NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration

Response to consultee and commentator comments on the first ACD issued June 2007

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Pfizer		Pfizer disagrees with the NICE preliminary decision to not recommend pegaptanib for any patients with wet AMD.	Comment noted
Pfizer		Our response focuses on three key concerns. There are summarised below and more detail is provided in the attachment: 1) An inequitable approach to decision making has been adopted, leading to a recommendation for ranibizumab in patients with predominantly classic lesions and no recommended use of pegaptanib We note that an inconsistent approach to generate the cost-effectiveness estimates has been employed. Ranibizumab is recommended for the treatment of patients with predominantly classic lesions based on a treatment period of one year (12 injections). The cost-effectiveness estimates for pegaptanib, and the remaining lesion sub-types treated with ranibizumab, were, however, based on a treatment period of two years. It is clear that this differential treatment period is driving the cost-effectiveness results and decision making. We demonstrate in the attached response that under the same decision criteria of one-year treatment (9 injections), pegaptanib is highly cost-effective (£7,500 per QALY) for patients with all lesion sub-types of AMD.	The Committee considered this point and considered analysis that assumed 2 year treatment for ranibizumab predominantly classic lesions. See FAD sections 4.3.10, 4.2.4.6, 4.2.4.7 and 4.3.22.
Pfizer		2) We maintain that pegaptanib is cost-effective for 2 years of treatment versus usual care. We challenge two key elements of the NICE analysis: a) NICE has not adequately recognised the value of pegaptanib for the treatment of early stage disease As stated in the Pfizer response to the Technology Assessment Report, Pfizer strongly recommends that pegaptanib should be available as a treatment option for patients with wet AMD at an early stage of disease, i.e. when their visual acuity lies between 6/12 and 6/24. This is consistent with	The Committee considered the cost effectiveness of pegaptanib treatment in the 6/12 to 6/24 subgroup and concluded that pegaptanib treatment was not a cost effective use of NHS resources in any subgroup when a policy of treating the first eye to come to clinical attention was considered. See FAD sections 4.3.18, 4.3.21, 4.3.23 and 4.3.24.

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		pegaptanib's Summary of Product Characteristics, which confirms that the data over a two-year period indicate treatment should be initiated as early as possible. The NICE economic model is unsuitable to estimate cost-effectiveness for this patient sub-group. Pfizer has demonstrated that pegaptanib is cost-effective for this sub-group of patients when appropriate modelling of baseline vision and time dependence is applied.	
Pfizer		b) NICE has generated overly conservative estimates of cost-effectiveness by (i) costing administration as a Day Case Procedure and (ii) under-estimating the costs of blindness (i) Pfizer has consulted with ophthalmologists and understands that intravitreal injections for pegaptanib are being administered as an outpatient procedure in many UK centres. Additionally, a recent document published by the Royal College of Ophthalmologists: "Commissioning Contemporary AMD Services: A guide for commissioners and clinicians" outlines the resource requirements for establishing and running an AMD service. This document is based on clinician experience and research and it does not recommend that intravitreal injections should be administered as a Day Case Procedure. As there are no regulatory or clinical requirements for treatment to be administered as a Day Case Procedure, the lower cost-effectiveness estimates using costs of an outpatient procedure should be used by the Committee to inform decisions. (ii) Significant uncertainty surrounds the patient uptake and costs of services for people who progress to blindness. The actual cost of blindness to the NHS is fundamental to this appraisal because, by reducing progression to blindness, it is possible that pegaptanib provides more benefit for less cost than usual care. We ask the Committee to consider a higher cost of blindness based on up-to-date information and expert opinion; this will result in an improved cost-effectiveness for pegaptanib.	The Committee considered the costs of appropriate facilities and staffing for intravitreal injection. The results of the Assessment Group and Decision Support Unit extra analysis showed that costs based on the Royal College of Ophthalmology commissioning guidelines were higher than previously assumed day-case costs. The Committee was persuaded that in practice, for the foreseeable future, a mixture of day-case and outpatient procedures would occur. It concluded that a reasonable approach, as suggested by one of the consultees, would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an outpatient appointment. The Committee also believed costs of blindness that were between the base case AG analysis and the combined high cost high uptake assumption explored in the Assessment Report. See FAD sections 4.3.16 and 4.3.17.
Pfizer		3) Treatment choice has been restricted without full consideration of the potential safety concerns of treating with ranibizumab, a non-selective VEGF-A agonist Pfizer are concerned that the preliminary guidance recommends ranibizumab as the only anti-VEGF treatment to treat wet AMD. This would restrict physician and patient choice. Physicians should be able to prescribe the most appropriate treatment to each individual patient based on an informed assessment of risk as well as benefit. This is an important consideration in light of the evidence suggesting an increased risk of stroke associated with ranibizumab.	The Committee concluded that pegaptanib was not a cost effective use of NHS resources. The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). It concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD section 4.3.24).

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Pfizer		For the above reasons, Pfizer maintains that pegaptanib should be recognised as a cost-effective treatment for patients with all lesion sub-types of wet AMD and we urge the Committee to revise their draft recommendation.	The Committee considered the cost-effectiveness of pegaptanib using both the manufacturer's and Assessment Group's economic models. It considered that there could be differential gains from pegaptanib for different subgroups of patients according to their starting visual acuity. It considered whether it could and should recommend pegaptanib for a specific subgroup. After considering all the Committee's preferred assumptions in the economic models, it concluded that for all visual acuity subgroups, pegaptanib was not a cost-effective use of NHS resources (see FAD sections 4.3.8 to 4.3.24).
Pfizer		ATTACHMENT Pfizer would like to provide additional detail supporting our three concerns for the Committee's attention:- 1) An inequitable approach to decision making has been adopted, leading to a recommendation for ranibizumab in patients with predominantly classic lesions and no recommended use of pegaptanib In our original submission, and in our response to the Technology Assessment Report (TAR), Pfizer provided cost-effectiveness estimates modelled using two year clinical trial data from the VISION trial. Two year data was also used by Novartis to model out the cost-effectiveness estimates for ranibizumab in minimally classic and occult sub-types using MARINA trial data. The Assessment Group model, built by the Southampton Health Technology Assessment Centre (SHTAC), also modelled out the cost-effectiveness using the two-year data from VISION and MARINA; neither pegaptanib or ranibizumab were considered to be cost-effective by NICE.	As above
Pfizer		However, the ACD recommendation of ranibizumab for patients with predominantly classic lesion sub-type has been based on a maximum of 1 year of treatment (Sections 4.2.3.13 and 4.3.14 in the ACD). The treatment duration for these patients was assumed to be 1 year presumably because follow-up of the ANCHOR trial was restricted to 1 year at the time of the analysis. Hence, recommendation for ranibizumab in predominantly classic lesions has been based on one year data despite recognition that treatment	As above

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		will persist beyond this timeframe. This is inequitable as pegaptanib would be cost-effective for all lesion sub-types of AMD if modelling was based on one year of treatment.	
Pfizer		Pfizer have addressed this inequity by modelling outcomes data for pegaptanib based on the same approach undertaken by the Assessment Group using 1 year data (9 injections for pegaptanib) from the VISION trial using the Pfizer model.	As above
Pfizer		It can be demonstrated that pegaptanib is cost-effective when patients with early stage disease were treated with 9 injections in 1 year. The base case ICER is £7,580. The deterministic sensitivity analyses performed by the Assessment Group (reported in Table 4.24, page 138 of the TAR) were repeated for this analysis and all scenarios were cost-effective. All cost-effectiveness estimates are presented in Appendix 1, Table 1.	As above
Pfizer		Having already demonstrated that pegaptanib was cost-effective in the "treat early" population using 2 year data (TAR response); we have now shown that pegaptanib represents even better value for money to the NHS when 9 injections are modelled in this sub-group of patients with visual acuity (VA) between 6/12 and 6/24 with all lesion sub-types of AMD.	As above. The Committee discussed the duration of treatment and concluded that it was more appropriate to consider the scenarios in which 2 years of treatment were assumed rather than one year (see FAD sections 4.3.9 and 4.3.10).
Pfizer		We request the Committee address the question "How many injections can be considered cost-effective for these treatments?"	As above.
Pfizer		2) We maintain that pegaptanib can be shown to be cost-effective for 2 years of treatment. a) NICE has not adequately recognised the value of pegaptanib for the treatment of early stage disease In our response to the TAR, we provided a cost-effectiveness estimate of £15k per QALY which: • was modelled using two year clinical trial data from the VISION trial, • adopted all monitoring and administration costs from the SHTAC model, and • was specific to the SHTAC base case population of patients at an early stage of disease categorised by VA between 6/12 and 6/24. When the data for the "treat early group" was modelled by the Assessment Group to generate the "base case" cost-effectiveness estimate using 2 year data, the incremental cost-effectiveness ratio (ICER) was £31,000, which we acknowledge is at the upper limit of what would be acceptable to the NHS as representing good value for money.	The Committee considered the cost effectiveness of pegaptanib treatment in the 6/12 to 6/24 subgroup and concluded that pegaptanib treatment was not a cost effective use of NHS resources in any subgroup when a policy of treating the first eye to come to clinical attention was considered. See FAD sections 4.3.18, 4.3.21, 4.3.23 and 4.3.24.

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Pfizer		However, as we have already demonstrated in the Pfizer response to the TAR, comparison of the Assessment Group model prediction for outcomes in the first two years with those observed in the VISION trial demonstrates that the Assessment Group model substantially underestimates the benefit of pegaptanib during the period of trial follow-up for the "treat early group".	The Committee considered results by the DSU for pegaptanib based on the manufacturer's model in addition to its considerations of the Assessment Group model. See FAD sections 4.3.23 and 4.3.24.
Pfizer		The inaccuracy of the Assessment Group model may be explained by the simplistic approach to modelling outcomes. Most notably, no attempt was made to account for the time-dependency of VA changes. Although it has been recognised by others that VA change is dependent on pre-treatment VA levels (time to transition to lower VA level was found to be highly dependant on baseline Snellen; p=0.0065) probabilities derived from the VISION trial population with a VA range of 6/12 to 6/95 were used to model VA change for patients with a pre-treatment VA of between 6/12 and 6/24. The clinical data from the VISION trial did not support this assumption.	As above.
Pfizer		The Pfizer model more accurately models the benefit in this "treat early" group. The figure using the Pfizer model was £15,000 per QALY, which is often considered cost-effective and good value for money. The Pfizer model has now been accepted for peer-reviewed publication in Pharmacoeconomics (Wolowacz SE, Roskell N, Kelly S, Maciver FM, Brand CS. Cost-effectiveness of pegaptanib for the treatment of age-related macular degeneration in the UK. Pharmacoeconomics: Accepted; In Press).	As above.
Pfizer		Emphasis on treating early is clinically responsible as patients will have the greatest capacity to benefit from treatment. In addition, as disease awareness, diagnosis, and services improve, patient accessibility to receive earlier treatment will increase.	Comment noted
Pfizer		Furthermore, treating patients at an early stage of disease is supported by the wording in the Summary of Product Characteristics for pegaptanib which states that "Data over a two-year period indicate that Macugen treatment should be initiated as early as possible. In advanced disease the initiation and continuation of Macugen therapy should consider the potential for useful vision in the eye."	Comment noted
Pfizer		b) NICE has generated overly conservative estimates of cost-effectiveness by (i) costing administration as a Day Case Procedure and (ii) underestimating the costs of blindness (i) Cost of administration as a Day Case Procedure Pfizer note that in the ACD (section 4.3.11) the Committee have been advised by clinical specialists that administration of the intravitreal injections will be given as a Day Case Procedure and the (higher) associated costs for a Day Case should be adopted in the economic model. Pfizer have	As above

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		consulted with ophthalmologists who have advised that intravitreal injections for pegaptanib are being administered as an outpatient procedure in the UK centres.	
Pfizer		Pfizer would also like to draw the Committees attention to a recent document published by the Royal College of Ophthalmologists:- http://www.rcophth.ac.uk/docs/scientific/publications/FinalPDFV2CommissioningContemporaryAMDServices.	As above
Pfizer		This outlines the resource requirements for establishing and running an AMD service. This document is based on clinician experience and research and it does not recommend that intravitreal injections should be administered as a Day Case Procedure.	As above
		(ii) Costs of blindness and uptake of these services The wide variation in the outcomes presented in Table 4.24 of the TAR demonstrates that there is considerable uncertainty associated with the costs and uptake of services for the blind. For example, if the costs are high and the uptake is high, pegaptanib was shown to be a dominant therapy (providing more benefit at less cost than usual care). Pfizer have consulted with our key customer groups who have advised that the uptake of services for the blind is actually higher than currently estimated; therefore pegaptanib will demonstrate cost-effectiveness.	The Committee discussed the assumptions for uptake of costs related to blindness and considered sensitivity analyses with higher assumptions for uptake – see FAD sections 4.2.4.3, 4.2.4.5 and 4.3.16.
Pfizer		3) Treatment choice has been restricted without full consideration of the potential safety concerns of treating with ranibizumab, a non-selective VEGF-A agonist Pfizer are concerned that the preliminary guidance states that ranibizumab should be the only anti-VEGF treatment which is recommended to treat wet AMD. This would restrict physician and patient choice. Physicians should be able to prescribe the most appropriate treatment to each individual patient based on an informed assessment of risk as well as benefit. Ranibizumab is a non-selective VEGF-A agonist and pegaptanib is a selective VEGF treatment. The VISION study has shown that pegaptanib is well tolerated; the majority of ocular adverse events were attributed to the injection procedure. Systemic events attributable to pegaptanib occurred at a rate similar to the control group after two years. Three year safety data has produced no serious systemic safety signals and the ocular safety profile was sustained.	The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). It concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD section 4.3.24).
Pfizer		Safety data from ranibizumab studies ANCHOR (n=423) and MARINA (n=716) indicate a trend in the occurrence of serious adverse events	As above.

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		potentially related to systemic non-selective VEGF inhibition (such as arterial thromboembolic events and non-ocular haemorrhage). In particular, in the one-year ANCHOR study there was an apparent increase in arterial thromboembolic events from 2.1% in the verteporfin group to 4.3% in the 0.5mg dose ranibizumab group. Additionally in ranibizumab Summary of Product Characteristics under the section 4.8 Undesirable Effects; hypertension/elevated blood pressure is reported as very common.	
Pfizer		A recent correspondence in the New England Journal of Medicine between principal investigators of ranibizumab trials and other clinical experts in the field reflects the current uncertainty of the significance of these safety signals. They concluded that better estimates of the rates of the above adverse events would come from continued follow-up of patients. Pfizer support post-marketing surveillance studies to better establish the risk:benefit of anti-VEGF treatment options.	As above.
Pfizer		Section 4.3.5 in the ACD discusses the adverse events associated with both treatments and states that "they have a broadly similar profile, there is a suggestion that ranibizumab may be associated with an increased risk of stroke (although it is currently inappropriate to draw conclusions)". Treatment should be tailored to the individual patient and therefore the physician may feel it is necessary to recommend treatment with pegaptanib for patients who may have an increased cardiovascular risk; particularly patients who have already experienced a stroke.	As above.
Pfizer		The wet AMD patient population is generally older and present with co-morbidities. This is supported by a recent study comparing co-morbid conditions of patients with wet AMD and those without wet AMD.9 Results showed an 11.6% higher risk of stroke, a 31.5% higher risk of hypertension and a 36.4% higher risk of lipid disorders in the wet AMD population. Therefore, cardiovascular safety becomes an important treatment consideration in this patient population when treating with anti-VEGF therapy.	As above.
Pfizer		We would therefore recommend that the Committee reconsiders the potential safety issues associated with a non-selective VEGF-A agonist. Access to both anti-VEGF treatments would ensure that eligible patients have access to the most appropriate treatment to manage their disease, with consideration of potential benefit and risk for the individual.	As above.
Pfizer		APPENDIX 1 The results of the cost-effectiveness analyses when 9 injections are administered, i.e. 1 year of treatment with pegaptanib is presented in Table 1**(Deterministic Sensitivity Analysis: 1 Year Treatment (Pre-treatment VA of 6/12 to 6/24) adopting Assessment Group Treatment Costs –**	As above.

