clarification that emergency referral is not required.<br>Multiple stakeholders commented that, for eyes with late AMD (wet active), the target of 21 days from |

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| | | | | that optometrists 'universally understand an 'urgent' referral as one that should be made within 7 days'.<br><br>Notwithstanding this, we do not understand why referral cannot take place immediately and, where possible, the same working day. We question the concern that specifying referral should take place on a shorter timescale than 'urgent' would lead to the 'drastic' steps imagined.<br><br>We strongly object to any lengthening of the current recommended maximum timescales for the referral pathway set out in the Royal College of Ophthalmologists AMD: Guidelines for management. We consider that Recommendation 12, which extends the time limit from referral to treatment from 14 to 21 days runs counter to statements in the guideline, such as:<br><br>"The committee noted that included evidence demonstrated a clear association between visual loss and time delay in diagnosis and treatment for people with AMD. In some studies, the rate of loss was as rapid as 1 ETDRS letter every 3 days. Evidence from the included RCTs in section 10.1 was also considered. This suggests that eyes with late AMD (wet active) that were randomised to placebo anti-VEGF or sham PDT lost approximately 15 ETDRS letters over 1 year's follow-up. The committee interpreted this evidence as providing a clear mandate for the swiftest possible patient journey from suspicion to treatment of late AMD (wet active)." | referral to first treatment proposed in the draft guidance was unduly long, and that a target of 14 days (in line with current recommendations from the Royal College of Ophthalmologists) is achievable in practice. No stakeholders supported the committee's stated concern that a 14-day target should be viewed as 'aspirational', and that 'it is often not possible to provide treatment within 2 weeks'. The committee took this as evidence that its previous concerns about the achievability of a shorter target had been unfounded. Therefore, the committee agreed to revise the guideline to specify a 14-day target, in the knowledge that a shorter delay would maximise chances of preserving vision. |

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| | | | | Wet AMD is an urgent sight threatening condition and vision loss occurring due to disease progression may not be recovered. Some forms of disease can be aggressive and lead to rapid vision loss. Patients are also at risk of severe sight-threatening macular haemorrhages when disease is active. It is not possible at the time of referral to work out which types of patient are at higher risk so it is best to treat all patients with an equal level of urgency.<br><br>As supporting evidence we would like to highlight the natural history arm in the PIER study because all subgroups of wet AMD were enrolled (Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1 Regillo, Carl D. et al. American Journal of Ophthalmology , Volume 145 , Issue 2 , 239 - 248.e5). There was a 5 letter ETDRS loss by 4 weeks and 5 letters is a clinically significant drop in vision. Setting a target close to a time interval at which this much vision might be lost is not appropriate. If treatment is commenced early there is also the potential for better visual outcomes (Rasmussen, A., Brandi, S., Fuchs, J., Hansen, L. H., Lund-Andersen, H., Sander, B. and Larsen, M. (2015), Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Ophthalmol, 93: 616–620. doi:10.1111/aos.12781).<br><br>We do not consider it acceptable to extend the target on the basis that it is not currently achievable in some areas. The fact | |

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| | | | | that it is achievable for some hospital eye clinics should be something to which other clinics aspire.<br><br>Below is the experience of one member of the Macular Society:<br><br>"In my case the optometrist referred me the same day to the hospital after I had consulted her regarding the blurred and distorted vision in my left eye at 6/10. Two days later at the hospital I was diagnosed with neovascular AMD and an FFA was completed on the 7th day following the referral by which time the acuity was 6/15. Thereafter, I was advised that it could be 9 weeks since referral before treatment with Eylea.<br><br>On a daily basis I was experiencing central vision loss. Eventually I was offered treatment that would effectively have been 5 weeks since referral. However, as I had been earlier advised by the hospital that the outlook for treatment could be 9 weeks, I had opted for private treatment with Avastin at 3 weeks. Both of these delays were caused by a wholly inadequate treatment service at the referred hospital. In contrast other hospitals in the region were accomplishing the full pathway to treatment ranging from same day to 7 days.<br><br>It is a post-code lottery with many patients, as myself, experiencing unnecessary permanent macular damage and vision loss because of inadequate hospital bureaucracy." | |
| Vision 2020 | Short | General | General | VISION 2020 UK is the umbrella organisation which leads collaboration and co-operation between organisations with an | Thank you for your comment, and acknowledging the value of the guideline. |

