

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 second ACD issued December 2007

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Pfizer		<p>After consideration of the stakeholder responses to the additional economic re-analysis, Pfizer would like to acknowledge and thank the Appraisal Committee for issuing a second ACD.</p> <p>Despite the additional re-analysis and considerable uncertainty concerning, in particular, where anti-VEGF treatments should be administered and the cost of treating the first eye, Pfizer are disappointed to learn that the Appraisal Committee have concluded that pegapatanib is not a cost-effective option to treat wet AMD. Pfizer are surprised and disappointed by this recommendation and are concerned that the Committee have made significant errors when arriving at this decision. Hence, Pfizer would like the Committee to address the following concerns:-</p> <ol style="list-style-type: none"> 1. The ACD reports inadequate and insufficient estimates for the cost-effectiveness of pegaptanib in the subgroup of patients with wet AMD and a baseline visual acuity of 6/12 to 6/24 2. There is a lack of transparency as to the estimates on which the Committee have based their decision making. Several modelled scenarios for pegaptanib in the subgroup 6/12 to 6/24 present cost/QALY estimates below £30,000; including: <ol style="list-style-type: none"> a. Treatment for two year assuming a greater uptake in outpatients 	See below for responses to comments 1, 2 and 3 separately.

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		<p>b. Treatment for two years for the better seeing eye c. Treatment for one year</p> <p>There is no clear justification in the ACD for why the Committee has rejected these scenarios.</p> <p>3. For patients with high cardiovascular risk, it is important to maintain physician and patient choice with regards the potential safety advantage that pegaptanib, a selective anti-VEGF treatment, may offer when compared to a non-selective VEGF treatment for patients.</p> <p>These points are explored in more detail in the attachment accompanying this letter.</p> <p>In conclusion, we would recommend that the Committee reconsiders the weight of evidence for cost-effectiveness of pegaptanib versus the potential safety issues associated with a non-selective VEGF-A antagonist. 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.</p>	
Pfizer		<p>1. The ACD reports inadequate and insufficient estimates for the cost-effectiveness of pegaptanib in the subgroup of patients with wet AMD and a baseline visual acuity of 6/12 to 6/24</p> <p>Pfizer are concerned that the Committee has given its negative decision for pegaptanib based on an inadequate and insufficient assessment of the modelling estimates for the subgroup 6/12 to 6/24.</p> <p>Throughout the appraisal process, Pfizer has demonstrated that pegaptanib is a cost-effective treatment option over both one and two years for patients with wet AMD for the 6/12 to 6/24</p>	<p>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</p>

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		<p>sub-group. The Committee have also acknowledged that this is the most cost-effective subgroup.</p> <p>The Committee have acknowledged that the Assessment Group model may inaccurately model the treatment effect of pegaptanib for this sub-group and Pfizer therefore support the additional modelling which was undertaken by the Decision Support Unit (DSU). This modelling approach resulted in a cost per QALY of £25,583 or £26,329 (year 3 disease modifying effect or Brazier utilities respectively). This assumes that 100% of procedures are conducted as a Day Case.</p> <p>In the second ACD, Pfizer note with concern that it is unclear what the particular assumptions adopted by the Committee are as these are not explicitly stated in the document for this sub-group. The resulting cost/QALY estimates are not presented either. It is therefore hard to understand how a decision was made by the Committee in the absence of the relevant information being made available. Pfizer therefore request that all of the Committees assumptions and the cost/QALY outcomes are explicitly presented for the sub-group 6/12 to 6/24. Pfizer also requests that the Committee provides a copy of the DSU economic model which has been produced in support of the second ACD, as a fully accessible and working version.</p> <p>Hence, as the second ACD has omitted to present some important scenarios for the sub-group 6/12 to 6/24, Pfizer has therefore conducted some additional analysis based on the best interpretation of the assumptions described in the second ACD. The outputs from this analysis are presented in Table 1, below and should assist the Committee to re-consider their initial decision for pegaptanib.</p>	<p>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 for more details).</p>

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		<p>Table 1: ICER outputs for additional scenarios for the 6/12 to 6/24 subgroup using the DSU model. Not reproduced here – see consultee’s comments on the ACD</p> <p>Pfizer would like to challenge the Committee on three of the assumptions which it has adopted in its modelling which may have led to the negative recommendation:</p> <ul style="list-style-type: none"> • The split of patients treated as an Outpatient is 25% and those treated as a Day Case is 75% <p>The Committee have failed to present the cost/QALY output when the above split is assumed. Pfizer request that this is provided.</p> <p>Pfizer are confident that as more procedures are performed in the less costly Outpatients setting, pegaptanib can be delivered cost-effectively. Pfizer have demonstrated that the cost/QALY is highly sensitive to the proportion of patients treated in Outpatient or Day Case settings. For example, sensitivity analyses, presented to the Committee by Pfizer, when all procedures are undertaken as an outpatient resulted in the cost/QALY being £12,826 compared to a cost/QALY of £23,104 when all procedures are undertaken as a Day Case (Table 1). The Committee has concluded in its second ACD that ranibizumab should be recommended to treat all patients with AMD. Over the last year or more, many Primary Care Trusts have been waiting for the NICE guidance on anti-VEGF treatments before developing an effective and efficient AMD service to deliver anti-VEGF treatments. The current service provision in England and Wales is therefore under-developed and in its infancy and probably led the Committee to conclude that only 25% of administrations would occur in Outpatient setting compared to 75% of administrations occurring in the</p>	<p>The Committee discussed the assumptions in the models for the costs of administering intravitreal injections and concluded that a reasonable approach would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an outpatient appointment (see FAD section 4.3.17).</p>

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		<p>Day Case setting. Service provision will need to change over the coming months and years to cope with the increase in patient numbers. This will lead to economies of scale whereby delivery of pegaptanib will also be a cost-effective option. Implementation of the NICE guidance will require the service to expand; it is therefore logical to assume that new and existing patients will be treated in the less costly Outpatient setting. As a point of reference, the Committee may want to take note of the situation in Scotland where the service provision for anti-VEGF's has been established longer and it is now more usual for the administrations to occur in the Outpatient setting. For these reasons the negative decision for pegaptanib is therefore partly dependent on the evolution of services; an important fact which the Committee has failed to take into consideration when making their decision and thereby have stifled the introduction of an innovative medicine that has the potential to be delivered cost-effectively in the NHS.</p> <ul style="list-style-type: none"> • Assumption that the cost of treating the first eye will increase the cost/QALY by 50% <p>The Committee has estimated that the cost per QALY for pegaptanib (and ranibizumab) would increase by 50% if the first eye was to be treated as opposed to the better-seeing eye only. There is no evidence or justification supporting this estimate and importantly no testing of the impact of the uncertainty associated with the 50% estimate on the cost/QALY. Pfizer consider the figure of 50% is an inappropriate one to apply to the sub-group 6/12 to 6/24 since these patients typically present at a later stage of disease. It is therefore unlikely that VA will lie between 6/12 and 6/24 in the first eye. The more likely scenario for this sub-group will be patients presenting with disease in their second eye and requiring treatment. As demonstrated in Table 1, pegaptanib is cost-effective when the second eye is</p>	<p>The Committee discussed whether it would be appropriate to consider recommending treatment in the better-seeing eye only, and the impact of this issue on cost-effectiveness (see FAD sections 4.3.18 to 4.3.21 and 4.3.23 to 4.2.24).</p>