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		table received but not reproduced). The results have been generated using the Pfizer model, for a population of patients whose visual acuity at the start of treatment lies between 6/12 and 6/24. We have chosen to adopt the administration and monitoring costs provided by SHTAC (Assessment Group Model).	
Pfizer		The ICER was estimated as £7,580/QALY (£5,249 to £12,571) over 10 years. The probability of cost-effectiveness was 100% at a threshold of £20,000/QALY. Hence using the Pfizer model with the above input parameters, pegaptanib is cost-effective when effectiveness for 9 injections of treatment is modelled for patients with early disease.	As above.
Pfizer		The deterministic sensitivity analyses performed by the Assessment Group (reported in Table 4.24, page 138 of the TAR) were repeated for this analysis and are also presented in Table 1. If all injection procedures were assumed to be performed as day case procedures in the operation theatre (at a cost of £395), the ICER estimate rose to £14,010 per QALY. The ICER estimate remained below £20,000 per QALY in all analyses with the exception of time-frames of 5 years or less.	As above.
Novartis		Thank you for your invitation to comment on the above referenced Appraisal Consultation Document (ACD) and accompanying documents, which were released on the 7th June 2007. Whilst Novartis are pleased that patients with predominantly classic lesions will be allowed access to ranibizumab treatment, the decision to deny ranibizumab to patients with minimally classic and occult lesions is not consistent with the available evidence base, nor does it take into the account the degree of unmet clinical need in these patients. In addition, the restriction which limits treatment to the better seeing eye for predominantly classic lesions, cannot be justified on scientific, moral or ethical grounds. We believe, therefore, that the ACD is perverse in the light of the evidence submitted and that, accordingly, the preliminary recommendations therein do not constitute a reasonable or scientifically sound basis on which to develop guidance to the NHS.	The FAD has been amended - see FAD sections 1.1 and section 4.3.6
Novartis		We do not believe that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. We do not believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate. We do not consider that all of the relevant evidence has been taken into account.	Comments noted.
Novartis		Novartis' main concerns regarding the preliminary recommendations, are summarised below:- 1. The decision not to recommend ranibizumab for patients with minimally	The FAD has been amended – see sections 1.1, 1.2, 4.3.9 to 4.3.13, 4.3.22, 4.3.18 and 4.3.4.

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		classic and occult lesions relies on an estimate of cost-effectiveness which is based on 24 injections over the course of 2 years, day case procedure costs and an underestimate of the costs of blindness. The combination of these factors has resulted in an incremental cost-effectiveness ratio (ICER) which grossly underestimates the cost-effectiveness of ranibizumab. 2. The recommendation that ranibizumab treatment should be limited to the better seeing eye is not supported by the available evidence base. 3. The implication that the recommended posology for ranibizumab may result in a reduction in benefits compared to those observed in the MARINA and ANCHOR studies is inaccurate and misleading.	
Novartis		However, in order to demonstrate our continued commitment to patients, and Novartis' desire to collaborate with the Institute to facilitate broader patient access to innovative and valuable treatments, Novartis is willing to consider capping the dose of ranibizumab. This concept was discussed, in principle with Dr Carole Longson on 9th July 2007 and the Department of Health, NICE liaison team, on 11th July 2007. As agreed, after further discussion with the Department of Health and NICE, further details of the scheme will be provided prior to the Appraisal Committee meeting on the 9th August 2007.	The Committee considered the suggested scheme. See FAD section 4.3.22
Novartis		These issues, as well as our other comments, are addressed in more detail below and are set out as per the requested headings. A. We do not believe that the provisional recommendations as detailed in the ACD are justified nor do they constitute a reliable basis for the provision of sound guidance to the NHS. A1. The decision not to recommend ranibizumab for patients with minimally classic and occult lesions relies on an estimate of cost-effectiveness which is based on 24 injections over the course of 2 years, day case procedure costs and an underestimate of the costs of blindness. The combination of these factors has resulted in an incremental cost-effectiveness ratio (ICER) which grossly underestimates the cost-effectiveness of ranibizumab.	As above.
Novartis		Reduced dosing frequency vs monthly injections. The SHTAC model assumes that 24 injections are administered over the course of 2 years. This is inconsistent with the posology recommended by the EMEA, which represents a pragmatic and clinically directed approach to dosing. Therefore, the estimates from the Assessment Group's model grossly underestimate the cost-effectiveness of ranibizumab. In routine practice, and as acknowledged by clinical specialists in the ACD, most patients will receive considerably less than 24 injections. Two year results from the published PrONTO study using ranibizumab, demonstrate a mean improvement in visual acuity of 10.7 letters, and an improvement in visual acuity by ≥ 15 letters in 43% of patients. These results are similar to those	As above.

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		observed in the MARINA and ANCHOR studies and were achieved with an average dose of 9.9 injections over 24 months. Although, this is a relatively small, open label study, the pragmatic dosing regimen used in the study and its results strongly support the view that in routine clinical practice, a dosing strategy based on clinical need will significantly reduce the number of injections administered without compromising the level of benefits achieved. Following receipt of the ACD, Novartis conducted a survey involving 47 ophthalmologists who have considerable experience with ranibizumab. So far 19/47 ophthalmologists have responded. Results from this survey suggest that 58% patients will receive between 3 and 6 injections over 12 months and 38% will receive more than 6 injections but less than 12 injections. This is consistent with the drug and disease model submitted by Novartis on the 1st August 2006, which suggests that on average 8 injections are likely to be required in the first year and 6 injections in the second year.	
Novartis		The PIER trial demonstrated that an initial loading dose of monthly injections of ranibizumab for 3 months, followed by fixed quarterly injections, is superior to sham treatment for the primary endpoint and a number of secondary outcomes. In terms of the primary endpoint, the mean change in visual acuity from baseline, the difference between ranibizumab and sham injection observed in the PIER trial is similar (16.1 letters) to results from the MARINA and ANCHOR trials (17.7 to 20.8 letters). In addition, an initial improvement in mean visual acuity was seen at month 3, which is consistent with the findings from the MARINA and ANCHOR studies. In the PIER study 49% patients, compared to 70% and 75% MARINA and ANCHOR respectively lost fewer than 5 letters (1 line) visual acuity between baseline and 12 months. This suggests that the fixed, quarterly, dosing regimen employed in the maintenance phase of PIER was adequate for a large proportion of patients to achieve the results observed in the MARINA and ANCHOR trials. It also suggests that some patients are over-treated using the monthly dosing regimen. In order to address this, the licensed dosing recommendations have been adopted to tailor the dose according to clinical need, rather than a fixed dosing interval regardless of response.	As above.
Novartis		Section 4.3.10 of the Appraisal Consultation Document (ACD) states, "The Committee was mindful of the results of the PIER study showing that the reduced frequency regimen was associated with reduced benefits." This erroneously implies that a reduced dosing regimen will result in reduced benefit. The key distinction is that PIER is based on treating all patients in a fixed dosing manner, irrespective of patient response, where as the recommended UK posology for ranibizumab is a flexible approach and means that re-treatments, following the loading phase, are dictated by	As above.

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		patient response to therapy. In practice, this means that the dose of ranibizumab will be individualised to achieve maximum benefit with minimum dosing. As well as being pragmatic, this dosing strategy represents a more effective and efficient strategy than the fixed dosing regimen employed in the PIER study.	
Novartis		Results from the published, PrONTO trial demonstrate that an "as required" dosing strategy can achieve benefits comparable to those achieved in the MARINA and ANCHOR trials with an average of 9.9 injections over the course of 2 years. In summary, the recommended posology for ranibizumab represents a pragmatic, effective and efficient dosing strategy for the treatment of wet AMD, which is likely to result in a level of benefits similar to those observed in the MARINA and ANCHOR studies.	As above.
Novartis		Day case procedure costs vs. outpatient visits. As set out in "The Royal College of Ophthalmologists Intravitreal Injections Procedure Guideline", intravitreal injections may be carried out either as an outpatient procedure or as a day case procedure. In practice, there is likely to be variation in the setting used, however, the assumption, used in the SHTAC model, that the cost of administering treatment will be broadly in line with the cost of a day case procedure, is an overestimate as it represents the upper extreme rather than a realistic treatment scenario.	The Committee considered the costs of appropriate facilities and staffing for intravitreal injection. The results of the Assessment Group and Decision Support Unit extra analysis showed that costs based on the Royal College of Ophthalmology commissioning guidelines were higher than previously assumed day-case costs. The Committee was persuaded that in practice, for the foreseeable future, a mixture of day-case and outpatient procedures would occur. It concluded that a reasonable approach, as suggested by one of the consultees, would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an outpatient appointment. The Committee also believed costs of blindness that were between the base case AG analysis and the combined high cost high uptake assumption explored in the Assessment Report. See FAD sections 4.3.16 and 4.3.17.
Novartis		Cost of Blindness. Section 4.3.13 of the ACD acknowledges the fact that clinical specialists consider the costs of blindness used in the Assessment Group's model to be too low. This effectively means that cost effectiveness of treatment will also be underestimated. The Appraisal Committee argue that this is balanced by the "overestimation of the QALY gain". However, this is neither a fair nor reasonable evaluation as the "overestimation of QALY gain" is purely speculative, whilst the underestimation in the costs of blindness can be	The Committee considered the most plausible assumption for the costs of blindness to be between the base case AG analysis and the high cost high uptake assumption explored in the Assessment Report. See FAD sections 4.3.16.

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		quantified and is verified by clinical experts.	
Novartis		A2. The recommendation that ranibizumab treatment should be limited to the better seeing eye is not supported by the available evidence base. Section 1.1 of the ACD states that ranibizumab treatment should only be reserved for the better seeing eye. The available evidence does not support this view and it is not clear from the ACD what evidence has been used to support this decision. In practice, this will mean that patients will be allowed to go blind in one eye before being eligible for treatment, which is morally and ethically unacceptable.	See FAD section 1.1 and 4.3.18
Novartis		Patient reported outcomes from MARINA and ANCHOR demonstrate statistically significant and clinically meaningful improvements in near activities, distance activities, and vision-specific subscales of the VFQ-25 instrument. These benefits were demonstrated regardless of whether patients received ranibizumab in the better- or worse seeing eye. In addition, results from the ANCHOR, MARINA and PIER trials all demonstrate that, in patients who received ranibizumab in the first or worst seeing eye, experienced improvements in visual acuity at 12 months of the same order of magnitude as results observed in the second or better seeing eye. These results are summarised in the following graphs **(graphs received but not reproduced).**	The Committee considered whether it would be appropriate to consider recommending treatment in the better-seeing eye only. It concluded that its considerations of cost effectiveness should relate to starting treatment with the first eye to come to clinical attention. See FAD sections 1.1, 4.3.18 to 4.3.21.
Novartis		A study by Williams et al, which assessed the psychological impact of macular degeneration in older persons who were legally blind in one or both eyes, found that psychological distress in both groups was significantly worse than that in non-affected older people. The level of psychological distress was comparable to reports from patients with melanoma, acquired immunodeficiency syndrome and bone marrow transplant. Participants who were legally blind in one or both eyes were limited in their ability to carry out basic daily activities. In the study, patients who were legally blind in only one eye recorded higher scores (more severe distress) in almost all areas than patients who were blind in both eyes. The authors also found that for older persons with advanced AMD, greater emotional distress was then reflected in worse quality of life and more difficulty in carrying out daily activities. This study, therefore, confirms that the presence of a single affected eye exerts substantial adverse effects on functional ability and quality of life comparable to those experienced with bilateral visual impairment.	As above.
Novartis		Brown et al compared quality of life associated with monocular and binocular vision using a time trade off method. The authors concluded that patient preference based quality of life was better in patients with eye disorders who had good bilateral visual acuity, than in those with only good unilateral visual acuity.	As above. See FAD sections 4.2.2.4 and 4.3.19.
Novartis		In summary, the preliminary recommendations do not take into account the	As above.

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<tr><th>Consultee or Commentator</th><th>Section of ACD (if specified)</th><th>Comment</th><th>Institute Response</th></tr>
<tr><td></td><td></td><td>relative benefits of binocular and monocular vision, or the distress caused by an untreated affected eye. There, to our knowledge, is no evidence to support the restriction of treatment to the better seeing eye. Conversely, the available evidence suggests that there are significant improvements in patient reported outcomes, regardless of whether treatment was administered to the better or worse seeing eye. In addition, a vast majority (88%) of the ophthalmologists responding to our survey are of the view that it would be unethical to restrict treatment to the better seeing eye.</td><td></td></tr>
<tr><td>Novartis</td><td></td><td>B. The current recommendations do not take into account all of the available evidence. In addition, the summaries of clinical and cost effectiveness are not reasonable interpretations of the available evidence base.
B1. The implication that the recommended posology for ranibizumab may result in a reduction in benefits compared to those observed in the MARINA and ANCHOR studies is inaccurate and misleading.</td><td>As above.</td></tr>
<tr><td>Novartis</td><td></td><td>No other therapies are currently available on the NHS to treat patients with minimally classic and occult lesions associated with wet AMD. This means that patients will be denied access to a clinically and cost effective treatment, which could prevent progression to blindness with its devastating consequences for patients and their families and/or carers.
The results from the MARINA and ANCHOR trials demonstrate that ranibizumab is effective regardless of lesion type or size. These results are summarised in the following table (shown below).
There is no other available therapy that has shown these benefits in randomised controlled clinical trials of either stabilisation or improvement in vision in 95% and 34%-40% respectively.</td><td>The FAD has been amended - See sections 1.1 and section 4.3.6.</td></tr>
<tr><td>Novartis</td><td></td><td>Summary of results from MARINA and ANCHOR trials
<table>
<tr><th></th><th>Minimally classic and occult lesions (MARINA)</th><th>Predominantly classic lesions (ANCHOR)</th></tr>
<tr><td>Loss of <15 letters (3 lines) on the EDTRS chart at 12 months</td><td>95%</td><td>94.3%</td></tr>
<tr><td>Difference in mean change from baseline visual acuity</td><td>17 letters (p=0.0001)</td><td>20.7 letters (p=0.0001)</td></tr>
<tr><td>Proportion of subjects gaining at least 15 letters visual acuity</td><td>33.8% ranibizumab vs. 4.6% control</td><td>40.3% ranibizumab vs. 5.6% control</td></tr>
</table></td><td>Noted</td></tr>
<tr><td>Novartis</td><td></td><td>B2. The combined impact of a number of conservative assumptions significantly underestimates the cost-effectiveness of ranibizumab treatment.</td><td>As above.</td></tr>
</table>