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| | | | | interest in eye health and sight loss. Our response reflects the views of our members and we are happy to endorse the separate responses of our Members specifically the responses of the RNIB, the Macular Society, the Thomas Pocklington Trust and the Royal College of Ophthalmologists.<br><br>VISION 2020 UK welcomes the NICE Clinical Guideline on age-related macular degeneration (AMD) as an opportunity to improve and provide consistency across the country for the diagnosis and management of AMD. Listening to those with lived experience of AMD we hear that is that, depending on where you live, prompt access to hospital services and timely treatment (where required) is highly variable. It is acknowledged that demand for treatment of late AMD (wet active) is severely straining NHS ophthalmology departments and we welcome the creative ways in which some hospitals are adapting their services to meet the timescales for diagnosis and treatment recommended by the Royal College of Ophthalmologists in their AMD: Guidelines for management.<br><br>VISION 2020 UK notes that there is little mention of multi-morbidities within the guidelines and as many patients with AMD will be in the older age brackets this is an oversight. Treating the patient holistically means it is important for NICE to acknowledge within these guidelines that the patient may have other issues which will impact on treatment. | On considering these comments and others, the committee agreed it would be useful to add a cross-reference to NICE's guidance on the assessment and management of multimorbidity.<br>Although the committee believe that there is no known association between learning disabilities and macular degeneration – as a specific form of visual impairment – it wholeheartedly agrees that the needs of people with such disabilities should be met. NICE's generic guidance on patient experience in adult NHS services and the assessment and management of multimorbidity, to which cross-references are now made, contains important recommendations that seek to optimise the experience of people with learning disabilities in the NHS. |

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| | | | | We also note the lack of mention of patients with learning disabilities and their additional needs. People with learning disabilities are ten times more likely to have sight loss (The Estimated Prevalence of Visual Impairment among People with Learning Disabilities in the UK) and less likely to get the help and support they need. The Royal College of Ophthalmologist produced the Quality Standards for Services for Patients with Learning Disabilities which should be considered within the guidelines. | |
| Vision 2020 | Short | 5 | 6-9 | VISION 2020 UK supports and advocates for the provision of information to patients in a format that is accessible to them. This is now a requirement covered by the NHS Accessible Information Standard (2016).<br><br>VISION 2020 UK Recommends that the NHS Accessible Information Standard be explicitly included and highlighted in section 1.2.1 with particular note of the requirement to undertake a patient assessment to identify, capture and record the person's accessibility requirements.<br><br>RNIB's 'My Voice' survey revealed that 37 percent of registered blind and partially sighted people with AMD said that in the preceding 12 months they had never received information from health care providers in an accessible format (My Voice, RNIB, 2015, http://www.rnib.org.uk/sites/default/files/My%20Voice%202015%20-%20Full%20report%20-%20Accessible%20PDF_0.pdf). | Thank you for your comment. In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |