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		<p>treated and therefore pegaptanib should be recommended as a treatment option for the second eye.</p> <p>Pfizer therefore conclude that the availability of these medicines should not be dependent on this estimate. This decision should be consistent with the previous NICE guidance for photodynamic therapy, where no adjustment was made for treating the first eye.</p> <ul style="list-style-type: none"> • Use of Brazier utilities. <p>Table 1 above demonstrates that if Brazier utilities are adopted the cost/QALY increases by £3,225. The second ACD states that the use of Brazier utilities for pegaptanib will increase the cost/QALY by £8,000 (Second ACD section 4.2.4.5). Pfizer request that the Committee clarifies this and corrects the error if appropriate.</p>	<p>The Committee discussed the utility values used in the economic models and the cost-effectiveness of pegaptanib based on models incorporating Brazier utilities (see FAD sections 4.3.15, 4.3.23 to 24, and section 4.2.4).</p>
Pfizer		<p>2. There is a lack of transparency as to the estimates on which the Committee have based their decision making.</p> <p>Throughout this Appraisal, the Committee have chosen to undertake at least four modelling approaches (from the manufacturer Pfizer, the Assessment Group, the Decision Support Unit and further modelling outputs from the Assessment Group) which have resulted in numerous scenarios being modelled and numerous cost/QALY outputs being available. Pfizer conclude that the wealth of outputs has generated a confused view of the appropriate cost-effectiveness estimates for pegaptanib. Key modelling scenarios and resulting outcomes appear to have been omitted from the ACD and therefore may not have been made available to the Committee to inform and guide them in their decision making.</p> <p>Pfizer have confidence that many scenarios modelled have demonstrated that pegaptanib is cost-effective for both two</p>	<p>The Committee considered the cost-effectiveness of pegaptanib based on both the manufacturer's and the Assessment Group economic models. It considered the results from both models incorporating its preferred assumptions. (See response to comment 1. above and sections 4.3.8 to 4.3.24, and 4.2.4, of the FAD).</p>

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		<p>years treatment and one year treatment (whereby it is even more cost effective). Pfizer would like to draw the Committees attention to these scenarios, and the cost/QALY outputs are presented in Table 2 below.</p> <p>Pfizer conclude that pegaptanib is a cost effective treatment option for patients with wet AMD and a baseline VA of 6/12 to 6/24. These outputs are for the treatment of the second eye; however some remain below £30,000 per QALY even applying the 50% estimate for treating the first eye.</p> <p><u>Table 2: ICER outputs for some relevant scenarios for pegaptanib, 6/12 to 6/24 sub group</u></p> <p>Not reproduced here – see consultee’s comments on the ACD *calculated by Pfizer as the cost QALY using the DSU model for the 6/12 to 6/24 subgroup has not been provided by the Committee</p>	
Pfizer		<p>3. For patients with high cardiovascular risk, it is important to maintain physician and patient choice with regards the potential safety advantage that pegaptanib, a selective anti-VEGF treatment, may offer when compared to a non-selective VEGF treatment for patients.</p> <p>Despite the Committee acknowledging that ranibizumab’s Summary of Product Characteristics shows that the overall incidence of arterial thromboembolic events from the MARINA, ANCHOR and PIER trials was higher for patients treated with ranibizumab 0.5 mg (2.5%) compared with the control arm (1.1%), patient and physician choice has been restricted. The wet AMD patient population is generally older and present with co-morbidities. An interim analysis of data from the SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) study showed a “higher incidence of stroke in the 0.5-mg dose group compared with the 0.3-mg dose group (1.2% vs. 0.3%,</p>	<p>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).</p>

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		<p>respectively $P = 0.02$). “ Additionally, it was noted that “patients with a history of stroke appeared to be at higher risk for a subsequent stroke”¹. Pfizer would like to point out to the Committee that these cardiovascular safety signals described for ranibizumab are based on one year data from the PIER and ANCHOR trials and less than one year of treatment (230 days) for the SAILOR interim analysis. Only the MARINA trial reported two year safety data. The outstanding second year safety data from PIER and ANCHOR are now becoming available and may provide additional evidence of this potential cardiovascular safety risk.</p> <p>Based on the above information, Pfizer therefore conclude that ophthalmologists should have access to pegaptanib to facilitate an informed decision between treatment options for each individual patient.</p> <p>In addition it is important that treatment choice is available where Lucentis may be contraindicated for clinical reasons other than cardiovascular risk. Again, referring to ranibizumab’s Summary of Product Characteristics section 4.3 states that patients with active severe intraocular inflammation are contraindicated. In section 4.4 “Special warnings and precautions for use”, it is stated that “<i>As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis. Patients should be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.</i>”</p> <p>In consideration of all the reasons presented above, both anti-VEGF treatments need to be available to support and facilitate physician and patient choice.</p> <p style="text-align: center;"><u>REFERENCES</u></p>	

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		<p>1. Food and Drug Administration (FDA). FDA drug alert; Genentech, January 2007a. Available at: http://www.fda.gov/medwatch/safety/2007/Lucentis_DHCP_01-24-2007.pdf. Accessed Oct 26, 2007.</p>	
Novartis		<p>Thank you for your invitation to comment on the above referenced Appraisal Consultation Document (ACD) 2, received on 7th December 2007. Novartis welcomes the development of a new ACD and the opportunity to comment on the preliminary recommendations.</p> <p>We are pleased that the preliminary recommendations will allow patients with all wet AMD lesion types, affecting either eye, to benefit from treatment with ranibizumab in accordance with its licensed recommendations. In addition, we welcome the opportunity to collaborate with the Institute and the Department of Health to facilitate patient access by capping the dose of ranibizumab. A summary of the proposed dose capping scheme is provided in Appendix 1.</p> <p>Some further comments are detailed below regarding the recommendation limiting treatment to best-corrected visual acuity better than 6/60 and interpretation of the evidence.</p>	Comments noted. See below for responses to specific comments.
Novartis		<p>Recommendations, Section 1.1, 1st bullet point, page 3</p> <p>This recommendation states that the eye to be treated should have a best-corrected visual acuity better than 6/60. Section 4.3.23 states that this is appropriate because the majority of the trial participants had a visual acuity above 6/60 and 6/60 is the level where a person is considered to be legally blind in the UK. However, it should be noted that 6/60 is the threshold for being considered partially blind.</p>	The FAD has since been amended. See sections 1.1 and 4.3.25).

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		<p>In addition, a total of 74 patients with a baseline visual acuity of <6/60 were entered into the ranibizumab trials (cross the three Lucentis studies (MARINA n=27, ANCHOR n=34 and PIER n=13). Results from these studies demonstrate that some patients with visual acuity below 6/60 at baseline had improved to visual acuity >6/60 ie some useful vision, by month 3 and month 12. These results are presented in the table below.</p> <p>Table 1 – Visual Acuity Outcomes in Patients with a Visual Acuity of <6/60 at Baseline Following 3 and 12 Months of Treatment</p> <p>Not reproduced here</p> <p>Although the numbers of patients are too small to draw any firm conclusions, the data suggest that patients with a visual acuity of 6/60 or below may have the potential to obtain benefit from ranibizumab treatment. We therefore propose that the recommendation is amended to allow patients with a visual acuity of 6/60 or better in the affected eye are able to receive treatment.</p>	
Novartis	Section 4.3.8, page 23	<p>This section states,</p> <p><i>“It heard from clinical specialists that it is unclear how long treatment would be continued in practice, that there is an evolving evidence base, and that for some patients it would be appropriate to continue treatment beyond 2 years into the third or even fourth year. This would result in additional drug, administration and monitoring costs, which were not included in any of the economic models.”</i></p> <p>However, it should be noted that treatment would only be considered beyond two years if it were deemed by the clinician that the patient had a capacity to benefit. Therefore any analysis of cost-effectiveness beyond two years would need to take into account both the additional benefits as well as costs.</p>	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.