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		The decision not to endorse ranibizumab treatment for minimally classic and occult lesions relies on an estimate of cost-effectiveness, which is based on a number of conservative assumptions. These assumptions represent an excessive number of treatments (Ref. A1 above), overestimated administration costs (see A1 above), and underestimated costs of blindness. In summary, if more realistic assumptions were adopted, the ICERs relating to ranibizumab for the treatment of minimally classic and occult lesions would be reduced to a level deemed to be acceptable according to the conventionally accepted threshold.	
Novartis	3.3	Other comments Section 3.3, page 6 It should be noted that the risk of endophthalmitis with ranibizumab is low at a rate of 0.07% per injection. This should be specified in order to provide a comparison with pegaptinib which is stated in the ACD to have a 0.1% risk of endophthalmitis per injection.	See FAD sections 4.1.6 and 4.1.11.
Novartis	4.3.5	Section 4.3.5, page 19 This section of the ACD states: "However, the Committee considered a point raised by consultees that preliminary results of an ongoing study suggests that ranibizumab may be associated with an increased risk of stroke and agreed that although this was an important issue it was inappropriate to draw conclusions at this stage."	
Novartis		The report, suggesting a possible increased risk of stroke, was taken from the interim results of the SAILOR study based on an interim analysis comprising 77% of one of two cohorts. A statistically lower incidence of stoke was observed in patients on Lucentis 0.3 mg compared to patients on 0.5 mg (0.3% and 1.2%, respectively [p = 0.02]). Overall, the rate of stroke observed with Lucentis 0.5mg was consistent with data from the MARINA and ANCHOR trials (Brown et al, 2006; Rosenfeld et al, 2006). Furthermore, the rate of stroke observed with ranibizumab 0.5mg was no higher than the rate of stroke in the general population of a similar age and profile (Wong et al, 2006; Goehring et al,2006). Patients with a history of prior stroke appeared to be at a higher risk of subsequent stroke. It is important to note that, although the rate of stoke in the 0.3 mg treated patients was statistically lower, this dose of Lucentis is not thought to be protective of stroke.	Comment noted. See FAD sections 4.3.5 and 4.1.6.
Novartis		A subsequent and more recent interim analysis of the SAILOR data (performed on more patients from cohort 1) showed that the rates of stroke between patients on the 2 ranibizumab doses were 0.6% (3mg) and 1.2% (0.5mg), no longer a statistically significant difference. These data have been shared with the US Food and Drug Administration (FDA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA). Both the FDA and the MHRA have agreed that no changes to the	Comment noted

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		prescribing information are required as the incidence of stroke in the patients on ranibizumab 0.5mg was similar to that in the general population.	
Novartis		Section 4.3.10, page 21 This section of the ACD suggests that acceptance of the SHTAC base case scenario incorporating the cost of 24 injections is based on the fact that treatment may extend beyond 2 years. However, it should be noted that if costs are to be considered beyond 2 years then likely benefits beyond 2 years should also be taken into account and modelled appropriately as maintenance of the improved vision maintained in years 1 & 2.	The Committee considered both the costs and benefits although the benefits will be at a decreasing rate over time. See FAD section 4.3.13.
Novartis		Section 4.3.12, page 21 This section of the ACD suggests that utilities derived using the EQ-5D "might" result in a much smaller difference however, there is no evidence to support this view. The Assessment Group's economic model is based on a published study using VFQ 25 which is a validated assessment tool for patients with visual problems and which employed methods consistent with the NICE reference case. Similarly the Novartis model uses utility values derived from a study which used contact lenses in the general population to simulate different visual acuity states. The utilities were elicited using a preference based technique consistent with the NICE reference case.	The committee discussed the utility values used in the analysis. See FAD section 4.3.15
Novartis		In summary, the utility values adopted in the economic models are based on the best available evidence and are, therefore, the most appropriate for decision-making purposes. Furthermore, it should be noted that the utilities used in the models are based on visual acuity only. No account has been taken of other aspects of vision, such as contrast sensitivity, which are also likely to have an impact on health related quality of life. Consequently, QALY gain may be underestimated.	As above.
Novartis		Section 6.1, page 25 It should be noted that the research recommendations suggested in bullets 3 and 4 of this section are already being evaluated in ongoing Novartis sponsored studies. The SUSTAIN study is a 12-month open-label, multicentre, phase IIIb study assessing safety and efficacy of ranibizumab in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ranibizumab is administered in line with the UK licence, in that after the initial loading phase of 3 consecutive monthly intravitreal injections, further re-treatment is based on BCVA or OCT changes. Recruitment commenced in Q3 2006 and a total of 600 patients worldwide are targeted. UK recruitment targets were achieved in March 2007. This data will confirm the data seen in PrONTO, and also within clinical practice in the UK (as evidenced by the Retinal Survey)	Comment noted

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		The SUMMIT Mont-Blanc study is a 12-month randomised, double-masked, controlled, multicentre, phase II study assessing safety and efficacy of verteporfin PDT administered in conjunction with ranibizumab, versus ranibizumab monotherapy, in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. All therapies in this study will be given on an "as required basis", after the initial loading treatment (1 course of PDT and 3 injections of ranibizumab). Recruitment for this study has now started.	
Novartis		Section 6.1, page 25 This section states that further research should include an evaluation of the cost-effectiveness of bevacizumab. However, it should be noted that the bevacizumab evidence base lacks any formal clinical trial data in patients with wet AMD. This means that the safety and efficacy of bevacizumab for ocular treatment has not been demonstrated. In addition, the draft protocol outlining the planned head to head (IVAN) study comparing ranibizumab and bevacizumab, currently advocates a dosing strategy for ranibizumab which is not consistent with the recommended dosing regimen as detailed in the Summary of Product Characteristics (SmPC).	Comment noted
Novartis		In summary, the ACD is perverse in light of the evidence submitted and, accordingly, the preliminary recommendations do not constitute a reasonable or scientifically sound or suitable basis on which to base guidance to the NHS. For the reasons stated above the cost-effectiveness of ranibizumab has been systematically underestimated. Based on the available evidence ranibizumab represents a clinically and cost-effective treatment for patients with all lesion types of wet AMD. Furthermore, the restriction to predominantly classic lesions in the better seeing eye only cannot be justified on scientific, ethical or moral grounds.	As above.
DHSSPSNI			**Commentators**
DHSSPSNI		Comments on Pegaptanib & Ranibizumab for the Treatment of Age-related Macular Degeneration I don't have any substantive comments on the guidance issued on pegaptanib. I agree that the outcomes in the VISION trials show effectiveness in preventing moderate and severe vision loss but were not substantive enough for cost effectiveness. I have a number of comments on the guidance on ranibizumab.	Comments noted
DHSSPSNI		Restriction to predominantly classic CNV only. Such a restriction is illogical for several reasons. 1. There is increasing evidence that the classification of CNV by	The FAD has been amended - see sections 1.1 and 4.3.6.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		proportion of classic does not have any biological significance. This classification was primarily derived to facilitate treatment by laser based therapies where it was important to delineate the margins of the CNV. Also the classification became entrenched into the literature following on from the PDT studies where subgroup analyses showed differences in outcomes by proportion of classic CNV. However NICE themselves accepted that the subgroup analyses in the PDT trials were unlikely to represent true findings and this has been borne out by subsequent trials (VIO study). The morphological grouping of lesions based on proportion of classic CNV did not have any effect on outcomes both with pegaptanib or ranibizumab indicating that lesion subtype is irrelevant with VEGF blockade. Thus it is illogical to restrict treatment to predominantly classic only.	
DHSSPSNI		2. The decision to limit treatment to eyes with predominantly classic CNV only is driven by the ICER calculations. As the control arm in MARINA and the PDT treatment arm of ANCHOR (the comparator arms) both suffered equivalent losses of vision it would appear that the Southampton assessment group have made assumptions in their modelling that detract from the effectiveness of ranibizumab in the treatment of eyes without predominantly classic CNV. I do not understand the logic of this approach.	As above.
DHSSPSNI		Restriction to second eyes only. This is a cause of great concern for the following reasons 1. If treatment is denied to the first eye with a CNV (lets assume that it is predominantly classic as per current NICE guidance) and the second eye develops some other sight threatening disorder we will have lost the opportunity to treat. 2. If the second eye develops a CNV (40% of patients will have second eye involvement with wet AMD within 5 years) and if this is of the minimally classic or occult type (this is quite possible as there is only a small degree of symmetry between the eyes of a patient with respect to proportion of classic) again one will have lost the opportunity to treat.	The FAD has been amended – see sections 1.1 and 4.3.18.
DHSSPSNI		Applicability to Northern Ireland A rebuttal of NICE guidance is clearly needed. Scotland has approved the use of ranibizumab without restriction to type of CNV or whether the disease is bilateral. • If treatment is to be denied to first eyes, it is important to point out to NICE that all second eyes should be treated regardless of CNV subtype. • If treatment is to be restricted to predominantly classic only, then both first and second eyes should be allowed treatment.	As above.
DHSSPSNI		Numbers in NI. We expect some 780 persons per annum to develop CNV in NI. Of these 70% will be second eyes (approximately a third of people	Comment noted

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		who develop CNV in their first eye do not notice the onset of visual symptoms and present late thus minimising the benefit of any treatment). Based on the data collected over the last 3 years we expect to see between 120 and 140 patients with predominantly classic CNV per annum. Of these more than 2/3rds will have second eye involvement.	
NHS Quality Improvement Scotland			
Reviewer 1:		I welcome the recommendation that Ranibizumab should be used for the treatment of predominantly classic CNV but regret that it is not recommended for first eye involvement unless in the better seeing eye or even in the second eyes of patients with minimally classic and occult subfoveal CNV. Ranibizumab's effectiveness is undisputed and the only debate is over cost. If the drug costs were reduced there is no doubt that ranibizumab would be recommended for all lesion subtypes.	Comment noted
		1. I appreciate the need to limit treatment to those who will benefit most and I agree with the recommendations to limit treatment to those with a best corrected visual acuity between 6/12 and 6/96 and to lesions less than 12 disc areas in size. 2. In considering clinical effectiveness Ranibizumab is clearly the drug of choice and is the preferred agent in comparison with pegaptanib. 3. The drug regime used in calculating cost effectiveness for ranibizumab is not what most specialists expect to use. No patient will require 24 injections of Lucentis over 2 years. It is much more realistic to make recommendations based on the 'base case analysis as this is the expected regime i.e. 8 injections in year 1 and 6 in year 2 (experience using these drugs in private practice indicates there is some clinical consensus about this). 4. The non drug costs (i.e. the costs of administration and monitoring) are in my opinion overestimated. The procedure should be an Outpatient procedure. The investigative workup is also probably excessive. A fluorescein angiogram will be required at diagnosis (this is routine practice already even for untreatable lesions) and may not be required to be repeated for another 6-12 months. Most experts will utilise Optical Coherence Tomography images at visits after 3 months. Detailed repeat optometry work up is only relevant for research studies.	Comments noted. See FAD sections 1.1, 4.3.9 to 4.3.13 and 4.3.22 See FAD section 4.3.17.
		5. The advice issued by the Scottish Medicines Consortium (SMC) differs significantly from the draft guidance and the health economic assessment differs although it appears similar Markov cost utility models were used. The SMC however used the reduced dosing frequency in there	The Appraisal Committee has considered the evidence and views submitted to NICE in accordance with the Multiple Technology Appraisal process and the Guide to the

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		calculations and assumed that treatment would stop after 2 years. The SMC guidance states that for those with primarily classic AMD receiving photodynamic therapy a move to one year of treatment with ranibizumab was anticipated to result in an ICER of £4,489 per QALY. If these patients were receiving only best supportive care, the additional benefit rose to give an ICER estimate of £14,781 per QALY. For those with minimally classic or occult AMD a move to two years of treatment with ranibizumab saw a patient benefit of around 0.33 QALYs over the ten year modeling horizon, at an additional cost of between £8,494 and £9,125 to give an ICER of around £26,000 per QALY. 6. Also SMC indicates that modelling based upon the reduced dosing trial estimated an additional average benefit of 0.26 QALYs across all AMD types when compared with best supportive care at an additional cost of £3,120, to give and ICER estimate of £12,050 per QALY. There is therefore a considerable difference in the health economic assessment and most ophthalmologists would support the SMC guidance as more realistic.	Methods of Technology Appraisal.
		7. Bevacizumab is used widely throughout the world and case series and reports thus far indicate it is probably as effective as ranibizumab. The cost effectivity with bevacizumab is undoubtedly very high compared to ranibizumab. There is no doubt that the guidance as it stands will drive clinicians to seek to treat patients with bevacizumab. 8. Not recommending lucentis for the management of occult disease is regrettable. Clinicians who care for there patients will be under great pressure to either offer ranibizumab privately or try to persuade their trusts to use bevacizumab. 9. It will prove politically impossible to deliver treatment to the better seeing eye only. To deny treatment of a treatable and blinding condition in the first eye and only provide it for the second eye is morally indefensible. The natural history of wet AMD is variable with some patients presenting with severe visual loss with large haemorrhagic lesions. Such cases have a very poor prognosis. If someone had a treatable lesion in the first eye and then developed such a severe form of wet AMD in the second eye we would have denied such a patient the chance of saving good vision.	See FAD section 6.1. Comments noted. The FAD has been amended - see sections 1.1 and 4.3.6, 4.3.18
		10. The guidance to treat only the better eye will be unacceptable to all concerned in Eyecare. It is also illogical e.g. we could see the scenario of a patient presenting with classic or predominantly subfoveal classic CNV in the first eye being denied ranibizumab but qualifying for PDT and when the second eye is affected they will qualify for the more effective treatment of ranibizumab therapy! 11. Research – there is a great need to identify which subtypes of occult respond best. We recognise different types of occult CNV e.g. retinal	As above.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		angiomatous proliferation (RAP) lesions which account for about 30% of occult lesions, serous PEDs, etc, and this should be indicated in the recommendations. I expect different forms of occult respond better than others.	
Reviewer 2.		i) Whether you consider that all the relevant evidence has been taken into account. It would appear that the relevant RCT's have been considered. It is not clear how much direct evidence has been taken from interested patient groups to give direct feedback on patient benefits. There is one further trial recently published which should be considered " an optical coherence tomography guided variable dosing regime with intra-vitreal Ranibizumab (Lucentis) for neovascular age related macular degeneration". American Journal of Ophthalmology Volume 143, issue 4, pages 566-583, April 2007. This is known as the PRONTO Study.	The Committee considered the evidence from the PRONTO study. See FAD section 4.3.4.
Reviewer 2.		ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Given the better trial results with Ranibizumab compared to Pegaptanib it would appear reasonable to support use of the former. Estimating the cost effectiveness requires a lot of assumptions regarding treatment regimes and techniques of administration. It would appear the costings are based on the procedure being carried out as day case surgery, presumably in an operating theatre whereas many units are moving across to provision in an Out Patient area clean room with corresponding cost reductions. Similarly, whilst the trials were based on a fixed monthly dosing schedule for one or two years it is clear from clinical practice and the PRONTO Study that the number of doses can be safely reduced in patients who have responded to treatment and shown no leakage on angiography or OCT, significantly reducing the long term costs. I am not clear that the analysis of QALYs for minimally classic and occult disease are reasonable, given the major visual benefits patients with these conditions can achieve with treatment. In the light of the Pronto Study where the number of injections required over twelve months was reduced from 12 to an average of 5.6, the QALY and ICER figures should possibly be recalculated. The study also notes that once a fluid free macula has been achieved the mean injection free interval increased to 4.5 months which suggests that the long term cost implications will be dramatically reduced from those predicted.	The Committee considered the assumptions for the cost of administration of intravitreal injections (see FAD section 4.3.16), and evidence from the PRONTO study. See FAD section 4.3.4