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| Vision 2020 | Short | 5 | 11-28 | VISION 2020 UK recommends the addition of information about Charles Bonnet Syndrome in the information offered to patients in section 1.2.2.<br><br>Up top half of all people with macular degeneration suffer or will experience visual hallucinations(https://www.macularsociety.org/visual-hallucinations ). The Royal College of Ophthalmology AMD guideline states that "people see different images, from simple patterns of straight lines to detailed pictures of people or buildings. These can be disturbing, and may not be voluntarily mentioned by patients to friends, family or the medical profession as sufferers may be concerned that they might be developing a serious mental illness. The anxiety is more damaging than the hallucinations themselves. Patients should be alerted to the possibility of CBS which typically improves by 18 months but can last many years. The Macular Society is familiar with the condition and can talk to patients and provide a leaflet. It is recommended that clinicians educate all relevant clinic staff about CBS, including receptionists and technicians" (https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2013-SCI-318-RCOphth-AMD-Guidelines-Sept-2013-FINAL-2.pdf (P94))<br><br>Information should be provided to people with AMD to raise awareness and assure people that the hallucinations are a common feature of AMD and are not a sign of mental illness. | Thank you for this suggestion. The committee agreed it would be helpful to add 'the possibility of developing visual hallucinations associated with retinal dysfunction (Charles Bonnet syndrome)' to the list of topics that should be discussed with people with AMD (1.2.2) |

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| Vision 2020 | Short | 5 | 20 | VISION 2020 UK would like to express it's disappointment that the committee felt it was not able to include a recommendation on the benefits of Eye clinic liaison officers (ECLOs) due to the lack of AMD specific evidence in the literature. However, we are pleased that the committee acknowledge the importance of ECLOs in providing information to patients and their key role as part of the service provided at hospital eye clinics.<br><br>ECLOs, while not universally available, are a valuable resource to provide patient support and it is suggested that ECLOs are specifically included in this point.<br><br>RNIB investigated the impact of Eye Clinic Liaison Officers (ECLO impact tool: UK wide findings 2015-2016), finding that this provision increased emotional well-being as well as increasing patient understanding of the support available to them outside of the eye clinic. Additionally people who received support from an ECLO reported that as a result they felt reassured and more optimistic about the future.<br><br>Below are results from the above report available here: www.rnib.org.uk/ECLO-impact-tool | Thank you for your comment. The experience of committee members strongly echoes this comment; they were eager to point out the invaluable service provided by the ECLOs with whom they work. However, as stated in section 12.2.3 of the full guideline, 'due to the lack of AMD-specific evidence in the literature on the benefits of ECLOs, the committee was unable to recommend this directly.' |
| Vision 2020 | Short | 5 | 20 | VISION 2020 UK would like to express it's disappointment that the committee felt it was not able to include a recommendation on the benefits of Eye clinic liaison officers (ECLOs) due to the lack of AMD specific evidence in the literature. However, we are pleased that the committee acknowledge the importance of | Thank you for your comment. The experience of committee members strongly echoes this comment; they were eager to point out the invaluable service provided by the ECLOs with whom they work. However, as stated in 12.2.3, 'due to the lack of AMD-specific |

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| | | | | ECLOs in providing information to patients and their key role as part of the service provided at hospital eye clinics.<br><br>ECLOs, while not universally available, are a valuable resource to provide patient support and it is suggested that ECLOs are specifically included in this point.<br><br>RNIB investigated the impact of Eye Clinic Liaison Officers (ECLO impact tool: UK wide findings 2015-2016), finding that this provision increased emotional well-being as well as increasing patient understanding of the support available to them outside of the eye clinic. Additionally people who received support from an ECLO reported that as a result they felt reassured and more optimistic about the future.<br><br>Below are results from the above report available here: www.rnib.org.uk/ECLO-impact-tool | evidence in the literature on the benefits of ECLOs, the committee was unable to recommend this directly.' |
| Vision 2020 | Short | 7 | 8-9 | VISION 2020 UK support the RNIB's concerned that there is no protocol for monitoring people with asymptomatic AMD is specified in Section 1.4.3.<br><br>We support the RNIB recommendation that individuals with asymptomatic AMD are monitored every 6 – 12 months and issued an Amsler chart and information for self-monitoring. | Thank you for your comment. Amsler grids were amongst the technologies for which evidence was sought in our review question on self-monitoring strategies (chapter 11.2); however, no evidence meeting the eligibility criteria was identified. The committee made a research recommendation to assess 'the effectiveness and cost-effectiveness of self-monitoring strategies in improving the long-term visual, functional and quality of life outcomes of people with early, indeterminate or late AMD (dry)'. |