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Novartis	Sections 4.3. 10 and 4.3.21, on pages 24 and 29	<p>These sections of the ACD state,</p> <p><i>“However, the Committee remained concerned about the assumption that the benefit achieved in the pivotal trials could be matched with lower doses.”</i></p> <p><i>“The Committee discussed the number of injections of ranibizumab assumed in the model. It noted that if 8 injections would be required in the first year and 6 in the second, as suggested by consultees (see section 4.3.10), ICERs would be substantially lowered. However, it considered that many patients would be likely to require more injections than this to maintain benefit.”</i></p> <p>The statement that many patients would be likely to require more than 14 injections to maintain the level of benefit observed in clinical trials is purely speculative. Furthermore, all of the available evidence does not support this view. As detailed in our previous submissions, 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 published and are similar to those observed in the MARINA and ANCHOR studies and were achieved with an average of 9.9 injections over 24 months. [confidential information removed]</p>	The Committee discussed the results of the pivotal trials and the licensed dosing regimen. It concluded that there was some uncertainty about the number and frequency of injections required to achieve the results seen in the RCTs. See FAD section 4.3.3 to 4.3.4
Novartis	Section 4.3.11, page 25	<p>The ACD states,</p> <p><i>“...the assumption that no-one would receive further injections after 2 years was not probable.”</i></p> <p>The current evidence base clearly demonstrates that 15 doses of ranibizumab given over a two-year treatment period are cost-effective for the treatment of patients with wet AMD. There are</p>	The NICE Guide to the Methods of Technology Appraisal states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in cost or outcomes between the technologies being compared (see section 5.3.5).

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		<p>insufficient data at present to determine how many injections may be required beyond two years, although we do know that this will vary from patient to patient based on individual responses. However, where injections are given beyond two years the decision to treat will be based on potential benefit. Therefore benefits and costs beyond two years should be evaluated as and when appropriate data are available. Guidance should be based on the available evidence and not on speculation as to what may or may not happen beyond the current timeframes.</p>	
Novartis	Section 4.3.21, page 29	<p>The ACD states,</p> <p><i>“Additionally, continued administration and monitoring costs would also need to be considered as patients would require regular re-assessment on a monthly basis to monitor the progress of their disease.”</i></p> <p>It should be noted that the additional analysis conducted by SHTAC, dated 21st September 2007, includes an analysis which takes into account the monthly monitoring costs. The results of this analysis demonstrate that ranibizumab is cost-effective based on 15 injections administered over a two year period with a cost per QALY gained of £14,704 (See Table 41, page 33).</p>	<p>The NICE Guide to the Methods of Technology Appraisal states that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in cost or outcomes between the technologies being compared (see section 5.3.5). The analysis by the Assessment Group takes into account monthly monitoring costs, but only within a 2 year time frame. The Committee understood from clinical specialists that it would be appropriate for treatment beyond 2 years in some patients (see FAD section 4.3.9).</p>
Novartis		<p>Implications for the NHS</p> <p>As acknowledged in Guidance TA No.68 relating to photodynamic therapy, wet AMD can progress rapidly. Therefore, it is important that patients receive treatment early in order to retain as much vision as possible. In order to facilitate this, we propose that wording similar to that presented in Section 6.2 of Guidance TA No.68 is also included in the guidance for this appraisal,</p>	<p>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.</p>

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		<p>“For treatment to be as effective as possible, individuals with wet AMD should be fast tracked through the referral and waiting list processes in order to receive treatment before further loss of vision occurs.”</p> <p>In summary, although we do not entirely agree with all of the interpretations of the evidence, we believe that in general the recommendations represent a sound basis on which to provide guidance to the NHS. We welcome the opportunity to collaborate with the Institute and the Department of Health to define a scheme which will facilitate patient access to ranibizumab.</p> <p>Appendix 1: dose-capping scheme summary proposal</p>	<p>The Committee discussed a scheme suggested by the manufacturer in which the number of injections paid for by the NHS could be capped, with any remaining injections paid for by the manufacturer. See FAD sections 1.1, 1.2, 4.3.22, 4.3.25 and 4.3.26.</p>
<p>Royal college of ophthalmologists</p>		<p>Health technology Appraisal: Ranibizumab and Pegaptanib for the treatment of age-related macular degeneration</p> <p>Comments on the NICE 2nd Appraisal from The Royal College of Ophthalmologists</p> <p>The Royal College of Ophthalmologists have carefully scrutinised the current ACD. We note that a number of the concerns that we expressed following the previous ACD have been addressed, and we welcome these changes.</p> <p>In particular we are pleased that the Appraisal Committee recommends treatment with ranibizumab:</p> <ol style="list-style-type: none"> 1. in all types of wet macular degeneration 2. where there is evidence of recent disease progression 3. in the absence of permanent structural damage to the fovea. 4. and where the lesion size is less than or equal to 12 disc areas. 	<p>Comments noted</p>

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		However, we question the relevance of some of the other points made in the second ACD and we list these as follows:	
Royal college of ophthalmologists		<p>The ACD states that the visual acuity cut off for treatment should be better than 6/60 (i.e.6/48 or better) in the eye to be treated. It is our view that this is unjustifiable, as the clinical trials which form the evidence base for Lucentis therapy used a visual acuity cut off of 6/96 or better. We wondered whether the proposed cut off was an error as there is a statement in section 4.3.23 of the ACD that “6/60 was an appropriate level for treatment”. We would welcome clarification from the appraisal team that any eye with an acuity of 6/60 or better will be treatable.</p> <p>2. The ACD also states that a visual acuity of 6/60 is the level where a person is considered legally blind. This is incorrect. The current UK legislation as it stands indicates that an acuity of 6/60 (Snellen) in the better seeing eye is the level at which a person is eligible for registration as partially sighted.</p>	<p>The FAD has since been amended. See FAD sections 1.1 and 4.3.25.</p> <p>The FAD has been amended.</p>
Royal college of ophthalmologists		We would wish that pegaptanib should be recommended for those patients who are unable to tolerate ranibizumab, through allergy or adverse reaction, or where such treatment with ranibizumab is clinically problematic.	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).
Royal college of ophthalmologists		We would welcome a statement that treatment with anti-VEGFs including ranibizumab should be limited to units with expertise in the field of treatment and assessment of AMD and have access to the necessary technology – fluorescein angiography and optical coherence tomography.	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