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Reviewer 2.		iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Treating only second eyes seems unreasonable as it misses the opportunity to treat the first eye. I also do not think it is reasonable to exclude patients with minimally classic or occult disease from treatment as this group does get significant visual benefit. I have been using Lucentis in the private sector for almost a year and have two patients who would not meet the NICE guidelines for treatment who have both done extremely well. The first was a garage owner who developed a classic lesion in one eye, the other eye is normal. He was symptomatic and his visual acuity had reduced to 6/24. He had been treated with PDT with no improvement and subsequently had a single intra-vitreal injection of Lucentis six months ago following which his visual acuity recovered dramatically to 6/6 and he has been asymptomatic since. Another patient with end stage occult disease in one eye and deteriorating vision in his better eye had acuity reduced to 6/36. Following seven injections of Lucentis his visual acuity has improved to 6/9 with a dramatic improvement in his quality of life. I am sure both of these patients would be more than happy to give their personal feedback on their experience of treatment if you feel this would be helpful.	See FAD sections 1.1 and 4.3.18
Reviewer 2.		iv) Whether you consider that there are any potential policy implications for SEHD? The Scottish policy is much more open allowing all wet AMD to be treated with Lucentis or Macugen. I suspect that most practitioners will move across to Lucentis now it is available, given the better trial results. The Scottish policy does not preclude treatment of first eyes or occult or minimally classic disease so it does differ significantly from the NICE guidelines. However, in my opinion the Scottish guidelines should not be altered, given the 30% of patients with minimally classic or occult disease who will improve with treatment.	As above.
Reviewer 3		i) Whether you consider that all the relevant evidence has been taken into account. Evidence on QoL based on 1st/2nd-affected eye is lacking especially in relation to the treatment of patients. For example, in the Edinburgh PDT study we found the 2nd eye disease process was more aggressive than 1st eye disease in predominantly classic disease. The logic in treating the better eye only is flawed in many respects. The assumption that an individual will always have a better eye that will remain the better eye cannot be made as	See FAD sections 1.1 and 4.3.18

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		for many reasons (including co morbidity) the worse eye may become the better eye in later life, and a lost opportunity to maximise the visual function of this eye has profound QoL consequences and subsequent DALYs.	
		ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. The summaries regarding patients with progressive minimally classic and occult disease are not reasonable and ignore the benefit derived from treating this group for both the 1st and 2nd eyes of an individual suffering wet AMD. iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. The provisional recommendations are not sound and do not constitute a suitable basis for guidance as outlined above. iv) Whether you consider that there are any potential policy implications for SEHD? It would be prudent to maintain the SMC advice and I'd consider it likely that the ACD may be modified (a similar change occurred over PDT funding!)	See FAD sections 1.1 and 4.3.6
Reviewer 4		i) Whether you consider that all the relevant evidence has been taken into account. I do not know the literature in this field extensively but reference is made to those I am aware of. ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Yes- given the models from the assessment group, the summaries are reasonable interpretations of the evidence. iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. The provisional recommendations will cause implementation queries in NHS Scotland, given the current development work on services for ARMD which includes the use of pegaptanib by virtue of a positive SMC recommendation	Comments noted

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		in July 2006, followed by a letter from the DCMO.	
Reviewer 5		i) Whether you consider that all the relevant evidence has been taken into account. Yes ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. The summaries confirming the clinical effectiveness of Ranibizumab and Pegaptanib are reasonable. The cost-effectiveness assumptions are flawed and are therefore not reasonable interpretations of the evidence. iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. NO. The recommendations are based on many flawed assumptions and are clinically and morally unacceptable. iv) Whether you consider that there are any potential policy implications for SEHD? I do not think SEHD should alter their current policy, based on SMC recommendations, which is a much more pragmatic and sensible approach to the use of this developing technology.	Comments noted
Welsh Assembly Government		Thank you for giving the Welsh Assembly Government the opportunity to comment on NICE's Appraisal Consultation Document in connection with the above appraisal. We have a number of questions/points to raise with the Institute in response to the consultation, as follows:	Comments noted
Welsh Assembly Government		• Has NICE considered the treatment for patient specific wet AMD protocols in the light of best practice and the knowledge applied to the number of treatments per patient? How might a change in treatment patterns affect the cost assumptions? • Is the limit of visual acuity of 6/12 necessary in such cases? Wet AMD will affect vision to the extent that the recorded visual acuity can change and deteriorate rapidly. Is it not the case that wet AMD must be treated as soon as possible and all referral protocols from primary care are based upon this assumption and are treated as " urgent "?	The Committee considered the number of injections (see FAD sections 4.2.9 to 4.3.13); and the cost assumptions in the economic models (see FAD sections 4.3.8, 4.3.16 and 4.3.17). The Committee discussed the criteria for starting therapy with anti-VEGF treatments and thought that these should be in line with the population included in the underlying

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		• Is the recommendation by NICE that the diagnosis should be confirmed at a reading centre appropriate or in the best interests of the patient, bearing in mind the importance of rapid referral for treatment following diagnosis?	RCTs (see FAD section 4.3.25).
Welsh Assembly Government		• Is NICE aware of the accreditation and training undertaken within Wales, as part of the Wales Eyecare Initiative and subsequent referral refinement? This is especially applicable in the case of wet AMD and protocols for referral to HES have been agreed between ophthalmologists working in this specialised area and optometrists. A recent evaluation of the Wales Eye Care Examination/Primary Eye Acute Referral Scheme (WECE/PEARS) scheme shows a sensitivity of 93% accuracy in these referrals for secondary care treatment from Optometry. Current data shows that 30% of patients present with wet AMD in the first eye. If the patient is not treated for wet AMD in the first eye and develops dry AMD in the second eye (which is 85% of macular degenerative change) then the risk to the patient is being denied treatment for the condition which currently can be undertaken – there being no known treatment for dry AMD that can be offered at present.	Comments noted, see FAD sections 4.3.18 to 4.3.21.
Welsh Assembly Government		In addition to these points, we would also like to endorse those made by the Department of Health in its reply to the NICE consultation. Specifically, we agree that rapidly deteriorating vision has an impact on emotional well being, and individuals are likely to suffer depression and anxiety due to their loss of vision and reduction in independence. Loss of sight gives rise to ongoing costs for health and social care services, e.g. in terms of low vision services, rehabilitation and community care, and for the individual and carers. Is NICE satisfied that it has adequately assessed these ongoing costs in judging cost effectiveness and making its recommendations? Is NICE satisfied that the methodology adopted has adequately captured costs associated with depression, loss of independence etc? Furthermore, whilst recognition is made of sight-related falls, a full appraisal should be considered of the full impact of this subject beyond the specifics of those related to hip replacement surgery. The wider concerns of referrals to A&E, and subsequent diagnosis, together with the emotional impact to the patient and recognition of the threat to maintenance of an independent lifestyle.	See FAD sections 1.1, 4.3.8, 4.3.16, 4.3.17 and 4.3.18
Welsh Assembly Government		We are also aware that this is a subject that has understandably attracted a high degree of interest from patients, from the public and from stakeholders. We would again agree with the Department of Health in saying that any recommendation to restrict eligibility for treatment to the second eye, when patients are likely to have already suffered deterioration in the first eye,	Comments noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		would be controversial and the rationale for such a recommendation would have to be very clearly articulated and explained. Additionally, second eye treatment presupposes that other degenerative conditions will not develop – diabetic retinopathy and glaucoma being two examples. Therefore, a potential opportunity will have been lost to undertake treatment, which would have otherwise prevented or deferred sight loss.	
Welsh Assembly Government		Finally, the Welsh Assembly Government is concerned that the moral and ethical issues that arise from this draft guidance in its current form are not given sufficient weight in the economic appraisal undertaken. The psychological impact of depriving a potential patient of sight preserving therapy does not appear to be explicitly valued in the appraisal. We would therefore suggest that NICE should review the appraisal and take greater account of the psychological impact upon patients and their carers in producing the final version of the guidance.	Comments noted. The FAD has been amended - see sections 1.1 and 4.3.6
Nominated clinical specialist 1		Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) and evaluation report for the above appraisal. As requested I will direct my comments under the following general headings:	
Nominated clinical specialist 1		i) Whether you consider that all of the relevant evidence has been taken into account I do not think the committee has sufficiently considered the economic cost of blindness if treatment is restricted to only those patients with predominantly classic choroidal neovascularization e.g. in a paper just published the cost of blindness due to wet AMD is estimated at £7.4 million pounds p.a. for a health care authority of 500,000 people. Therefore the cost of blindness I believe is higher than has been calculated.	See FAD sections 4.2.4 and 4.3.16.
Nominated clinical specialist 1		ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate; The current proposal will deny the majority of patients with Wet AMD the only clinically effective treatment available to them. Treatment for minimally classic and occult no classic lesions would make the £30,000 QALY threshold if assumptions regarding costs of the procedure were based on outpatient costs rather than day case rates. The Royal College of Ophthalmology has produced a commissioning document on the costs of administering this treatment (attached). I would urge the committee to input these costs into their model to see if the £30,000 QALY is then met for all lesion types.	The Committee considered the costs of appropriate facilities and staffing for intravitreal injection. The results of the Assessment Group and Decision Support Unit extra analysis showed that costs based on the Royal College of Ophthalmology commissioning guidelines were higher than previously assumed day-case costs. The Committee was persuaded that in practice, for the foreseeable future, a mixture of day-case and outpatient procedures would occur. It concluded that a reasonable approach, as suggested by one of the consultees, would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an

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		Regardless of cost-effectiveness, Lucentis is extremely clinically effective for all forms of wet AMD and I believe the impact of allowing patients to go blind has been underestimated. Of note, other regulatory bodies in Scotland and Australia have not limited treatment by membrane sub-type and so NICE is at variance with other authorities which have also considered this technology. This I think reflects Nice choosing the worse case scenarios in the various economic models and hence with a more measured set of assumptions these technologies would make the QALY barrier.	outpatient appointment. The Committee also believed costs of blindness that were between the base case AG analysis and the combined high cost high uptake assumption explored in the Assessment Report. See FAD sections 4.3.16 and 4.3.17.
Nominated clinical specialist 1		If the current proposal stands then clinicians will have to repeatedly perform fluorescein angiograms to determine whether membranes have become predominantly classic (as they can do) and thus permitting treatment. There will be a considerable increase in management costs by having to repeatedly perform this invasive procedure (fluorescein angiography) on all patients with wet AMD to identify whether they are predominantly classic or not. This additional cost would be unnecessary if all membrane types could be treated and this additional cost should be weighed against the cost of offering an extremely clinically effective treatment to all patients with wet AMD. This extra cost does not appear to have been factored into the committee's calculations. Around 40 % of minimally classic lesions convert to predominantly classic lesions over time and so there will be a considerable increase in workload in having to follow patients to see if they become eligible for treatment. If we were allowed to treat all patients then most patients could be managed by non-invasive OCT assessments rather than having to have repeated fluorescein angiograms. It is also not clear whether (as per the cohort study for PDT) clinicians would be required to submit all fluorescein angiograms to a reading center for assessment. If this was the case this would also generate further costs which would be unnecessary if we were allowed to treat all membrane types.	The Committee considered the issues around lesion type. The FAD has been amended - see sections 1.1 and 4.3.6
Nominated clinical specialist 1		I also believe treating only one eye is an extremely flawed approach to treatment for several reasons: 1) Patients may only develop predominantly classic choroidal neovascularization in their first eye. Under current recommendations if a patient develops predominantly classic CNV in their first eye, treatment is not permitted and this eye is allowed to go blind. If this patient subsequently develops a minimally classic or occult choroidal neovascular membrane in their second eye then NICE guidance does not permit treatment for the second eye either and the patient is left severely visually impaired when if treatment in any eye was allowed he could have most likely been maintained with good vision in both eyes. Current	See above.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		NICE guidance of treating only the better eye will therefore result in many patients being denied clinically effective treatment in either eye and in my opinion is unworkable. It will also be extremely difficult for clinicians to deny a clinically effective treatment to patients.	
Nominated clinical specialist 1		2) Patients may not respond equally to treatment in both eyes. Again if a patient is allowed to go blind in their first eye and either is unresponsive to treatment in their second eye or suffers a complication such as endophthalmitis then you cannot roll back the clock and treat the first eye which by this stage is likely to have formed a disciform scar. Therefore there will be another cohort of patients who have been allowed to be blind in both eyes under the current proposals. If either eye treatment was allowed, these patients also could be saved from severe visual impairment. This is a very different situation to single eye cataract surgery where if there is a complication in one eye then surgery can proceed in the second eye. This is not possible for macular degeneration patients if the first eye has been allowed to become permanently scarred and irreparable.	The Committee considered the issue of treating the first eye to come to clinical attention. See FAD sections 1.1 and 4.3.18
Nominated clinical specialist 1		3) This decision is at variance with previous NICE guidance on the clinical effectiveness and cost effectiveness of photodynamic therapy for age related macular degeneration (http://www.nice.org.uk/TA068). As was discussed at the committee meeting, similar arguments regarding treating only one eye were initially suggested in the technology appraisal for photodynamic therapy for age related macular degeneration. NICE decided during that appraisal that it was valid to treat both eyes. Therefore the current proposals contradict previous NICE guidance. NICE made a very careful assessment of one versus two eye treatments at that time and I believe the same arguments over the benefits of treating both eyes stand. To allow only one eye treatment for one treatment for wet AMD and two eye treatment for another is irrational. Again it is unworkable to have one set of NICE guidance permitting photodynamic therapy in both eyes and a second set of NICE guidance limiting treatment for the same condition to only one eye	Comment noted. See above.
Nominated clinical specialist 1		4) There is clear evidence from studies in respected journals that being sighted in two eyes results in significant functional vision gains and I believe this benefit has been underestimated by the committee. I also believe that Macugen should be made available to the NHS as well. This is because of possible safety concerns with Lucentis as highlighted in the Sailor study and ongoing studies which suggest that initial dosage with Lucentis and maintenance dosage with Macugen is as effective in	The Committee concluded that pegaptanib was not a cost effective use of NHS resources. The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). It concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD section 4.3.24).

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		preserving vision as a Lucentis only treatment. At present I believe that most clinicians would choose to use Lucentis as it is more effective. However a combination algorithm may emerge in the future where Lucentis and Macugen are combined. The evidence for this is not fully available as yet but it would be useful to have the option of using Macugen in the future if preliminary data is confirmed.	
Nominated clinical specialist 1		iii) Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. I believe the current recommendations are fatally flawed and do a great disservice to the thousands of patients who will be allowed to become blind when their sight could be saved. I urge the committee to reconsider this recommendation.	Comment noted – the FAD has been amended.
Nominated clinical specialist 1		To summarise, I strongly feel that Lucentis should be offered to patients for either eye and all membrane sub-types of wet AMD. Macugen should also be permitted at the clinician's discretion. There will be additional costs related to blindness and additional fluorescein angiograms if this is not permitted and I do not think these additional costs have been considered. It would be tragic if patients in England and Wales are denied this clinically effective treatment while patients in Scotland can avail of it.	See above
Nominated patient expert 1		Thank you for inviting me to make comment. The technical and scientific nature of the paper seriously limits any contribution I could make, nevertheless I was able to read the paper with some appreciation due to the breadth of discussion engaged in at the meetings I have attended.	Noted
Nominated patient expert 1		After further study and discussion of your A.C.D. re: treatment of M D, the following concerns me: 1) Had my right eye and left eye been simultaneously diagnosed, would you have allowed me to go blind in one eye? 2) Symptomatology re: classic/occult form has differing progression rates, yet classic can occur in occult and vice versa - you state no treatment is offered to occult. I understand that treatment has been effective in occult form. 3) Findings state 73% of cases are "occult not classic" which represents a large number of casualties.	The guidance has changed since the ACD commented on here. See FAD section 1.