# Macular degeneration

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| Vision 2020 | Short | 8 | 1.5.1 | Pharmacological management of AMD<br><br>The Macular Society is disappointed that there is no recommendation for treatment of eyes with late AMD (wet active) where vision is better than 6/12 given the evidence on cost effectiveness of aflibercept and ranibizumab presented in Butt et al (2015) paper.<br><br>We note that bevacizumab is not licensed for intraocular use for late AMD (wet active) but we support the finding that the optimal strategy for treating wet AMD is:<br><br>• Bevacizumab<br>• Every 2 months<br>• No restriction to better seeing eye<br>• Include eyes with VA >6/12.<br><br>We note that recommendations in a NICE clinical guideline cannot contradict recommendations in NICE technology appraisal guidance and this is why the guideline cross refers to TA155 and TA 294 in relation to the use of ranibizumab and aflibercept.<br><br>We understand from NICE that ranibizumab and aflibercept are licensed for treatment of late AMD (wet active) where visual acuity is better than 6/12. This does not appear to be widely known and has implications for the current use of bevacizumab to treat late AMD (wet active) when patients present with visual | Thank you for your comment. Having considered feedback from stakeholders, the recommendations regarding anti-VEGF treatments have been amended. These note that there is no evidence of differences in safety or effectiveness between any of the 3 anti-VEGF agents and, consequently, that comparable regimens will be more cost effective if the agent used has lower net acquisition, administration and monitoring costs. The recommendations confirm that bevacizumab does not have a UK marketing authorisation for, and is considered by the MHRA to be an unlicensed medication in, this indication. They advise prescribers to be mindful of relevant professional guidance regarding the prescription of medicines outside their marketing authorisations, and they emphasise that, while the guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation, it does not amount to an approval of or a recommendation for such use.<br>The committee considered stakeholder comments and revised health economic modelling of relevance to the upper acuity threshold for initiating anti-VEGF treatment at its post-consultation meeting. It noted that the revised model suggested that, compared with restricting antiangiogenic therapy to the range recommended in TA155 and TA294, offering treatment to eyes with acuity greater than 6/12 invariably provides benefits at a cost that would conventionally be |

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| | | | | acuity outside the circumstances specified in TA155 and TA294. We are disappointed that all stakeholders have not been made aware of this important information and therefore able to tailor their comments accordingly. | considered an effective use of resources. However, the committee understood that, unless the agent used was either bevacizumab or very low-intensity ranibizumab, extending treatment was only cost effective compared with something that was, in itself, not cost effective. Because the analysis had convincingly shown that there are many strategies that would deliver greater net benefit to the NHS than simply extending current treatment to a wider range of eyes, the committee considered it inappropriate to make a recommendation explicitly mandating such an approach. However, the committee noted that offering anti-VEGF to eyes with acuity better than 6/12 could provide cost-effective benefits, depending on the regimen used. |
| Vision 2020 | Short | 8 | 6-11 | Any local pathway that commissioners agree for people with AMD should be defined by the Adult UK eye health and sight loss pathway and include referral to local authority social care for a vision rehabilitation assessment. The assessment should result in a vision rehabilitation plan tailored to the needs of the individual, maximising independence and confidence. Local authorities and the NHS also benefit from effective vision rehabilitation as it can reduce the risk of falls and other conditions, such as depression. The RNIB has recently launched research showing the economic value of vision rehabilitation which shows significant cost avoidance. The local pathway should include how and when referrals to local authority social care are made. Where available, an Eye Clinic | Thank you for your comment. In as much as these consideration bear on all forms of visual impairment, they are beyond the scope of this guideline. However, recommendations have been added to ensure that people with AMD are advised of 'the benefits and entitlements available through certification and registration when sight impaired or severely sight impaired' and to emphasise that all eligible patients should be offered 'certification of visual impairment… soon as they become eligible, even if they are still receiving active treatment.' |