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			Guidance has been developed with that objective.
Royal college of ophthalmologists		It is hoped that there will be robust on going audit to allow collection of adverse events data. The Royal College of Ophthalmologists recommends on going robust data collection for surveillance of both outcomes and adverse events. The College wishes to be the host organisation of such data collection and management if adequate funding is provided by the Department of Health or other outside source.	The Appraisal Committee considered that further research into the effectiveness of anti-VEGFs in wet AMD could include studies to investigate the long-term effects of anti-VEGFs in patients with AMD, including effects on visual acuity, anatomical damage to the macula, quality of life and adverse events (see FAD section 6.1).
Royal college of ophthalmologists		As some patients may require more treatment than others, and it may be difficult to monitor treatment frequencies for each individual patient, average treatments in particular periods may be easier to determine. This may be helpful if pharmaceutical companies are to pick up costs of 'excess' treatment. A life time cap of 14 treatments with ranibizumab is impractical.	The Committee discussed a scheme suggested by the manufacturer in which the number of injections paid for by the NHS could be capped, with any remaining injections paid for by the manufacturer. See FAD sections 1.1, 1.2, 4.3.22, 4.3.25 and 4.3.26.
Nominated Clinical Specialist 1		<p>Thank you for providing the opportunity to respond to the second ACD issued by NICE on the use of pegaptanib and ranibizumab.</p> <p>In my opinion, the recommendations made in the second ACD are broadly speaking acceptable. However, similar to other consultees I believe that a number of changes and additions are required to ensure that the Final Appraisal Determination will meet the needs of patients. In particular I would welcome:</p> <p>1.1. The approval of pegaptanib as second-line treatment</p> <p>1.2. A lower treatment threshold with patients being treated in</p>	Comments noted. See below for responses to specific comments.

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		<p>line with the recommendations of the Royal College of Ophthalmologists</p> <p>1.3. The FAD to be issued quickly</p> <p>1.4. The speedy implementation of NICE's guidance and greater efforts by NICE's implementation unit to monitor and enforce the implementation deadline.</p> <p>1.5. A recommendation that Primary Care Trusts provide the necessary funding to introduce appropriate infrastructure and not just the price of the drug.</p> <p>1.6. Clarification of NICE's position with regard to Primary Care Trusts which commission an Anti-VEGF service using bevacizumab rather than with ranibizumab or pegaptanib.</p>	
<p>Nominated Clinical Specialist 1</p>		<p>The decision not to recommend the approval of pegaptanib</p> <p>2. I believe that clinicians and their patients should have the option to choose what treatment is in the patient's best interest. Certainly at present ranibizumab will be the preferred treatment choice for most patients. However, some patients with wet AMD may not be able to tolerate ranibizumab, have an allergic reaction to this drug or may have a history of heart disease or stroke. One or more of these factors may make pegaptanib the preferred treatment option.</p> <p>In addition I am aware of research combining ranibizumab and pegaptanib in the same treatment pathway. In this research, patients are initially given ranibizumab resulting in vision improvement and then they are maintained with pegaptanib which stabilises their vision at the improved level. This research is not published yet but merely presented at scientific meetings.</p>	<p>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).</p>

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		<p>However possibly this may be a safer option for patients with cerebrovascular or cardiovascular disease if it shows equal benefit to treatment with ranibizumab alone. Therefore it would be useful at this stage to have pegaptanib available as an option for treatment so that clinicians could quickly respond to changes in treatment protocols as new evidence from clinical trials becomes available.</p>	
<p>Nominated Clinical Specialist 1</p>		<p>The treatment threshold</p> <p>3. Throughout the ACD a visual acuity of 6/60 is equated with the threshold for legal blindness in the UK. Most significantly the fact that 6/60 is presumed to be the threshold for legal blindness is used as a justification to set the eligibility threshold for treatment at better than 6/60 (effectively 6/48).</p> <p>4. 6/60 is the threshold for being registered as partially sighted, not blind. The threshold for being registered as blind is 3/60. I believe that the false assumption that 6/60 is the threshold for legal blindness has confused the committee's thinking. I would like to remind NICE that the eligibility threshold for PDT is 6/60 or better, that the Scottish Medicines Consortium has set no eligibility threshold for ranibizumab and a threshold of 6/60 or better for pegaptanib. Significantly, the Royal College of Ophthalmologists recommends that treatment should be considered until a patient's visual acuity falls persistently below 6/96 (or logMar 1.2). Evidence and clinical experience show that providing there is not irreversible sub-foveal scarring patients vision can recover even from these very low levels of vision with resolution of retinal fluid.</p> <p>5. At present many patients only present with their second eye</p>	<p>The FAD has been amended - see sections 1.1 and 4.3.25.</p> <p>The FAD has been amended. See sections 1.1 and 4.3.25.</p>

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		<p>8. In addition, I would like to raise the issue of treatment standards. Given the high cost of treatment PCTs and Local Health Boards may be tempted to lower the standard of care by allowing under-qualified staff to perform the injections. In the interest of patient safety I feel that the FAD should contain a requirement to follow Royal College of Ophthalmologists' treatment guidelines.</p> <p>9. I would also welcome a recommendation that Primary Care Trusts provide the necessary funding to introduce appropriate infrastructure as per Royal College of Ophthalmology guidelines and not just the price of the drug. Otherwise it may prove impossible for hospital trusts to provide this treatment. My personal experience is that some Primary Care Trusts will only pay for the drug costs. This is similar to paying for a scalpel but not the operating theatre or surgeon.</p> <p>10. Finally, I would also welcome clarification of NICE's position regarding Primary Care Trusts who commission an Anti-VEGF service using bevacizumab as the drug choice rather than ranibizumab or pegaptanib. If this occurs will these Primary Care Trusts face financial penalties for not introducing NICE guidance? Or will NICE consider this is satisfactory? Clarification of this from NICE would greatly help planning of anti-VEGF macular degeneration services around the country.</p> <p>Thank you for your careful appraisal of this technology</p>	<p>Comments noted. Guidance is issued in accordance with the marketing authorisation. The Summary of Product Characteristics states that ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.</p> <p>The objective of this Technology Appraisal is to appraise the clinical and cost effectiveness of ranibizumab and pegaptanib within their licensed indications for age-related macular degeneration. Guidance therefore relates only to the technologies being appraised. The Appraisal Committee considered that further research into the effectiveness of anti-VEGFs in wet AMD could include studies about the cost effectiveness of ranibizumab compared with bevacizumab (see FAD section 6.1).</p>

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DOH		<p>The Committee sought comments under four broad headings and our comments are:</p> <p>i) Do you consider that all of the relevant evidence has been taken into account?</p> <p>We have no comments on this point.</p> <p>ii) 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?</p> <p>To what extent NICE has taken account of non-drug costs (eg case volume increase/more visits/demands on staffing and theatre space)? It would be helpful if NICE could explain in the documentation how these costs have been taken into account.</p>	<p>In its appraisal of the cost effectiveness of ranibizumab and pegaptanib, the Appraisal Committee considered non-drug costs including those related to administration of intravitreal injections, monitoring of the underlying disease and response to treatment, costs of managing adverse events, and costs related to blindness and sight impairment. Costs related to blindness included those of the administrative costs of registering as blind or partially sighted, low vision aids, low vision rehabilitation, community care, residential care, depression treatment and hip replacement (see FAD sections 4.2.3.3, 4.2.4.3, 4.2.4.5, 4.3.8, 4.3.16, 4.3.17 and 4.3.22).</p>