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		It would appear that the seriously debilitating social and psychological effect on sufferers and their family of losing sight and independance has been marginalised, also the economic cost of this dependency both to sufferer and state.	The Appraisal considered the effect of AMD on patients' quality of life. See FAD sections 4.3.15, 4.3.18 and 4.3.19.
Nominated patient expert 2		As a specialist nurse working in ophthalmology, I'm deeply troubled by some of the recommendations made by the appraisal committee. I'm absolutely convinced that the routine use of AntivegF drugs by retinal specialists to stabilise vision for all patients with wet AMD is fully justified by the evidence base that I have read and has been put to the committee. I'm amazed to find that important elements of the evidence submitted by all the consultee's have been disregarded. I challenge the appraisal committee's recommendations and ask that the committee to give serious consideration to the points I raise in this reply.	Comments noted
Nominated patient expert 2		Point 1 It is unethical and unacceptable to allow someone to go blind in one eye before being eligible for treatment in the second eye. Are the appraisal committee suggesting that only one functioning eye is required for normal life? This is patently untrue and there is enough literature available which describes this and the consequences of it. To limit these new treatments to 'second eyes' only would also be setting a disastrous precedent for other ophthalmic treatment areas such as cataract, diabetic retinopathy and glaucoma, all of which are bilateral in nature. An ophthalmic clinician's goal is to prevent preventable loss of sight. This is also the aim of all national and international organisations concerned with vision and the notion that avoidable blindness should be allowed and indeed, encouraged is not something I'd expect an appraisal committee comprising of lead health care workers to recommend!	The FAD has been amended – see sections 1.1 and 4.3.18.
Nominated patient expert 2		Point 2 The terminology 'no permanent structural damage' to the central fovea is misleading. How can you judge permanent damage unless you mean fibrosis that is long standing? The very fact that the patient has a subfoveal choriodal neovascular membrane (CNV) means there will be some damage in the foveal area. Therefore your recommendations are excluding the majority of patients with 'Wet AMD'! Even patients with some central fibrosis at the fovea need treatment to	This was an inclusion criteria for the body of evidence The Committee discussed criteria for starting therapy and thought that these should be in agreement with the eligibility criteria of the underlying clinical trials (see FAD section 4.3.25). It also considered responses, including this one, from the consultation period on the second Appraisal Consultation

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		control the disease process and prevent a large central scotoma that would grossly diminish their ability to self care and remain independent. A study by Wagner (2006) using combined PDT and ranibizumab demonstrated that in patients with occult CNV, absolute scotoma decreased or remained stable in 83%. Severe relative scotoma also decreased or remained stable in 83% and mild relative scotoma had increased in 50% of patients. Areas of normal macular function improved or stabilized in 83%. In AMD patients this will enhance their ability in relation to visual rehabilitation and possibly preserve their dignity and independence.	document (see also comments from the Royal College of Ophthalmologists above).
Nominated patient expert 2		Point 3 Not recommending the use of antiVegF treatment for minimal classic and occult CNV is to disregard a group of patients for whom currently there is no NHS treatment option and thus they will be forced to seek private health care or loose vision! To exclude these patients regardless of clinical need leaves them with no effective treatment and at high risk of increased dependence and injury. Therefore I can only reasonably infer that the Committee has not taken account of the available evidence of clinical need and national health priorities, focusing only on financial aspects of these therapies.	The FAD has been amended –see sections 1.1 and 4.3.6.
Nominated patient expert 2		Point 4 By limiting treatment to only the predominantly classic subgroup of patients is adding to the moral dilemma and burden of NHS workers. Already we have to inform our patients that their wet AMD is treatable and there is a good chance that we can prevent further sight loss but unfortunately because they don't have a predominantly classic lesion we cannot provide their treatment on the NHS!. This causes distress to both parties and has an added burden on clinic time as these patients need time and empathy not only to except their diagnosis but understanding why there is no treatment available to them! In addition the costs to the individual, the family and the community are massive. We know from the vast evidence produced by the Royal National Institute for the Blind and the Macular Disease Society and my own clinical practice that visual impairment leads to loss of employment, dependency on state benefits, restricted mobility, family break-up and social exclusion. Surely the benefits of preventing blindness vastly outweigh the costs of treatment.	The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.3.3.1. of the Guide to the Methods of Technology Appraisal (Available from URL http://www.nice.org.uk/page.aspx?o=201974).
Nominated patient expert 2		Point 5 The number of treatments used in the manufacturer's model is the number	Comments noted. See FAD sections 4.3.4, 4.3.9 and 4.3.10.

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		indicated in the licence indication for Ranibizumab based on the scientific findings of the PRONTO study. In this study, following an initial 3 injections over the first three months, retreatment with Ranibizumab was performed only if there was an increase in central OCT thickness of at least 100 µm, a loss of 5 letters in conjunction with recurrent fluid by OCT, new onset classic neovascularisation, or new macular hemorrhage. I feel based on this protocol, the number of treatments quoted in the model is a realistic guide on which to map costs to the NHS. As a clinician I'm very aware that few interventions continue to be used in routine practice in precisely the same way as that reported in RCTs. However, this is more because RCTs are by their very nature are insufficiently flexible to allow for individualisation of treatment than because the treatment regimens evaluated in RCTs need to be entirely reconsidered.	
Nominated patient expert 2		The optimal treatment is likely to be patient dependent and appropriate treatment regimens for the individual patient can only be properly determined in routine clinical use. It's true that we don't know what the optimal regimen is at this point in time, but the right thing to do is to implement as close to the trial protocol as possible and then set up studies to answer questions on dosage regimen and also the effects of substituting lucentis with other agents in a graded manner. This can be monitored under the clinical governance agenda of the providers. All routine practice is presently monitored through clinical audit and quality assurance outcome measures. The committee can be reassured that in the current climate all clinicians are painfully aware of their accountabilities to the NHS as well as their patients and therefore will make the best evidence based cost effective clinical decisions for all concerned.	See FAD section 6.1.
Nominated patient expert 2		Point 6 I note that you have estimated the cost these new treatments as a day case rather than an out patient procedure. The introduction of anti-VegF intravitreal treatments will mean a considerable increase in workload. In addition many units will need to provide additional services i.e. 'fast track' clinics, and because patients will potentially need monthly visits, staff numbers will need to increase to sustain demand. Therefore, despite the fact that the assessment and injection procedure takes no loner than that of photodynamic therapy (PDT), centres will need this additional funding as cost for day cases to develop services but the cost should be balanced against the fact that, over time as clinical experience and knowledge re- use of these treatments grows, the number of treatments will be less as seen	See FAD section 4.3.16

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		with PDT, and therefore cost to the NHS will decrease.	
Nominated patient expert 2		Point 7 You suggest that cost effectiveness is sensitive to uptake. I suggest that there will be a very high uptake in these new treatments in the NHS, therefore costs will be lower and outcomes for wet AMD patients better. Already our eye unit has seen an increase in referrals and enquiries as to whether or not we can offer treatment. Patients, relatives and carers are prepared to spend money travelling to clinics at frequent intervals and to remain under observation for years if we can save even a small amount of their sight. If this is the case surely we should not deny them the opportunity.	See FAD section 4.3.16.
Nominated patient expert 2		Point 8 I find it difficult to understand how a governing body whose remit is to examine evidence and recommend best practice, is recommending a head to head trial with a drug that is not licensed for use in the eye! I welcome the fact that you recommend an investigation into the long term effects and optimal regimen of antivegF treatments but I strongly recommend that this be done via a national audit not as with PDT a 'study' that diverted necessary funding way from the clinical area .	Comment noted. See FAD section 6.1 and Guide to the Methods of Technology Appraisal section 5.9.6.
Nominated patient expert 2		Summary I know the appraisal committee has a very difficult job reviewing numerous new therapies available to the NHS but I ask them to re-examine the evidence for antiVegF treatments for all wet AMD in the light of this response. I strongly believe, as do my colleagues that the evidence justifies the routine use of antiVegF treatments by retinal specialists to stabilise vision for all patients suffering the debilitating effects of wet AMD. We are already seeing dramatic results in our clinical practice. Our patients are not only getting stability but improvement in vision when VegFs are used. We owe it to these vulnerable elderly patients to allow them the dignity to remain as independent as possible by providing these treatments on the NHS.	
Age Concern		Thank you for your letter of 7 June 2007 inviting comments on the Appraisal Consultation Document for the Health Technology Appraisal of Ranibizumab and Pegaptanib for the treatment of age-related macular degeneration. Age Concern does not believe that all of the relevant evidence has been taken into account in developing the appraisal consultation. We believe that the provisional recommendations of the Appraisal Committee are not sound and that they do not constitute a suitable basis for the preparation of	Guidance has since changed. See FAD section 1.1

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		guidance to the NHS. Directions from the Secretary of State require NICE, in the exercising of its functions, to have regard to 'the broad clinical priorities of the Secretary of State....as set out, for instance, in National Priorities Guidance and in National Service Frameworks'. We could find no evidence that NICE has followed this requirement in the preparation of the Appraisal Consultation Document. The priorities and strategic direction for health and social care have been set out clearly in a White Paper, Our health, our care, our say (Department of Health, 2006). This places emphasis on putting people more in control of their own care, rapid and convenient access to high-quality, cost effective care, and enabling an supporting health, independence and well-being. The strategic approach emphasises a shift for the NHS from responding to crises to early intervention to promote good health and well-being. This has been given further focus in the Operating Framework for the NHS for 2007/08 and the draft commissioning framework for health and social care.	
Age Concern		It is clear from the Secretary of State's Directions to NICE that its work and recommendations are not meant to exist in a vacuum but to actively promote Government priorities. We could find no evidence that NICE has followed these Directions, as there does not appear to be an analysis of Government priorities and the role which the technology under review might play in achieving them. The recommendation to wait until there is a problem in the second eye before intervening appears to be in direct contradiction of the direction of Government policy. Furthermore we do not believe that NICE has taken sufficient account of the impact of wet AMD on the quality of life of sufferers. Age Concern has worked with the RNIB to identify that the quality of life of patients with wet AMD is affected as much as the quality of life in patients who have had a stroke, severe cardiovascular disease, coronary artery disease or cancer. In a Canadian study (Public Awareness and Attitudes about Age-Related Macular Degeneration, An Environics Poll commissioned by CNIB, unpublished, presented to the Symposium on the Cost of Blindness, Toronto, February 2004) those who had reached the threshold of being registered partially sighted (6/60) were willing to trade off 60% of their remaining life to regain vision.	See above See FAD sections 4.3.15, 4.3.18 and 4.3.19.
Age Concern		In comparison to a control group with normal visual function, people who have lost their sight through wet AMD have:	Comments noted. See above

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		• Only one third of the ability to perform everyday activities such as reading a newspaper, cooking and reading street signs. • Half of the ability to recognise faces and watch television • Twice the risk of developing clinical depression due to the loss of independence associated with wet AMD • Four times increased assistance needs overall with particularly high assistance needs in the areas of transportation and administrative tasks. • Double the risk of falls and therefore the risk of fractures and treatment for falls We hope therefore that the Appraisal Committee will return to the impact on the quality of life of people with wet AMD and that formal consideration will also be given to the links between this appraisal and established Government policy. I hope that these comments will be helpful	
Department of Health		Context To set the context for the Department's comments it should be noted that the Government has supported the objectives of the World Health Organisation's resolution on the elimination of avoidable blindness by 2020. The Department very much welcomes the development of any clinically and cost effective treatments that support this wider objective.	Noted
Department of Health		Comments This is of course a subject that has understandably attracted a high degree of interest from patients, from the public and from stakeholders. Any recommendation to restrict eligibility for treatment to the second eye, when patients are likely to have already suffered deterioration in the first eye, would of course be controversial and the rationale for such a recommendation would have to be very clearly articulated and explained. Rapidly deteriorating vision has an impact on emotional well-being, and individuals are likely to suffer depression and anxiety due to their loss of vision and reduction in independence. Loss of sight gives rise to ongoing costs for health and social care services, e.g. in terms of low vision services, rehabilitation and community care, and for the individual and carers. Is NICE satisfied that it has adequately assessed these ongoing costs in judging cost effectiveness and making its recommendations? Is NICE satisfied that the methodology adopted has adequately captured costs associated with depression, loss of independence etc?	Comments noted – the FAD has been amended – see sections 1.1 and 4.3.18.

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Department of Health		In making the draft recommendation that treatment be for the better seeing eye only, is NICE satisfied that it has considered and given appropriate weight to evidence on the likelihood of a patient developing AMD in their second eye and the probability of developing a treatable form? Has NICE assessed the risk of AMD in the second eye not being treatable, whilst AMD in the first eye could have been (but was not) treated? If guidance were to recommend that treatment should be of the better seeing eye only, is it correct to assume that visudyne would continue to be the recommended treatment for patients who develop wet classic AMD in one eye i.e. the weaker eye? If so, does NICE consider there is a need to explain the interaction between guidance on ranibizumab and the guidance previously issued on visudyne? Is NICE satisfied that there would be a clear case in terms of relative clinical and cost effectiveness to recommend visudyne as the only treatment for the first eye for classic wet AMD?	See above. The FAD has been amended – see sections 4.3.6 and 4.3.18.
Department of Health		For its draft recommendation that treatment be restricted to those patients with wholly or predominantly classic AMD, NICE has assumed 24 treatments in its cost assumptions (para 4.3.10). However, the suggested treatment guidelines are for less frequent treatment (para 3.2). Could NICE set out more clearly why it has assumed 24 treatments in the cost assumptions rather than follow the suggested treatment guidelines? If treatment patterns followed the suggested treatment guidelines, which are for less frequent treatment, this would reduce the assumed costs. Would this affect the assessment of cost effectiveness in relation to minimally classic or occult lesions? Would using the lower frequencies in cost assumptions affect the cost effectiveness judgement in relation to treatment of the first eye?	The FAD has been amended – see sections 1.1, 1.2, 4.3.4, 4.3.9, 4.3.10 and 4.3.22.
Department of Health		In setting out criteria for eligibility the draft recommendation is that patients should have best corrected visual acuity between 6/12 and 6/96. Is NICE satisfied that having an upper limit i.e. 6/12 is necessary? The guidance on photodynamic therapy allowed for treatment with best corrected visual acuity of 6/60 “or better”. This allowed for treatment as soon as the condition was detected whereas having an upper limit of 6/12 may mean that patients who have wet AMD detected are not treated as early as possible. Has NICE considered whether waiting until vision reaches 6/12 will have any adverse consequences? NICE may wish to note that the required standards for car-driving are taken as being around 6/10 vision. Therefore if a patient has 6/12 vision in their better seeing eye they would already be unlikely to be able to drive and be facing restrictions in their daily life. Has NICE considered the advantages of earlier treatment to support people in continuing active lives and maintain independence?	See FAD section 4.3.25.
Department		The draft guidance does not recommend pegaptanib for the treatment of wet	The Committee considered the cost-