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| | | | | Liaison Officer (ECLO) should be involved in the referral process. | |
| Vision 2020 | Short | 11 | 18-27 | VISION 2020 UK recommends the inclusion of advice on visual standards for driving in Section 1.6.<br><br>The Royal College of Ophthalmologists has published guidance on Vision Standards for Driving outlining the duty of care of Ophthalmologists towards patients to give information if driving is threatened.<br><br>VISION 2020 UK Supports the RNIB Recommendation of the inclusion of the following wording:<br><br>Consider giving appropriate advice with regard to driving to people with AMD taking into account visual acuity and visual field. | Thank you for your comment. In line with this suggestion, the committee agreed it would be helpful to add 'vision standards for driving' to the list of topics that should be discussed with people with AMD (1.2.2) |
| Vision 2020 | Short | 11 | 19-21 | VISION 2020 UK would like to draw attention to the fact that the NICE guideline on depression in adults with a chronic health problem was last updated in November 2015 and therefore does not take the Accessible Information Standard into account. It states that, "When working with patients with depression and a chronic physical health problem…ensure that comprehensive written information is available in the appropriate language and in audio format if possible". Please can you acknowledge that the detail around communication within the NICE guideline is out of date and is superseded by the more recent Accessible Information Standard. | Thank you for your comment. In line with your suggestion, recommendation 1.2.1 has been revised to refer directly to the NHS Accessible Information Standard. |

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| | | | | Thomas Pocklington Trust's research into access to psychological therapies for people with sight loss and depression has identified the need for extensive training for professionals who support people with sight loss, to improve recognition of depression and enhance a facilitated pathway to psychological treatments.<br><br>According to the Depression in Visual Impairment Trial (DEPVIT) (Guide Dogs and Cardiff University), 43% of people who lose their sight go on to battle depression, however NHS low vision services focus only on the physical need, and psychological screening or therapy is not yet an integral part of rehabilitation. | |
| Vision 2020 | Short | 11 | 22-23 | Low vision services are not consistently available across England. Please note the recent publication by the Clinical Council for Eye Health Commissioning, Low Vision, Habilitation and Rehabilitation Framework published in 2017 which calls for more joined up commissioning to ensure better access and consistency of services. This should be reflected in the guidelines.<br><br>The majority of people who had been referred to low vision services mentioned how helpful the low vision clinic had been in administering aids and giving them support.<br><br>VISION 2020 UK Supports the RNIB recommendation that the wording of section 1.6.3 should be changed to ensure that where AMD is causing visual impairment all patients are given | Thank you for your comment. A recommendation has been added to emphasise the importance of certification: 'Offer certification of visual impairment to all patients as soon as they become eligible, even if they are still receiving active treatment.' (1.6.4)<br>The reasoning for the weaker form of recommendation adopted in 1.6.3 is explained in section 9.2.3: 'Having reviewed the included evidence, the committee agreed that the evidence was not sufficiently robust to make a strong recommendation for low vision services. However based on committee members' experience of the benefits of the support provided, and the evidence available from non-AMD populations (Binns et al., 2012), it agreed to recommend that the provision of such services should be considered for people with |