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		<p>iii) 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?</p> <p>Did the Appraisal Committee consider whether there was a case for allowing use of pegaptanib in particular cases where there were indications of intolerance of ranibizumab? In addition, did it consider whether in such cases it would stabilise vision more effectively than visudyne and therefore improve overall outcomes? Are NICE happy that they have properly considered this issue and could this be explained?</p> <p>iv) Are there any equality related issues that may need special consideration?</p> <p>As the document acknowledges, AMD is a condition which usually affects people aged over 50, and risk increases significantly with age. The possibility of successful treatment is therefore clearly of particular significance to older people.</p> <p>The Department will be separately considering the detail of any proposed scheme Novartis puts forward for capping the cost to the NHS of the cost of ranibizumab, and we will write to you separately about this if such proposals are made.</p>	<p>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).</p> <p>In developing guidance, the Appraisal Committee takes into consideration the principles (including those with regard to age) reflecting the views of the Citizens' Council in its documentation on Social Value Judgements. For further details, see http://www.nice.org.uk/media/873/2F/SocialValueJudgementsDec05.pdf</p> <p>Comment noted.</p>
Derbyshire County PCT		It is noted that many of the points raised in the initial response from Derbyshire County PCT have been specifically addressed	

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		<p>in the December 2007 ACD. That is gratifying to see.</p> <p>2 The PCT remains concerned that the quality of life estimates are based on the effects immediately after loss of vision, either using data obtained from clinic patients or by means of simulated ARMD in volunteers. This over-estimates the consequences compared to when patients have accommodated to their central visual loss. The average loss of QoL seems high given how great are the achievements of many totally blind people.</p>	<p>Comments noted. The Committee discussed the utility values used in the economic models and concluded that the Brazier utility values provided the most plausible set of utility values for use in the economic models (see FAD sections 4.3.15, 4.2.2.4, 4.2.2.8, 4.2.3.4, 4.2.4.4, 4.2.4.5 and 4.2.4.8).</p>
Derbyshire County PCT		<p>The drug cost cap.</p> <p>3.1 Data would suggest that, given the slow rate of deterioration once on treatment (as per PrONTO), treatment is likely to be lifelong for the vast majority of patients (90%?).</p> <p>The major determinant of cost is actually clinic costs which exceed drug costs. Thus the suggested cap of 14 injections would only reduce costs by a small amount as clinic charges will continue to fall to the NHS.</p> <p>3.2 A financial model has been attached. Assuming an average 10 years on treatment and 39 injections over that period, the cap reduces the lifetime costs of ranibizumab by 2/3rds but overall costs by only 1/3rd. Yellow cells permit</p>	<p>Comments noted. The Committee considered the duration of treatment, noting that treatment beyond 2 years would be clinically appropriate for some patients, that there would be drug, administration and monitoring costs associated with this, and the there was uncertainty how benefits would accrue in the long term (see FAD sections 4.3.9 to 4.3.12).</p> <p>The Committee discussed a scheme suggested by the manufacturer in which the number of injections paid for by the NHS could be capped, with any remaining injections paid for by the manufacturer. The Committee estimated that ranibizumab was likely to be cost effective if the cost of treatment to the NHS was limited to 14 injections per eye. See FAD sections</p>

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		variations in cost estimates to be made. Indeed such is the burden of clinic costs, even using bevacizumab is very costly.	1.1, 1.2, 4.3.22, 4.3.25 and 4.3.26.
Derbyshire County PCT		<p>Thresholds</p> <p>4.1 The low end visual acuity threshold of 6/60 is supported but should also be recommended as a cessation threshold, beyond which treatment will cease.</p> <p>4.2 There is no recommended upper end commencement visual acuity threshold. PCTs have commonly been using 6/12</p>	The FAD has been amended (see sections 1.1 and 1.2, 4.3.25 and 4.3.26).
Derbyshire County PCT		<p>One or two eyes?</p> <p>5.1 It is unclear whether this is a first eye policy or a both eyes policy. If the former, guidance should be given as to what to do if the second eye becomes affected: should treatment be switched to the second eye if the vision is better in that eye at that time? What if, having started treatment on the better eye, sight deteriorates faster than the other eye despite treatment?</p> <p>5.2 If this is a two eye policy the cost implications are significantly higher. If the second eye is treated, it may be that only a single clinic cost is charged to test both eyes but it may not be possible to inject both eyes at the same time (so incurring just one 'daycase' charge) if treatment is triggered by deterioration in vision. If deterioration is random (ie rate is not the same in both eyes) then an additional 2 injection visits would be required further increasing costs. A two eye policy is included in the financial model, though zero costs for clinics is assumed, and clinic usage is set as per first eye. The model could be altered to cover more</p>	The Committee discussed whether it would be appropriate to consider recommending treatment in the better-seeing eye only, and the impact of this issue on cost-effectiveness. It concluded that its considerations of cost effectiveness should relate to starting treatment with the first eye to present clinically, (see FAD sections 4.3.18 to 4.2.24).

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		<p>complexity but a simple estimate could be made of the effect of an extra two injection clinics by changing the formula in cells D23-L23 to =2*(B10-B9).</p> <p>5.3 Any second eye 'insurance policy' designed to prevent blindness in two eyes should be subject to a proper actuarial analysis of likelihood vs cost of avoidance to calculate its value for money. The DH has encouraged PCTs to use actuarial techniques!</p>	
Derbyshire County PCT		<p>Financial implications</p> <p>6.1 As will be seen from the model the financial consequences of the ACD are very considerable indeed. The model includes information on all PCTs concerning the proportion of the population over 50 whom this disease affects. The DH has announced a flat increase in resource allocation of just under 5.5%. After taking off general inflation at 2.1%, the real uplift is 3.4%. For the whole of England the ARMD ACD proposal if for 2 eyes would account for 10.9% of this real uplift. However the burden will fall inequitably amongst PCTs because of the differences in the proportion of their population over 50. For Dorset, with 45% over 50, the figure is 15.1% but only 4.2% in Tower Hamlets (where population over 50 is 17.4%). The consequences are therefore very different until the allocation formula is adjusted to give greater age specific allocations for those over 50. **</p> <p>6.2 Such a large proportion of the uplift appears disproportionate. The financial consequences continue to rise for 10 years, by which time it is estimated that this treatment might consume between 0.5 and 0.8% of total NHS financial resources even allowing for a continued</p>	<p>The objective of this Technology Appraisal is to appraise the clinical and cost effectiveness of ranibizumab and pegaptanib within their licensed indications for age-related macular degeneration.</p> <p>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.</p>