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of Health		AMD. Para 4.3.15 notes that NICE discussed whether there was clear evidence of cost effectiveness of pegaptanib in any particular subgroup and concluded that this was not the case. Did NICE consider whether there was a case for allowing use of pegaptanib in particular cases if it would stabilise vision, for instance in the first eye, more effectively than visudyne and therefore improve overall outcomes? Para 4.3.5 refers to the possible risk of stroke associated with ranibizumab but notes that these are preliminary results of a study and that it was inappropriate to draw conclusions at this stage. Is NICE satisfied that the evidence is sufficient to recommend only ranibizumab rather than recommending that pegaptanib be used in cases where stroke might be a particular risk for a patient?	effectiveness of pegaptanib. It considered that there could be differential gains from pegaptanib for different subgroups of patients according to their starting visual acuity. It considered whether it could and should recommend pegaptanib for a specific subgroup. The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). After considering all the assumptions it thought to be most plausible in the economic models, it concluded that for all visual acuity subgroups, pegaptanib was not a cost-effective use of NHS resources (see FAD sections 4.3.8 to 4.3.24).
Department of Health		The guidance on photodynamic therapy recommended treatment for patients if they had classic wet AMD and best corrected visual acuity of 6/60 or better. In addition to these elements, with slight differences, the draft guidance on ranibizumab includes three further eligibility criteria. Could NICE explain why these additional criteria are necessary for ranibizumab when they were not considered relevant in the case of visudyne? In the guidance on visudyne NICE stressed the importance of rapid referral following diagnosis due to the nature of the condition which can progress very rapidly. Does NICE consider that this point should be reiterated in the guidance on ranibizumab? The guidance on visudyne steered towards having diagnosis confirmed at a centralised reading centre. Should the guidance refer to the need for confirmatory diagnosis again, or is NICE assuming this arrangement would continue, or is it satisfied that the quality of diagnosis is sufficient for this to be no longer necessary? Data from the visudyne cohort study, which has made use of reading centres, would show the quality of referrals to inform a view.	See FAD section 4.3.25. The Appraisal Objective is to appraise the clinical and cost effectiveness of ranibizumab and pegaptanib within their licensed indications for age-related macular degeneration. The Guidance has been developed with that objective.
Department of Health		If NICE considers that there is a case for confirmatory diagnosis, does it consider that treatment with ranibizumab should begin immediately after diagnosis at a hospital (with further treatment conditional upon confirmation of diagnosis by the reading centre) or should it wait until after confirmation by a reading centre? If the latter, the reading centres would clearly need to confirm diagnosis quickly to allow for rapid treatment. NICE may be wish to be aware that the Department funded a pilot project	Comments noted. The NICE Implementation directorate produces develops tools to help organisations implement Technology Appraisal Guidance. This information has been brought to the attention of the Implementation Directorate.

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		testing the use of specially trained optometrists to carry out differential diagnosis (between wet and dry AMD) followed by rapid referral of suspected cases of treatable wet AMD to the Hospital Eye Service. The evaluation concluded that the pilot did not present a clear case for wider roll out, from the perspective of referral accuracy and costs. This highlights the importance of rapid diagnosis within the hospital. As a new treatment, ranibizumab would entail additional work and the greater frequency of administration than visudyne would need to be planned for. These are issues that will need to be assessed further subject to NICE's final guidance.	
RNIB and Macular Disease Society		Introduction 1. In this document the RNIB and Macular Disease Society respond jointly to the appraisal consultation document (ACD) for Pegaptanib and Lucentis. 2. We find the recommendations in the ACD unacceptable and believe that there should be a thorough reworking of the evidence and assumptions.	Guidance has since changed. See section 1.1
RNIB and Macular Disease Society		3. Our detailed comments are set out in the document. In summary the key points are these: 3.1. The second eye policy for wet AMD patients is an indefensible rationing decision. Outcry about a similar policy that NICE tried to introduce for PDT led to its reversal. There are no sound medical reasons to deny treatment to patients who present with their first eye. 3.2. The decision to exclude pegaptanib was apparently not based on a review of baseline visual acuity. We believe that this should be included in the models used and we agree with the Royal College of Ophthamologists that clinicians should have the freedom to choose the best available treatment for each individual patient.	See above The Committee considered the cost-effectiveness of pegaptanib. It considered that there could be differential gains from pegaptanib for different subgroups of patients according to their starting visual acuity. It considered whether it could and should recommend pegaptanib for a specific subgroup. The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). After considering all the assumptions it thought to be most plausible in the economic models, it concluded that for all visual acuity subgroups, pegaptanib was not a

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			cost-effective use of NHS resources (see FAD sections 4.3.8 to 4.3.24).
RNIB and Macular Disease Society		3.3. We believe that treatment should be made available for all lesion types. The decision to restrict treatment to 20% of eligible patients by allowing it for only predominantly classic patients has been based on some incorrect cost assumptions leading to unreasonable rationing. Notably the assumption that treatment will be on a day case basis is wrong and does not reflect current practice. While out-patient tariffs are insufficient to cover the full costs of treatment, an appropriate tariff would lie somewhere between the day case scenario and the cost of an out-patient procedure. Using the day case scenario therefore leads to unjustifiably inflated costs. 3.4. The ACD does not take adequate account of the costs of blindness and underestimates the take-up of services for blind and partially sighted people. In this document we have expanded our information on these costs which weigh strongly against letting people go blind unnecessarily.	See FAD section 4.3.6 See FAD section 4.3.16.
RNIB and Macular Disease Society		Expansion of our comments Second eye policy 4. Paragraph 4.3.16 of the ACD is short and leads to the devastating conclusion for patients that AMD, wet or dry, in their first eye should be ignored. They will only be treated when their second eye is affected. It includes this sentence as substantial justification for the policy : 'It understood that the reduction in quality of life of moving from binocular vision to monocular vision was much smaller than the reduction in quality of life from moving from monocular vision to very poor vision'. While we accept that the impact of monocular vision on a person's quality of life is not as severe as the impact of binocular sight loss there are strong arguments against NICE's recommendation to restrict treatment to second eyes.	See above
RNIB and Macular Disease Society		5. The cursory treatment in the report of this hugely important aspect of who and who not to treat fails to address the factors involved. Unusually for NICE the paragraph is superficial and unscientific. The conclusion implies that treatment of the second eye will invariably be successful and therefore it does not matter that the first eye has been ignored. This is an unjustifiable and dangerous assumption. Patients are subjected to a gamble with their sight. If they lose they become blind in both eyes with all the ensuing social, psychological and medical dependencies which arise for them and their families. 6. First of all, both ranibizumab and pegaptanib are clinically effective	See above

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		in first and second eyes. At present, approximately one third of patients present with first eye. Denying treatment to patients who have developed wet AMD in their first eye is not reasonable. Patients with cataracts or glaucoma are treated in their first eye.	
RNIB and Macular Disease Society		7. While there are only few studies of the impact of monocular vision loss on a person's quality of life one study suggests that it may lead to even higher psychological distress than binocular vision loss. This in turn will have an adverse effect on the person's functional ability and quality of life. 8. The assumption that a "presenting eye" policy is mainly based on ethical grounds is therefore erroneous. It is very much based on the need to safeguard a patient's quality of life.	See FAD sections 4.3.18 and 4.3.19.
RNIB and Macular Disease Society		9. Furthermore, we would like the Committee to consider a very frequent scenario that illustrates the increased risk of blindness in patients with wet AMD: Patient A has dry AMD in the better seeing eye and has developed wet AMD in the other eye. She is told that no treatment will be provided because the first eye still has good visual acuity. If the patient is then left to lose her sight in the eye that has developed wet AMD and does not develop wet AMD in the other eye she will inevitably go blind since dry AMD is not treatable. The same can happen if she develops wet AMD in the second eye but does not respond to treatment, or if she develops another condition (glaucoma or diabetic retinopathy) or has an accident. 10. It is therefore clear that a decision to restrict treatment for wet AMD to patients who have developed the condition in their second eye cannot be justified on medical or functional grounds.	See above
RNIB and Macular Disease Society		Use of pegaptanib 11. The ACD recognises that there have not been any head-to-head trials of pegaptanib and ranibizumab and that due to the differences in the trial populations, precise direct comparisons are not possible. We would therefore like the Committee to review its decision to recommend against the approval of pegaptanib for use in the treatment of wet AMD. This is particularly relevant for the group of people with good baseline visual acuity (6/12 to 6/24) where results for pegaptanib have shown a significantly increased chance of vision gain compared with patients with a lower visual acuity at baseline. Baseline visual acuity therefore needs to be included in the cost model for pegaptanib. We recognise that this may lead the Appraisal Committee to recommend the use of pegaptanib in patients with good baseline visual acuity only. However, given the different profiles of the two drugs we continue to support the position of the Royal College of	See above

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		Ophthalmologists that calls for both treatments to be made available without restrictions so that clinicians can decide what treatment is best for individual patients.	
RNIB and Macular Disease Society		Rationing of treatment to exclude all lesions except the 20 per cent of patients with predominantly classic CNV 12. Clinical effectiveness. 12.1. All the evidence presented to NICE suggests that ranibizumab is equally effective for all lesion types. The only reason why subtypes were included in the analysis is to determine whether both pegaptanib and ranibizumab are cost-effective in comparison with PDT, which is only effective in patients with predominantly classic CNV. All cost-effectiveness models and scenarios bar one have shown that ranibizumab is cost-effective in all sub-types. Please find below our arguments why the cost-effectiveness data chosen does not reflect current practice either in relation to the costs of treatment or in relation to the costs of blindness.	See above
RNIB and Macular Disease Society		13. Cost effectiveness 13.1. To establish the true costs of blindness that should be included we would like to present additional evidence that shows that current costs of blindness are higher than assumed by the Assessment Group even if we use the parameters set by NICE and do not include additional costs such as loss of productivity, disability benefits and informal care.	See above
RNIB and Macular Disease Society		14. Registration and continuing ophthalmic care 14.1. Due to the nature of the condition with patients progressing over time from registration as partially sighted to registration as blind, registration is not a one-off event. Once patients have been registered partially sighted they have to continue to be seen by their consultants on a regular basis to monitor their deterioration. Because blind registration is linked to additional benefits (Blind person's personal income tax allowance, reduction of 50 per cent on the television licence fee, car parking concessions, free postage for "articles for the blind" and other entitlements) it is important for patients to establish the level of their sight loss. At present 45 per cent of blind and partially sighted people report that they were registered partially sighted first before being registered as blind.	See sections 4.2.4, 4.3.16 and 4.3.17 of the FAD.
RNIB and Macular Disease Society		14.2. In addition, it is important to recognise that people who are registered blind or partially sighted continue to require ophthalmic care. It is wrong to assume that they are no longer seen by medical professionals (optometrists and ophthalmologists) once the medical treatment for their	See above

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		condition has ceased. They continue to require check-ups and under the GOS eye tests for blind and partially sighted people are free. This explains why 57 per cent of a sample of blind and partially sighted people have seen an optician in the past year and 80 per cent had seen an optician in the past three years.	
RNIB and Macular Disease Society		14.3. This if further confirmed by figures that suggest that 50 per cent of registered blind and partially sighted people are currently attending an eye clinic (as measured by an appointment in the last six months, or an arranged appointment in the future). Of these, the majority visit the eye clinic for a "check up" (92 per cent) and/or "to see the ophthalmologist" (77 per cent).	See above
RNIB and Macular Disease Society		15. Take-up of services 15.1. We welcome the fact that the model recognises that the vast majority of people with wet AMD (95 per cent) will get registered as blind or partially sighted. However, in light of this high rate of registration the suggested take-up figures for people receiving low vision aids and low vision rehabilitation need to be revised.	See above
RNIB and Macular Disease Society		15.2. The reason for this is that the take-up figures are taken from a study that looks at all people with sight loss, including those with visual acuity better than the current registration threshold of 6/60. Whilst many of these people will benefit from low vision aids and rehabilitation, Social Services do not pay for their services. By contrast every patient certified by an ophthalmologist as blind or partially sighted will be registered with Social Services and 80 per cent will receive an assessment visit by a rehabilitation officer. Following this, a low vision assessment and appropriate rehabilitation training for daily living skills (including mobility training) is arranged, and carried out, with the provision of non-optical aids such as daylight bulbs, liquid level indicators, UV shields, signature guides, guide/symbol cane, etc. and training in their use.	See above
RNIB and Macular Disease Society		15.3. The take-up of low vision aids and rehabilitation is therefore likely to be much higher than 33 per cent and 11 per cent respectively, and much more closely correlated with uptake of registration. Please see further information below to substantiate this assertion.	See above
RNIB and Macular Disease Society		16. Low vision aids 16.1. A survey of 500 service users carried out in England and Wales in 2005 showed that a large majority of respondents used canes (66 per cent), hand-held magnifiers (77 per cent) and 63 per cent used other optical aids. In 70 per cent of cases canes were funded by the local authority whereas hand-held magnifiers were funded in 69 per cent and optical aids in 73 per cent of cases. This is confirmed further by another survey , which states that	See above

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		74 per cent of blind and partially sighted people have been offered a magnifier following their assessment. 16.2. In addition, the more recent network 1000 study reported that 71 per cent of the registered blind and partially sighted population have used magnifiers for reading and the likelihood of using a low vision aid (LVA) increased with age (73 per cent in those aged over 75).	
RNIB and Macular Disease Society		16.3. Equipment funded by local authorities varies considerably. Home adaptations do not seem to have been included in the cost analysis. The equipment most commonly funded here are bump-ons/tactimarks (used by 46 per cent of respondents and funded by 63 per cent of local authorities) and liquid level indicators (used by 57 per cent of respondents and funded by 70 per cent of local authorities). Also, 73 per cent of blind and partially sighted people used better lighting. This is usually included in a needs assessment because of its importance in falls prevention. 16.4. Not only is the take-up of services higher than estimated, it is also important to recognize that low vision aids are not one-off costs. Given the deterioration of the condition over time, people with AMD require repeat assessments to establish whether they need a different magnifier or other low vision aid. Social Services have a statutory obligation to reassess service users on an annual basis. Where no deterioration has taken place this may be limited to a phone call but under best practice service users are called every six months and receive a full re-assessment once a year.	See above
RNIB and Macular Disease Society		17. Low vision rehabilitation 17.1. As pointed out above, an assessment by a rehabilitation officer will always include an assessment for a patient's mobility needs. This is confirmed by a survey of services providers carried out by the AMD Alliance UK in 2005 which indicates that 94 per cent of Social Services, 65 per cent of specialist teachers and 47 per cent of Local Societies for Blind People provide mobility training. Also, 54 per cent of people surveyed in the "Unseen" report and 66 per cent of those surveyed in the "Equipped for Living" report had been offered a white cane. Latest figures suggest that as many as 79 per cent of those aged between 60 and 80 use white canes. The survey of low vision services providers shows that 86 per cent of services providers always or usually provided training in the use of daily living aids. Most of them also provide more than one training appointment.	See above
RNIB and Macular Disease Society		17.2. We recognise that it is difficult to present a complete picture. The Guide Dog report shows that 39 per cent of those offered services following an assessment were offered mobility training, 23 per cent were offered orientation training, 27 per cent daily living skills training, 60 per cent training	Comments noted.