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| | | | | the opportunity to access low vision services. Patients should also be made aware that they have the option for vision rehabilitation (which does not need to be group based) and where appropriate considered for CVI:<br><br>1.6.3 Offer people with AMD causing visual impairment a referral to low vision services and rehabilitation. Where appropriate consider CVI. | AMD when they experience vision problems. Due to the conflict between the committee's understanding of the benefits of low-vision services and the lack of any high-quality evidence to substantiate this, the committee agreed that more research would be useful to understand the impact of improving low-vision services specifically on people with AMD and made a research recommendation to this effect.' |
| Vision 2020 | Short | 12 | 14-15 | VISION 2020 UK supports section 1.7.4, and recommends that 'healthcare professional' be specified. VISION 2020 UK believes that it is not advisable for people with AMD to approach their GP about changes in their sight as this will slow down the referral process. We support the RNIB recommadtion that 'healthcare professional' be specified as 'Optometrist'. | Thank you for your comment. As it may sometimes be appropriate for a patient to consult their GP (if they have been closely involved in their eye-care) and some other patients may have direct access to secondary care professionals, it was agreed that a better form of words would be that people consult their eye-care professional. |
| Vision 2020 | Short | 12 | 8 | Refers to recommendation 1.8.5, which does not exist within the short version document. | Thanks; this has been corrected. |
| Visionary | Short | General | General | There is very limited mention of the certification and registration process, therefore, we would like to see this addressed as a separate point either in its own section or within an existing section. The number of Certificate of Visual Impairment (CVI) has fallen, despite the increase in people diagnosed with low vision, therefore, it's important that clinicians consider this option and are aware of the process. Also, the revised CVI Form and Explanatory Notes were launched on 17th August 2017 so including it in the NICE guideline would a timely reminder for clinicians. | Thank you for your comment. A recommendation has been added to emphasise the importance of certification: 'Offer certification of visual impairment to all patients as soon as they become eligible, even if they are still receiving active treatment.' (1.6.4) |

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| Visionary | Short | 5 | 20 | We would like to see reference made to the ECLO or volunteer-led service (if there is one), Local Authority's Sensory Team, local and national charities, etc. | Thank you for your comment. The committee agreed it would not be practical to provide an exhaustive list of sources of support that may (or may not) exist in any given locality, and it would not be helpful to provide a partial or vague list. |
| Visionary | Short | 5 | 28 | We would like to see examples stated of whom clinicians can signpost patients to, including the ECLO or volunteer-led service (if there is one), Local Authority's Sensory Team, local and national charities, etc. | Thank you for your comment. The committee agreed it would not be practical to provide an exhaustive list of sources of support that may (or may not) exist in any given locality, and it would not be helpful to provide a partial or vague list. |
| Visionary | Short | 6 | 1 | We would like to see reference made to the patient's preferred accessible format. Although it's important to have a range available, each person will have a different need which should be established early on in the referral process. This will ensure that the patient has a positive experience and the clinic is working in line with the Accessible Information Standard (DCB1605 Accessible Information). | Thank you for your comment. Recommendation 1.2.1 has now been revised to refer directly to the NHS Accessible Information Standard. |
| Visionary | Short | 11 | 22-23 | Suggest rewording "Consider referring…" to "Offer to refer…" as all such patients will be eligible for a low-vision assessment. | Thank you for your comment. The reasoning for the weaker form of recommendation adopted in 1.6.3 is explained in section 9.2.3: 'Having reviewed the included evidence, the committee agreed that the evidence was not sufficiently robust to make a strong recommendation for low vision services. However based on committee members' experience of the benefits of the support provided, and the evidence available from non-AMD populations (Binns et al., |

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| | | | | | 2012), it agreed to recommend that the provision of such services should be considered for people with AMD when they experience vision problems. Due to the conflict between the committee's understanding of the benefits of low-vision services and the lack of any high-quality evidence to substantiate this, the committee agreed that more research would be useful to understand the impact of improving low-vision services specifically on people with AMD and made a research recommendation to this effect.' |
| Visionary | Short | 12 | 4-8 | As some patients are reluctant to consult with a healthcare professional, consider adding in examples of others who they may already be linked in with and feel more comfortable approaching, for example the ECLO or volunteer-led service (if there is one), Local Authority's Sensory Team, local and national charities, etc. who could then encourage them to contact the relevant person. | Thank you for your comment. This recommendation has been revised to refer to the person's 'eye-care professional'. This might include some of the people on the suggested list (e.g. ECLOs). As suggested, such professionals will be able to signpost patients to the most appropriate next step, if they are not able to provide reassessment themselves. |

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*