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		<p>rise in NHS funding at 5.5%. The PCT requests that the Committee is made aware of these estimated costs with demonstrations of the effects of the variables using the model. The opportunity costs are very considerable and unequal amongst PCTs as allocations currently stand.</p> <p>6.3 Such is the burden of clinic costs, even using bevacizumab is very costly but about half the costs for 2 eyes and 1/3rd cheaper for first eye only.</p> <p>6.4 If the second eye clinic costs were £0 and bevacizumab used, the marginal costs are quite small (£5m vs £175m for ranibizumab in the first year). Indeed, under a zero cost for clinics for second eye scenario, using bevacizumab in the second eye would probably have a better ICER than first eye treatment, despite the smaller benefits of binocular vision.</p>	
Derbyshire County PCT		<p>Implications for ophthalmology services</p> <p>7.1 The implications for ophthalmology are also considerable. We have looked at ophthalmology activity and costs for 06/07 for DCPCT. Outpatient activity (just for eye tests) will need to rise by 5% each year for the next 10 years. Day case (if that's where injections are to be done) increase by 18% in year one for first eye only, reaching a 190% increase by year 10. If 2 eye injections are not simultaneous, then the figure will be larger. Our TOTAL ophthalmology costs were £8.8m. ARMD first eye only policy would cost DCPCT £2.67m year 1, £10.8m year 10. This would represent an interesting challenge for Programme Budgeting.</p>	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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		<p>8 Research</p> <p>8.1 NICE has recommended research to compare ranibizumab with bevacizumab. However once a ranibizumab based policy is issued such research is unlikely to happen: this was a problem in the case of Alzheimers disease when research recommended by NICE became impossible after the Guidance was issued and AD2000 had to be curtailed.</p> <p>8.2 The second eye might represent an ethical research opportunity, though from the evidence as bevacizumab is likely to be as effective and safe, there seems to be no ethical bar to a head-to-head trial.</p> <p>8.3 Urgent research is needed on whether there are early predictors of rate of progression that could determine the intervals for testing in an individual in a modified PrONTO 'test and treat' regimen.</p> <p>8.4 The previous suggestion that research into early detection/screening should be recommended, is</p>	<p>Comments noted. In reaching the decision, the Institute and Appraisal Committee take into account the factors listed in the directions of the Secretary of State for Health and the Welsh Assembly Government, namely: the broad clinical priorities of the Secretary of State for Health and the Welsh Assembly Government; the degree of clinical need of the patients with the condition under consideration; the broad balance of benefits and costs; any guidance from the Secretary of State for Health and the Welsh Assembly Government on the resources likely to be available and on such other matters as they think fit; and the effective use of available resources (see the Guide to the Technology Appraisal Process).</p> <p>The Appraisal Committee considered that further research into the effectiveness of anti-VEGFs in wet AMD could include studies about to establish the appropriate duration and optimal treatment regimen in terms of frequency of injections.</p> <p>Recommendations for further research in Technology Appraisals Guidance</p>

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		repeated.	can be identified on the basis of evidence gaps identified by the systematic review and cost-effectiveness analysis. These may be best prioritised by considering the value of additional information in reducing the degree of decision uncertainty (See the Guide to the methods of technology appraisal).
Nominated patient expert 1		<p>On reviewing the second ACD re- Pegaptanib and Ranibizumab for the treatment of age-related macular degeneration I was pleased to note that there has been a positive change in the overall recommendations which will result in greater number of patients suffering from this visually devastating condition getting NHS funded treatment.</p> <p>I would like to express my thanks to the appraisal committee for taking into account, not only the research evidence base but the comments from consultee's.</p> <p>Despite the change I still feel we should not restrict treatment to just patients with best corrected vision equal to or better than 6/60. As to do so will restrict access for a number of patients, that the evidence base clearly shows benefit in visual and thus improved quality of life outcome if they receive anti-Vegf treatment.</p> <p>It must be noted that objective measurement of visual acuity in the clinical area is only one way of assessing a patients suitability for treatment and can be variable depending on a number of issues that aren't always predictable i.e.- patient compliance, anxiety due to stressful situation etc. I understand the need to set a visual limit, but strongly advise that the threshold be reduced. The clinician can then have greater</p>	<p>Comments noted.</p> <p>The FAD has been amended (see sections 1.1 and 4.3.25).</p>

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Nominated patient expert 1		<p>power to decide whether or not individual patients' retina is amenable to treatment and judge to whether or not that patient has a chance of benefiting from treatment.</p> <p>It is my experience that no retinal specialist will subject a patient to an interventional procedure unless they thought that it was in the patient's best interests. I suggest the committee needs to clarify the point 'there is no structural damage to the central fovea'. How are we to interpret this? The majority of patients by the fact they are suffering with Wet ARMD will have some structural damage to the fovea!</p> <p>The recommendation that beyond 14 injections the cost of treatment should be met by the manufacturer is certainly an innovative way of limiting NHS funds to essential treatments. I would support this recommendation but have reservations as to how this will be implemented nationally.</p> <p>It would require very prescriptive rules as to how the funding will be released to the NHS should the patient require greater number of treatments. I wouldn't want to see a case where the patient was delayed from receiving treatment because NHS and manufactures were in dispute over the funding.</p> <p>Also, what would be the time delay from last NHS injection to the time of requiring further treatment? We could have a scenario that a patient having received 14 injections in the first</p>	<p>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 document (see also comments from the Royal College of Ophthalmologists above).</p> <p>Comments noted. The Committee discussed a scheme suggested by the manufacturer in which the number of injections paid for by the NHS could be capped, with any remaining injections paid for by the manufacturer. It estimated that ranibizumab was likely to be cost effective if the cost of treatment to the NHS was limited to 14 injections per eye. See FAD sections 1.1, 1.2, 4.3.22, 4.3.25 and 4.3.26.</p> <p>The Committee noted that there could be a long gap between one dose and the need for the next dose and</p>

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Nominated patient expert 1		<p>24mths then had a recurrence at 30mths and needed additional treatment. Would this be classed as a new course of treatment or failure of existing course?</p> <p>I note that the committee is not recommending Pegaptanib for patients with ARMD, I would like to suggest that they give the retinal experts the flexibility of offering this treatment to the patients for whom Lucentis may not be an option by making a recommendation in the final guidance that in these circumstances Pegaptanib can be offered on the NHS.</p> <p>I would like to conclude my comments by urging the NICE appraisal team to recommend that anti-VegF treatment be made available on NHS for all Wet AMD patients as a matter of urgency.</p> <p>We are already experiencing local providers delaying funding decisions on the premise that they are awaiting NICE recommendations! We currently have at least 7 PCT's in our locality and surrounding area all with different 'interim' recommendations which is totally an unmanageable and unethical situation for both clinicians and patients.</p>	<p>concluded that in this situation treatment should be considered as continuous regardless of whether a patient had been discharged from a clinic between doses (see FAD section 4.3.26).</p> <p>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).</p> <p>Comments noted.</p>
WAG		<p>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 would like to make the following questions/points in response to the consultation.</p>	

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		<p>We very much welcome the Appraisal Committee's decision to remove the recommendation relating to the treatment of wet AMD for the second eye only. We agree with the Committee's statement at paragraph 4.3.17 that if treatment was given to the second eye only, then this could result in a lost opportunity to preserve vision in the first-presenting eye, and that the second eye could be affected by an untreatable cause of visual loss or might not respond to anti-VEGs.</p>	<p>Comments noted.</p>
<p>WAG</p>		<p>We are not convinced by the reasoning for basing costs upon delivery of treatment on the basis of 75% day case and 25% outpatient treatment modules (paragraph 4.3.1.6). The costs are based upon 24 injections of ranibizumab over two years and this might (as is acknowledged in the ACD) be an overestimate. Therefore, costs of ranibizumab 12 injections per year over two years = £18300 per patient, whereas 8 injections in year 1 and 6 in year two = £10700 per patient would appear to be more appropriate.</p>	<p>The Committee discussed the assumptions in the models for the costs of administering intravitreal injections and concluded that a reasonable approach would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an outpatient appointment (see FAD section 4.3.17). The analysis by the Assessment Group incorporating this assumption varies the administration cost in line with the number of injections assumed in each scenario without reducing the assumed frequency of monitoring costs (see FAD section 4.2.4.7).</p>
<p>WAG</p>		<p>There appears to be some ambivalence and unsupported evidence as to what happens to the visual state and visual acuity if treatment is stopped after two years. We do not believe this necessitates any research commissioned in this area, and is more a case of collating the data. Further analysis would be required to address the comments made in paragraph 4.3.8 as to the numbers of patients who experience rapid deterioration in vision after cessation of treatment.</p>	<p>Comments noted. See FAD sections 4.3.13 and 6.1).</p>