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		in the use of their low vision aids, 30 per cent received communication training, 22 per cent counselling and 22 per cent a guide dog assessment. 17.3. However, even though it is difficult to match the figures from different surveys it is clear that the assumption of a 33 per cent take-up of low vision aids and an 11 per cent take-up for low vision rehabilitation in no way reflects current practice.	
RNIB and Macular Disease Society		18. Community care 18.1. The Appraisal Group model assumes that only 6 per cent of people with AMD receive community care from a home care worker. The Network 1000 survey indicates that significant numbers of people (52 per cent) employ paid help and that the likelihood of this increases with age. Whilst we realise that many older people pay for home care out of their own income, this is less likely in the case of people with sight loss since 82% of them live in or on the margins of poverty ["Unseen" Report].	See FAD section 4.3.16.
RNIB and Macular Disease Society		19. Additional costs of blindness through higher use of health resources 19.1. Falls. We welcome the fact that sight-related falls are included in the analysis. However, we are not sure why the only element included is hip replacements. People with wet AMD double their risk of fall-related admissions to hospital and the need for medical treatment. This goes well beyond hip replacements. The Audit Commission estimated in 2000 that there had been 190,000 A&E attendances in 1999, which resulted from falls by people with a visual impairment. Nearly half of these happened as a direct result of the visual impairment. The cost of these falls was £130 million. There are two aspects that suggest that fall-related cost in people with wet AMD may be even higher: • People with wet AMD double their risk of developing clinical depression, thereby further increasing their risk of experiencing falls. • The 2000 Audit Commission report states that it is likely that the number of deaths following hip fractures is underestimated.	See above
RNIB and Macular Disease Society		19.2. Overall use of health resources. The annual average cost per patient across Europe is significantly higher for people with wet AMD than for control patients in general medical care. For the UK it is estimated that the average annual per patient cost is £3,823.89 for people with AMD against £517.05 for the control group . These figures include direct vision related and non-vision related medical costs as well as direct non-medical related costs such as government-sponsored assisted living facilities or nursing homes, assistance for daily activities, and social benefits received.	Noted

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RNIB and Macular Disease Society		19.3. We recognise that NICE can only include in its calculations costs incurred by the NHS and Social Services. Nonetheless we would like to reiterate once more the importance of seeing the wider picture and recognising that the costs of blindness to society go well beyond NHS and Social Services costs. In the majority of cases people who have lost their sight due to AMD are supported by informal carers who may have to give up their own jobs to take on the role of carer. What is more, many people with AMD are also carers. If they are allowed to lose their sight this will have a considerable knock-on effect in terms of costs to society when they become unable to continue in their carer role and the State has to pay for professional care or admissions to nursing homes. This is a common scenario that reinforces the argument that it is cheaper to treat patients with wet AMD than to let them lose their sight.	Comments noted.
RNIB and Macular Disease Society		20. Conclusions regarding the cost of blindness. The evidence presented above shows that the cost model used by the Assessment Group does not reflect the true costs of blindness. And this is based on an assessment of current standard practice, not best practice or indeed need. The models used show a poor grasp of the reality of blindness through wet AMD and the health and social care costs associated with it. The ACD recognises that assumptions about the take-up of low vision services have a major impact on the cost-effective analysis. We believe that the model needs to be adjusted to include the costs presented above. As a minimum the Assessment Group should use the scenario that assumes a high take-up of the services.	See above
RNIB and Macular Disease Society		Final Assessment of the ACD 21. Finally, we recognise that NICE has to take difficult decisions about resource allocation in the NHS. Treatments that are provided on the NHS have to be cost-effective. NICE plays an important role in assessing cost-effectiveness against established criteria. Unfortunately, in this instance, the evidence presented to NICE has been interpreted in a way that overestimates the costs of treatment and under-estimates the enormous clinical benefits of the new treatments as well as the cost of non-treatment. 22. We believe that a revision of the ACD is in the best interest of patients and the health economy.	Comments noted. The FAD has been amended.
Heywood, Middleton and Rochdale PCT		1) Do you consider that all of the relevant evidence has been taken into account? This appears to be a thorough review of the currently available evidence in addition to which the committee has noted the lack of evidence relating to	Noted

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		the lasting effects and best possible maintenance regimens beyond 2 years of treatment (using Ranibizumab). Both evidence of effectiveness and the cost effectiveness evidence appear to have been reviewed in full and the limitations have been noted.	
Heywood, Middleton and Rochdale PCT		2) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate? The cost effectiveness of the treatment regimens under consideration have been fully explored despite the differing methodologies used. However the total cost to the NHS of these treatments, alongside the impact of the underlying condition on NHS budgets overall, has not been fully explored. The costs and opportunity costs need to be more fully assessed prior to implementation of the guidance. In particular the costs of care other than drug costs will not be negligible in the treated groups, which alongside the ageing population (and therefore an increased incidence of the condition) will see increasing support costs as well as the actual treatment costs which need to be more accurately accounted for. However the recommendations do include the need for trials of the alternative therapy Bevacizumab which is a cheaper drug, the initial use of which has shown indications of its being as effective as Ranibizumab. The NHS will need to provide the driver for these trials as commercial interests may not do so. The recommendations for additional trials, both of Bevacizumab as an alternative and of the effectiveness of both Bevacizumab and Ranibizumab beyond 2 years, needs to be strengthened.	See FAD sections, 4.3.16, 4.3.17 and 4.2. Comment noted. See FAD section 6.1 and Guide to the Methods of Technology Appraisal section 5.9.6.
Heywood, Middleton and Rochdale PCT		3) Do you consider that the provisional recommendations of the appraisal committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? • The inclusion criteria relating to the identification of individuals to whom the treatment would be offered is comprehensive, is in line with the evidence reviewed and also matches the views that our local clinicians have given to our commissioning group. • The recommendation to no longer offer Pegaptanib is supported by the evidence provided but will have significant cost implications if patients currently on this drug wish to change to Ranibizumab. The recommendation	Noted

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		that current treatment can continue at the discretion of the clinician and patient is welcomed • The treatment regimens suggested appear to be in line with the evidence and the views of the expert clinicians • The recommendation to make funding available to fully implement this within 3 months may be problematic dependant on the timing of the release of the guidance in relation to the planning /commissioning cycle for Trusts • The proposed recommendations for further research are welcomed but would be strengthened by the recommendation that treatment with Ranibizumab should be funded as part of a trial to establish one or all of the following: i. Long-term effects of anti-VEGFs ii. The appropriate duration and optimal treatment regimen iii. Evaluation of cost effectiveness (including supporting service costs) • The proposed review date of April 2010 may not allow time for outcome of the trials into the long term effects to be available or from trials of Bevacizumab not yet established. Perhaps the optimal treatment regimens should be reviewed then, with the full review taking place in a timescale that allows the other trials to be completed or to have provided their initial interim results.	Comment noted. See FAD section 6.1. The guidance on this technology will be considered for review in April 2011 – see FAD section 8.2.
SHTAC		1. On page 15, point 4.2.3.6 they state that the ICER for 10-year model, assuming disease modifying effect for pegaptanib in year 3 only is £42,200. This is not the value reported in Table 4.24 of the Assessment Report (which is £26,896 - this is for the base case scenario, but with pegaptanib disease modifying effect in year 3). The value reported in the ACD is for disease modifying effect in year 3 AND with intra-vitreal injection costed as a day case procedure (rather than an out-patient procedure, which is the assumption in the base case scenario). 2. On page 16, point 4.2.3.11 they refer to a range of ICERs for the 10-year ranibiuzumab model as £11,000 to £15,000 and the range for 5-year model as £16,000 to £43,000. I think the range for the 10-year model should be £11,000 to £25,000 (to include the base case value for MC/OC). 3. On page 17, point 4.2.3.14 it is not very clear that they are talking about the sensitivity of cost-effectiveness estimates to variation in components of the cost of blindness. Might be clearer to start this point by stating "With	The FAD has been amended – see sections 4.2.1, 4.2.2, 4.2.3 and 4.2.4.

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		respect to the costs of blindness ..." or otherwise make clear within this section that the uptake and unit costs being referred to are uptake of services for people with vision loss below 6/60.	
RCN		With a membership of over 395,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. RCN members work in a variety of hospital and community settings in the NHS and the independent sector. The RCN promotes patient and nursing interests on a wide range of issues by working closely with the Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations.	Noted
RCN		Specialist nurses working in ophthalmology are astounded and deeply concerned by some of the recommendations made by the Appraisal Committee on the appraisal of the use of ranibizumab and pegaptanib for the treatment of age-related macular degeneration. When representatives of the RCN attended the consultees' information meeting for this appraisal, assurance was given by the panel that the appraisal group "had learnt lessons from the past in terms of the PDT findings" and that limiting to 'second eye' would not feature as part of this process, this clearly has not been carried through. We are absolutely convinced that the routine use of AntivegF drugs by retinal specialists to stabilise vision for all patients with wet AMD is fully justified by the evidence base that we have read and which has been put to the Committee. We are amazed to find that important elements of the evidence submitted by all the consultees have been disregarded.	Comments noted – the FAD has been amended – see sections 1.1, 4.3.6 and 4.3.18.
RCN		We, therefore, do not support the Appraisal Committee's recommendations that only the most aggressive, fastest progressing type of wet AMD ('predominantly classic') is treated with anti-VEGFs. 'Predominantly classic' type of AMD represents only about 20% of all wet AMD cases - but around half of patients with less aggressive disease (minimally classic or occult) will go on to develop predominantly classic wet AMD within a year, with further vision loss.	See above
RCN		Further, AMD is not the only disease process that patients of this age group may experience and imagine the scenario if the 2nd eye - the good eye were to develop say a vein occlusion and the patient had not had the first eye treated as they did not fit the criteria, clearly this has not been given serious thought. This recommendation is therefore a false economy and risks patients' sight.	See above

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RCN		We welcome the recommendation that Lucentis is used for AMD but would challenge the stipulation that it be the only option and that Macugen is not recommended for treatment of wet AMD at all. There are differences in action between these two drugs, which may be important in individual cases. Clinicians do not wish to be limited in our treatment options in this way.	The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). It concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD section 4.3.24).
RCN		With respect to treatment with anti-VEGFs, we are concerned that as in the Photo-Dynamic Therapy appraisal, treatment with anti-VEGFs is only recommended when the patient already has AMD in one eye, and is effectively blind in that eye, and has developed AMD in the second eye. This is completely unacceptable and we are convinced that the Committee would not make such a recommendation were it to be any other part of the anatomy (for instance denying treatment for peripheral vascualr disease until the patient has lost one leg) - what it means is that people will have to lose significant vision in one eye and then develop symptoms in the other before we attempt treatment which may or may not help - this is absolutely outrageous. We, therefore, challenge the Appraisal Committee's recommendations and ask that the Committee give serious consideration to the points raised in this response.	See above
RCN		Point 1 We reiterate that it is unethical and unacceptable to allow someone to go blind in one eye before being eligible for treatment in the second eye. Is the Appraisal Committee suggesting that only one functioning eye is required for normal life? This is patently untrue and there is enough literature available which describes this and the consequences of it. To limit these new treatments to 'second eyes' only, when only one eye is affected would also be setting a disastrous precedent for other ophthalmic treatment areas such as cataract, diabetic retinopathy and glaucoma, vitreo retinal surgery all of which are bilateral in nature! An ophthalmic clinician's goal is to prevent loss of sight. This is also the aim of all national and international organisations concerned with vision and the notion that avoidable blindness should be allowed and indeed, encouraged is not something one would expect an Appraisal Committee comprising of leading healthcare professionals to recommend!	See above
RCN		Point 2 The terminology 'no permanent structural damage' to the central fovea is misleading. How can the one judge permanent damage unless one means fibrosis that is long standing? The very fact that the patient has a subfoveal choriodal neovascular membrane (CNV) means there will be some damage	The Committee discussed criteria for starting therapy and thought that these should be in agreement with the eligibility criteria of the underlying clinical trials (see FAD section 4.3.25). It also considered responses, including this one, from the consultation period

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		in the foveal area. Therefore the Committee's recommendations are excluding the majority of patients with 'Wet AMD'! Even patients with some central fibrosis at the fovea need treatment to control the disease process and prevent a large central scotoma that would grossly diminish their ability to self care and remain independent. A study by Wagner (2006) using combined PDT and ranibizumab, demonstrated that in patients with occult CNV, absolute scotoma decreased or remained stable in 83%. Severe relative scotoma also decreased or remained stable in 83% and mild relative scotoma had increased in 50% of patients. Areas of normal macular function improved or stabilized in 83%. In AMD patients this will enhance their ability in relation to visual rehabilitation and possibly preserve their dignity and independence.	on the second Appraisal Consultation document (see also comments from the Royal College of Ophthalmologists on the second ACD issued December 2007).
RCN		Point 3 Not recommending the use of antiVegF treatment for minimal classic and occult CNV is to disregard a group of patients for whom currently there is no NHS treatment option and thus they will be forced to seek private health care or loose vision! To exclude these patients regardless of clinical need leaves them with no effective treatment and at high risk of increased dependence and injury. Therefore we can only reasonably infer that the Committee has not taken account of the available evidence of clinical need and national health priorities, focusing only on financial aspects of these therapies.	Comment noted. The FAD has been amended to recommend ranibizumab in all lesion types – see section 1.1 and response to comment above.
RCN		Point 4 Limiting treatment to only the predominantly classic subgroup of patients is unacceptable, particularly when there are good results with occult and mixed - so only patients with classic disease have a possibility of remission, adding to the moral dilemma and burden of NHS workers. Already we have to inform our patients that their wet AMD is treatable and there is a good chance that we can prevent further sight loss but unfortunately because they do not have a predominantly classic lesion we cannot provide their treatment on the NHS! This causes distress to both parties and has an added burden on clinic time as these patients need time and empathy not only to accept their diagnosis but understanding why there is no treatment available to them! In addition the costs to the individual, the family and the community are massive. We know from the vast evidence produced by the Royal National Institute for the Blind and the Macular Disease Society and from clinical practice that visual impairment leads to loss of employment, dependency on state benefits, restricted mobility, family break-up and social exclusion. Surely the benefits of preventing blindness vastly outweigh the costs of treatment.	See above
RCN		Point 5	See FAD sections 4.3.4, 4.3.9, 4.3.10, and

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		The number of treatments used in the manufacturer's model is the number indicated in the licence indication for Ranibizumab based on the scientific findings of the PRONTO study. In this study, following initial 3 injections over the first three months, re-treatment with Ranibizumab was performed only if there was an increase in central OCT thickness of at least 100 µm, a loss of 5 letters in conjunction with recurrent fluid by OCT, new onset classic neovascularisation, or new macular haemorrhage. We feel that based on this protocol, the number of treatments quoted in the model is a realistic guide on which to map costs to the NHS. As clinicians we are very aware that few interventions continue to be used in routine practice in precisely the same way as that reported in RCTs. However, this is more because RCTs are by their very nature insufficiently flexible to allow for individualisation of treatment than because the treatment regimens evaluated in RCTs need to be entirely reconsidered. The optimal treatment is likely to be patient dependent and appropriate treatment regimens for the individual patient can only be properly determined in routine clinical use. It is true that we do not know what the optimal regimen is at this point in time, but the right thing to do is to implement as close to the trial protocol as possible and then set up studies to answer questions on dosage regimen and also the effects of substituting Lucentis with other agents in a graded manner. This can be monitored under the clinical governance agenda of the providers. All routine practice is presently monitored through clinical audit and quality assurance outcome measures. The Committee can be reassured that in the current climate all clinicians are painfully aware of their accountabilities to the NHS as well as their patients and therefore will make the best evidence-based cost effective clinical decisions for all concerned.	4.3.22.
RCN		Point 6 We note that the Committee has estimated the cost of these new treatments as a day case rather than an out patient procedure. Cost should not be the driving factor but quality of life and the long term anxiety expressed by patients who have AMD in a first eye. Well documented findings have shown that patients have spent many hours worrying about how they will cope if their second eye develops the disease causing them anxiety and depression. The introduction of anti-VegF intravitreal treatments will mean a considerable increase in workload. In addition many units will need to provide additional services i.e. 'fast track' clinics, and because patients will potentially need monthly visits, staff numbers will need to increase to sustain demand. Therefore, despite the fact that the assessment and injection	See FAD section 4.3.16.