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WAG		We agree with the proposed recommendations (paragraph 6.1), especially the need to consider the cost effectiveness of ranibizumab compared with bevacizumab (avastin). This again raises the issue of undertaking trials in this area to compare not just the cost effectiveness but also the outcomes in terms of visual gain in acuity and safety, including potential side effects.	Comments noted.
WAG		Whilst the preliminary recommendations in paragraph 1.2 are noted, from the RCT results given in paragraph 4.3.3, it follows from the recommendation under 1.3 that further evaluation of the results of treatment with pegaptanib should be ongoing.	Comments noted.
WAG		<p>We note the Department of Health's concerns about the recommendation for the manufacturer to pay the cost after 14 injections, as they consider that this might increase the administrative burden on to the NHS. We would be interested to learn what safeguards are proposed with regard to continuing funding of treatment, beyond the 14 injections if considered to be clinically necessary, as this suggestion was made by the manufacturer.</p> <p>We consider a review of guidance on the technology in December 2010 to be appropriate.</p>	<p>Further documentation related to the scheme will be made available.</p> <p>Comments noted.</p>
NHSIQS		<p>I welcome the recommendations issued in December 2007.</p> <p>The Committee has thoroughly considered the clinical effectiveness and made the most reasonable and sensible conclusions for which I congratulate them. Many of the concerns of the previous consultation have been addressed, particularly that it is recommended for first eyes with wet AMD. The effectiveness of Ranibizumab is undisputed and the</p>	Comments noted

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		<p>agreement that the manufacturer will meet the cost of treatments beyond 14 injections is welcome.</p> <p>I have only relatively minor concerns and list them below.</p> <ol style="list-style-type: none"> 1. There is a need to limit treatment to those who will benefit most. I am concerned that treatment will be limited to patients with a best corrected visual acuity better than 6/60 and that there is no level of defined visual loss before commencement of treatment. The trials included best-corrected visual acuity between 6/12 and 6/96 and it would be reasonable to follow this criterion. Many patients with a visual acuity of 6/60 would benefit, and many with occult CNV with good acuities remain stable for long periods and some resolve spontaneously. It is rare for subfoveal CNV to have good vision and I would therefore advise treatment being limited to patients with a degree of defined visual loss e.g. visual loss of between 6/12 and 6/90. 2. The criterion of 'no permanent structural damage' needs to be clearly defined. It is almost impossible not to have some degree of structural damage in AMD. I think what is essentially meant by this criterion is that patients with significant subretinal fibrosis (implying CNV which has progressed to fibrosis and which is therefore fairly long standing) should not be treated. This should be clearly stated. 3. In considering clinical effectiveness Ranibizumab is clearly the drug of choice and is the preferred agent in comparison with pegaptanib. I agree that Pegaptanib 	<p>The FAD has been amended – see sections 1.1, 1.2, 4.3.25 and 4.3.26.</p> <p>Comments noted. The Committee discussed criteria for starting and discontinuing therapy (see FAD section 4.3.25 and 4.3.26, and sections 1.1 and 1.2). 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 above).</p> <p>Comment noted.</p>

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		<p>should not be recommended.</p> <p>4. 1.3 deals with patients currently receiving pegaptanib. Such patients should have the opportunity to convert to ranibizumab particularly for 2nd eye involvement.</p> <p>5. The cost analysis based on 14 injections over 2 years is reasonable. This will provide treatment for at least 2 years. The manufacturer's offer to pay for injections beyond 14 treatments may prove difficult to administer and requires further clarity. The comments regarding additional costs (para 4.3.21) for such additional treatments are appropriate</p> <p>6. The non drug costs (i.e. the costs of administration and monitoring) are still overestimated in my opinion. There should encouragement to establish the procedure as an Outpatient procedure (75% day case is far too high)</p> <p>7. Proposed recommendations for Research – assessment of the cost effectiveness of ranibizumab compared to bevacizumab and the long term effects of anti-VEGF therapy are the most pressing research needs. There is also a need to identify which subtypes of occult respond best. We recognise different types of occult CNV e.g. retinal 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.</p>	<p>Comment noted.</p> <p>Comments noted. Further documentation related to the scheme will be made available.</p> <p>Comment noted. The Committee discussed the assumptions in the models for the costs of administering intravitreal injections and concluded that a reasonable approach would be to assume 75% of the procedures at the cost of a day case and 25% at the cost of an outpatient appointment (see FAD section 4.3.17).</p> <p>Comments noted. The guidance on this technology will be considered for review in April 2011 (see section 8.2).</p>

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		<p>Basically all the pertinent points I feel worthy of mention are included in the response of the RCOphth. There is only one other very important point relevant to Scotland which is, our course, that the SMC have approved Macugen and so clinicians in Scotland do retain some autonomy regarding the selection of what they feel is the best drug to use for any individual patients. When NICE issued their FAD, it will be interesting to see if they do eventually approve Macugen use in principle as well as Lucentis after considering all the responses from the consultees.</p> <p>Reviewer 1.</p> <p>i) Whether you consider that all the relevant evidence has been taken into account. <i>The summaries relate to the evidence provided</i></p> <p>ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.. <i>I consider that the summaries interpret the evidence provided succinctly</i></p> <p>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>The recommendations on use or not use are sound based on the evidence – however the recommendation regarding the</i></p>	<p>Comment noted. The Committee concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD sections 1.3, 4.3.23 and 4.3.24).</p> <p>Comment noted.</p> <p>Comments noted.</p>

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		<p><i>dose-capping scheme will require further discussion between SGHD and NHS QIS.</i></p> <p>iv) Whether you consider that there are any potential policy implications for SGHD? <i>Yes – the dose capping scheme will need to be considered in the context of the policy on alternative pricing schemes which is being developed.</i></p>	
DHSSPSNI		<p>Most of the recommendations in the ACD are eminently sensible. It has taken a broad view of the ICER for both treatments given under different scenarios. The conclusion that there should be no restriction to second eyes only or by lesion type is to be welcomed. The recommended restrictions ie. by visual acuity cut off , lesion size and foveal architectural disruption are sensible. I am not entirely happy with te ACD’s decision in limiting therapy to Ranibizumab only for the following reasons</p> <ol style="list-style-type: none"> 1. Pegaptanib may be useful in patients who are unwilling or unable to return for monthly assessments 2. Pegaptanib may be safer in patients with a very strong history of cardiovascular disease 	<p>Comments noted.</p> <p>The Committee discussed the licensed dosing regimen for ranibizumab (which allows for injections less frequently than monthly. The Committee concluded that there was some uncertainty about the frequency of injections that would be required to achieve the results seen in the MARINA and ANCHOR studies (see FAD section 4.3.4).</p> <p>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</p>

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
			concluded that treatment with pegaptanib was not a cost effective use of NHS resources (see FAD section 4.3.24).
RNIB and Macular Disease Society		<p>1. In this document RNIB and the Macular Disease Society respond jointly to the Appraisal Consultation Document (ACD) sent out on 7 December 2007 to stakeholders participating in the appraisal of pegaptanib and ranibizumab.</p> <p>2. We welcome the second ACD issued by NICE on the use of pegaptanib and ranibizumab. We are pleased that the responses received to the first ACD from patients, their families and carers and those from the formal consultees have led the Appraisal Committee to amend the initial recommendations.</p> <p>3. The recommendations made in the second ACD are good for most patients. However, we believe that a number of changes and additions are required to ensure that the Final Guidance will fully meet the needs of the 26,000 people a year who are newly diagnosed with wet AMD. In our response we are calling for:</p> <ul style="list-style-type: none"> 3.1. The approval of pegaptanib as second-line treatment 3.2. A lower treatment threshold with patients being treated in line with the recommendations of the Royal College of Ophthalmologists 3.3. Clarification of the dose capping scheme 3.4. The FAD to be issued quickly 3.5. The speedy implementation of NICE's guidance and greater efforts by NICE's implementation unit to monitor and enforce the implementation deadline. 3.6. Guidelines regarding fast track referral from optometrists/GP to treatment centre. 	Comments noted. See below for responses to specific comments.