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		procedure takes no longer than that of photodynamic therapy (PDT), centres will need this additional funding as cost for day cases to develop services. The cost should be balanced against the fact that, over time as clinical experience and knowledge re- use of these treatments grows, the number of treatments will be less as seen with PDT, and therefore cost to the NHS will decrease. There appears to be no evidence in the document that the appraisal has looked at costs in terms of the family unit. Many of the patients that present at clinics are aged between 60 - 75 and these patients can be carers of grand children, spouse and also carers of elderly relatives thus by denying treatment to this one person could have a huge impact on all areas of family network! Further, costs related to blindness, including low-vision aids, visual rehabilitation and community care should be taken into account - these are added costs (to the state). The Committee also does not appear to have taken account of the losses incurred by the patient in terms of their salary or their spouse's, who has to care for them or both.	
RCN		Point 7 The Committee suggests that cost effectiveness is sensitive to uptake. We would suggest that there will be a very high uptake in these new treatments in the NHS, therefore costs will be lower and outcomes for wet AMD patients better. Already some eye units have seen an increase in referrals and enquiries as to whether or not they can offer treatment. Patients, relatives and carers are prepared to spend money travelling to clinics at frequent intervals and to remain under observation for years if we can save even a small amount of their sight. If this is the case surely we should not deny them the opportunity. Monthly treatments could also be restrictive for many patients and make it impossible for them to agree to commence on this therapy, a 6 weekly treatment could be an option that would be easier to comply with. In the current guidance this option has been discounted completely as macugen has not been recommended for any lesion type.	See FAD section 4.3.16.
RCN		Point 8 We find it difficult to understand how the Committee of an organisation whose remit is to examine evidence and recommend best practice, is recommending a head to head trial with a drug that is not licensed for use in the eye! Further, it is interesting to note that both drugs have been approved for use in Scotland, in all circumstances (i.e. not just the one eye and not for just occult) and they have obviously done similar appraisal work, yet this is refused in England and Wales. It would be ill-advised for such inequalities to	Comment noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		exist across the countries, particularly as the appraisal was based on similar evidence and the patients are governed by the same National Health Service principles. We welcome the recommendation for an investigation into the long term effects and optimal regimen of antivegF treatments but strongly recommend that this be done via a national audit not as with PDT a 'study' that diverted necessary funding away from the clinical area.	
		Summary We acknowledge that the Appraisal Committee has a very difficult job reviewing numerous new therapies available to the NHS but ask the Committee to re-examine the evidence for antiVegF treatments for all wet AMD in the light of this response. We strongly believe, as do other health professional colleagues that the evidence justifies the routine use of antiVegF treatments by retinal specialists to stabilise vision for all patients suffering the debilitating effects of wet AMD. We are already seeing dramatic results in clinical practice. Our patients are not only getting stability but improvement in vision when VegFs are used. We owe it to these vulnerable elderly patients to allow them the dignity to remain as independent as possible by providing these treatments on the NHS. We would recommend that macugen stays as an option as it has a different effect.	See above
Nominated clinical specialist 2		Thank you for asking my opinion on the Appraisal Consultation Document for the two technologies being considered by NICE for the treatment of AMD. I have read the guidance documents and have the following comments. This statement should be read as a supplement to the personal statement to the Appraisal Committee submitted on 15th April 2007 which included a declaration of interest.	Comments noted
Nominated clinical specialist 2	1.1	The ACD recommends the approval of ranibizumab for better seeing eyes with predominantly classic CNV secondary to AMD. In my opinion this recommendation is not appropriate for the following reasons: Better seeing eyes The Appraisal Committee is correct in stating that there is a lack of data on the cost effectiveness of treating the first involved eye. This does not mean that it is reasonable to restrict treatments to the second eye involved (the better seeing eye) for the following reasons: 1. the lack of data applies to most commonly applied ophthalmic treatments and to all treatments for AMD. 2. any given eye may not be treatable due to the natural history (eg. RPE rip, subfoveal haemorrhage) meaning that there can never be certainty	The FAD has been amended – see sections 1.1 and 4.3.18.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		that the better seeing eye will be eligible for treatment. The effect of this will be a number of patients will lose sight in both eyes when the first eye could have been treatable. 3. both eyes are always treated in clinical practice. Clinicians know that patients are very concerned about the loss of the second eye when the first has been lost. 4. in patients with bilateral disease there will be great difficulty in deciding which eye to treat.	
Nominated clinical specialist 2		The restriction was applied to photodynamic therapy in an early ACD in 2001. It was dropped in subsequent ACDs, the FAD and for the final guidance to the NHS. The reasons for this apply equally to pegaptanib and ranibizumab.	See above
Nominated clinical specialist 2	1.1 & 1.2	Restricting ranibizumab to predominantly classic CNV secondary to AMD is unexpected and does not fit with the opinion of clinicians in the UK. It is based on a cost-effectiveness sub-analysis with a number of uncertain assumptions: 1. 24 injections of ranibizumab over 2 years This is very unlikely to be followed in clinical practice 2. Cost of technology There is wide uncertainty around the costs of providing intravitreal services in the UK mainly depending on the use of outpatient or day case costs. The cost assumptions in the modelling performed for the appraisal try to fit a new service into existing NHS tariffs not designed to accurately cost a new service. In my submission of April 2007 I presented the indicative costs from the Liverpool service based on experience with delivery of an AMD clinical service. These fall part way between an outpatient cost which is too low and day case costs which are too high. 3. Subgroup analysis The use of a subgroup analysis does not appear to be appropriate. The clinical trials did look at subgroups as this allowed comparison with TAP and VIP. However there was no consistent evidence of a different effect across different subgroups. The ICERs for treating all lesion subtypes should be considered. 4. Costs of blindness. 5. These appear to have been underestimated, presumably because there has been an underestimate of the uptake of these services.	The FAD has been amended – see sections 1.1 and 4.3.8 to 4.3.24.
Nominated clinical specialist 2	1.1	Restriction to lack of permanent structural damage to the central fovea This cannot be assessed accurately and should be withdrawn.	The Committee discussed criteria for starting therapy and thought that these should be in agreement with the eligibility criteria of the underlying clinical trials (see FAD section

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			4.3.25). It also considered responses, including this one, from the consultation period on the second Appraisal Consultation document (see also comments from the Royal College of Ophthalmologists on the second ACD issued December 2007).
Nominated clinical specialist 2	1.1	Restriction to recent presumed disease progression The panel have misinterpreted the use of this criterion in the treatment of neovascular AMD. It is based on the eligibility criteria from the VIP trial and in clinical practice is only applicable to occult no classic lesions. It is therefore not relevant to 1.1 as it currently stands.	Comment noted. The FAD has been amended to recommend ranibizumab in all lesion types – see section 1.1 and response to comment above.
Nominated clinical specialist 2	1.3	Pegaptanib Therapy This should in my opinion be available for selected cases where the use of ranibizumab is inappropriate. For example patients may develop hypersensitivity to ranibizumab, be unable to attend every 4 weeks or have no response to ranibizumab.	The Committee considered the adverse effects of ranibizumab and pegaptanib (see FAD sections 3.3, 3.7, 4.1.6, 4.1.11 and 4.3.5). It concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD section 4.3.24).
Nominated clinical specialist 2		Registry I believe that it will be important for these technologies to be adequately monitored to measure compliance with its use within the NHS, its safety and its effectiveness in clinical practice. This approach was adopted for the introduction of PDT for AMD and has helped to set a high standard of clinical care within a managed introduction to the NHS as well as providing important information about safety and effectiveness. Many lessons have been learnt about how best to manage such a monitoring exercise. The most effective method would be to set up a registry linked to the newly established UK network for reading centres with the aim of capturing a minimum data set comprising: baseline: demographic details, independently assessed diagnosis, treatment delivered follow-up: distance vision, adverse events, treatment delivered	Comments noted. See FAD section 6.1.
Nominated clinical specialist 2		Recommendations to NICE 1. Remove restriction to better seeing eye 2. Review cost-effectiveness analysis with • recalculation of costs of blindness • recalculation of costs of service delivery • inclusion of all lesion subtypes in one estimate of ICER Recommend introduction of a data collection and monitoring registry	Comments noted
The Royal College of		We recognise that NICE has considered the published evidence but we do not believe that this Appraisal Consultation Document has considered all the	Comments noted.

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Ophthalmologists.		new evidence accruing which suggests that the number of injections will be less than in the pivotal studies.	
The Royal College of Ophthalmologists.		We have concerns that the economic modelling is incorrect in the following points, and that as a result the ICER of ranibizumab and pegaptanib are greater than reported. In particular we believe that ranibizumab would be shown to be a cost effective treatment in patients with occult and minimally classic lesions, if the economic modelling takes account of our concerns. Similarly, pegaptanib may be shown to be cost-effective, at least for some lesion types, if these concerns are taken into account.	The FAD has been amended – see sections 1.1 and 4.3.6. The Committee did not consider pegaptanib treatment to be a cost effective use of NHS resources – see FAD sections 4.3.23 and 4.3.24.
The Royal College of Ophthalmologists.		It is important to appreciate that eyes with minimally classic and occult CNV lesions also lose vision although the rate of vision loss may be slower than the predominantly classic in the short term. Furthermore, a significant proportion (at least 50%) of such lesions will convert to predominantly classic lesions within a year of follow up.	The FAD has been amended – see sections 1.1 and 4.3.6.
The Royal College of Ophthalmologists.		The ACD assumes that injections will be given as day case episodes, rather than outpatient procedures. We think this is incorrect because the nature of this procedure is unique, being neither a day case or outpatient procedure, but a procedure that most units are planning to deliver in an outpatient setting, in a dedicated clean room. We recognise that the length of time the treatment takes is longer than an ordinary outpatient appointment (4-6 hours), and that the indicative costing of this procedure is unique, neither fitting into an outpatient or day case procedure tariff. Therefore existing tariffs cannot be applied. (see The Royal College of Ophthalmologists document 'Commissioning Contemprary AMD Services: a guide for commissioners and clinicians' in Appendix 1 attached – table of indicative costs)	See FAD section 4.3.16.
The Royal College of Ophthalmologists.		A consensus amongst 160 medical retina specialists attending the Medical Retina Group meeting on 01/07/07, a representative professional society for ophthalmologists dealing with AMD and other medical retina conditions, shows that whilst currently about 50% of respondents are giving these injections as day cases in operating theatres, 90% of respondents expect to offer this service as an outpatient treatment once it became a NHS funded service.	See above
The Royal College of Ophthalmologists.		The ACD has based the cost effectiveness calculations for ranibizumab on a regimen of 24 monthly injections over two years. As the College pointed out in its previous comments the regimen advised by the drug manufacturer's licence (8 injections in first year, 6 in second) is likely to be the preferred regime followed by ophthalmologists in the UK. This is confirmed by the Medical Retina Group consensus (see appendix) which showed that less than 1% of medical retina specialists would expect to give monthly injections of ranibizumab.	See FAD sections 4.3.9 and 4.3.10.

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The Royal College of Ophthalmologists.	4.3.10	The College feels that the comments made in this regard in the ACD in paragraph 4.3.10 are misleading as the PIER Study (6 injections in the first year and a planned 4 in the second) had a different dosing regime to the licensing submission of ranibizumab.	See FAD section 4.3.4
The Royal College of Ophthalmologists.		The ACD has not taken account of the evidence from the PrONTO Trial, that monitoring with ocular coherence tomography (OCT), a non-invasive technique, is a means of reducing the number of injections of ranibizumab whilst not affecting the clinical response.	See FAD section 4.3.4.
The Royal College of Ophthalmologists.		We believe that pegaptanib should be recommended for NHS use for those cases in which treatment has proved clinically problematic. Examples of this would be patients unable to attend for four weekly injections, allergy or adverse reaction to ranibizumab and cases where ranibizumab is contraindicated due to the patient's general health.	See FAD sections 4.3.23 and 4.3.24.
The Royal College of Ophthalmologists.		The effects of visual impairment from disease on the patient, family and society are significant. However such effects seem to have been ignored in determining the effectiveness and cost effectiveness of anti-VEGF therapy.	The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.3.3.1. of the Guide to the Methods of Technology Appraisal (Available from URL http://www.nice.org.uk/page.aspx?o=201974).
The Royal College of Ophthalmologists.		It is our view that both first and second eyes should be treated with anti-VEGF therapy and that it is illogical to restrict treatment to the better eye.	Comment noted – see FAD section 4.3.18.
The Royal College of Ophthalmologists.		We think there is clinical risk in this policy for the following reasons: It assumes that all patients will always be able to present to an ophthalmologist for treatment to the second eye in time for it to be effective – which is untrue. It assumes that the fellow eye will always have a treatable condition – either from AMD or from a condition unrelated to AMD – which is not always the case. In addition, in the scenario of a patient presenting with an occult or minimally classic lesion in their better (second) eye and a predominant classic lesion in the worst (first) eye, such a patient would be denied all intravitreal anti-VEGF	Comment noted – see FAD section 4.3.18.

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		treatment, under the current ACD, despite the proven effectiveness of such treatment.	
The Royal College of Ophthalmologists.		The College is concerned that the proposed review date for the guidance of April 2010 is too late, in such a fast moving medical field, and would recommend April 2009.	The guidance on this technology will be considered for review in April 2011 – see FAD section 8.2. Consultees can request an early review if significant new data become available. Whether the review can be done earlier mainly depends on the availability of new evidence. Refer to the Guide to Methods of Technology Appraisal section 5.3.
The Royal College of Ophthalmologists.		The Royal College of Ophthalmologists recommends that: Ranibizumab intra-vitreal therapy should be made available to patients with neovascular age-related macular degeneration: • where any part of the lesion is subfoveal (within 200 μm of the foveal centre) • without restriction to first or second eye • irrespective of relative proportions of lesion components • with a visual acuity of logMAR1.2 or better (6/96 or 4/60)	The FAD has been amended – see sections 1.1, 1.2, 4.3.25 and 4.3.26.
The Royal College of Ophthalmologists.		Treatment should be discontinued where there is lack of a clinical response, for example where vision falls persistently below logMAR 1.2. Therapy should be delivered in centres with expertise in the diagnosis and management of macular disease, access to standardised vision assessment and lesion imaging, dedicated facilities for intra-vitreal injection and adequate capacity for follow up as indicated in The Royal College of Ophthalmologists Commissioning document. Pegaptanib intra-vitreal therapy should be made available, under the same criteria, where ranibizumab therapy proves to be clinically problematic. It is essential that adverse events associated with anti-VEGF should be collected and evaluated by the College.	The FAD has been amended – see sections 1.1, 1.2, 4.3.25 and 4.3.26.

Reply received but no comments:

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