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RNIB and Macular Disease Society		<p>The decision not to recommend the approval of pegaptanib</p> <p>4. We continue to believe that clinicians and their patients should have the option to choose what treatment is in the patient's best interest. For some patients with wet AMD, a selective VEGF inhibitor may be more appropriate, which would make pegaptanib the preferred treatment option. As we have pointed out previously, in reality most patients will be given ranibizumab. Nonetheless a decision to give pegaptanib on medical grounds should remain a possibility.</p>	<p>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 cost-effective use of NHS resources (see FAD sections 4.3.8 to 4.3.24).</p>
RNIB and Macular Disease Society		<p>The treatment threshold</p> <p>5. Throughout the ACD a visual acuity of 6/60 is equated with the threshold for legal blindness in the UK. Most significantly the fact that 6/60 is presumed to be the threshold for legal blindness is used as a justification to set the eligibility threshold for treatment at better than 6/60 (effectively 6/48).</p> <p>6. 6/60 is in fact the threshold for being registered as partially sighted, not blind. The threshold for being registered as blind is 3/60. We believe that the false assumption that 6/60 is the threshold for legal blindness has confused the committee's thinking. We would like to remind NICE that the eligibility threshold for PDT is 6/60 or better, that the</p>	<p>The FAD has since been amended. See FAD sections 1.1 and 4.3.25.</p> <p>The FAD has been amended.</p>

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		<p>Scottish Medicines Consortium has set no eligibility threshold for ranibizumab and a threshold of 6/60 or better for pegaptanib. Significantly, the Royal College of Ophthalmologists recommends that treatment should be considered until a patient's visual acuity falls persistently below 6/96 (or logMar 1.2).</p> <p>7. We hope that with growing awareness of the availability of treatment for wet AMD, increasing numbers of patients will be diagnosed at a relatively high level of visual acuity. However, at present many patients only present with their second eye once they have significant vision loss. Given the chance of improvement in vision through treatment with ranibizumab, these patients should be allowed to access treatment on the NHS. We support the Royal College position and urge NICE to revise its eligibility criteria accordingly.</p>	
RNIB and Macular Disease Society		<p>Clarification of dose-capping scheme</p> <p>8. We note that discussions between the distributors of ranibizumab and NICE have led to the proposal of a dose capping scheme which will place the financial burden for treatment on the pharmaceutical company after 14 injections. We would want the terms of this scheme to be clear and to be confident that patients who require continuing treatment will receive it for as long as they are likely to benefit.</p> <p>9. Similar considerations would need to apply if there was a decision to approve pegaptanib based on cost sharing.</p>	<p>Comments noted. Further documentation related to the scheme will be made available.</p> <p>Comment noted.</p>
RNIB and Macular Disease Society		<p>Speedy adoption of FAD</p> <p>10. We urge NICE to issue the FAD for this appraisal as quickly as possible. By the time the Appraisal Committee</p>	Noted

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		<p>meets again on 13 February 2008 it will have been two years since the draft scope for the appraisal was issued. Because of the delays that occurred throughout the decision-making process hundreds of people will have lost their sight unnecessarily. By issuing Guidance quickly, NICE can ensure that we do not have to add hundreds more to that list.</p>	
<p>RNIB and Macular Disease Society</p>		<p>Implementation</p> <p>11. We believe strongly that the usual three-month period for the implementation of guidance on pegaptanib and ranibizumab should apply. There is no justification for extending this period. Anti-VEGF treatments are being delivered at a large number of centres across England and Wales and as new patients come forward, capacity can be expanded. Experience from the implementation of final guidance on PDT for wet AMD shows clearly that if PCTs and Local Health Boards are given extra time, many will simply delay doing anything for as long as possible. A longer implementation period removes any sense of urgency from their internal decision-making and will again result in unnecessary sight loss.</p> <p>12. Finally, we would strongly urge the NICE Implementation Unit to work with PCTs and Local Health Boards to ensure that they meet the three month implementation deadline. Since NICE decisions are mandatory NICE itself should take a more active role to ensure the timely implementation of its guidance. As patient organisations we will continue our advocacy work to help patients access treatment and this will include work with PCTs, Local Health Boards and Hospital Trusts. However, we feel that a clear lead from NICE regarding the</p>	<p>Comments noted. For further details regarding directions from the Secretary of State on the funding of NICE Technology Appraisal Guidance, see http://www.dh.gov.uk/en/Publicationsandstatistics/Legislation/Directionsfromheseecretaryofstate/DH_4075685</p>

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		<p>implementation of its guidance would increase the likelihood that PCTs, Local Health Boards and Hospital Trusts will work together to increase treatment capacity and meet the implementation deadline.</p> <p>Guidelines regarding fast track referral from optometrists/GP to treatment centre.</p> <p>13. In the guidance on photodynamic therapy for wet age-related macular degeneration (TA68 issued on 24 September 2003) NICE included the following paragraph about fast-track referrals:</p> <p>"Wet ARMD can progress rapidly. For a PDT service to be as effective as possible, individuals with early wet ARMD and without serious loss of vision will need to be fast-tracked through the referral and waiting list processes in order to receive treatment before further loss of vision occurs." (p. 15).</p> <p>14. The importance of rapid referral applies irrespective of the treatment provided. We would therefore like to see the this reference included in the FAD on ranibizumab and pegaptanib.</p> <p>Final remarks</p> <p>15. RNIB and the Macular Disease Society have pooled resources to make joint submissions to the NICE appraisal of pegaptanib and ranibizumab. We have been committed stakeholders promoting the interests of the patients we represent. The process has taken longer than expected but we are pleased that we have come this far and can see a positive outcome for the great majority of patients with wet AMD.</p>	<p>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.</p> <p>Comments noted.</p>

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		16. We very much hope that the NICE Appraisal Committee will listen again and will make the final changes outlined above to bring this process to a satisfactory conclusion.	
RCN		<p>The RCN welcomes the opportunity to review and comment on the report of the additional analyses and Decision Support Unit for the technology appraisal of Pegaptanib and Ranibizumab for the treatment of age-related macular degeneration.</p> <p>RCN Response</p> <p>We were pleased to note that there has been a positive change in the overall recommendations which will result in greater number of patients suffering from this visually devastating condition getting NHS funded treatment.</p> <p>We commend the Appraisal Committee for taking into account, not only the research evidence base but also the comments from consultees in drawing up the recommendations in the second appraisal consultation document.</p> <p>Despite the change, we still feel, that treatment should not be restricted to just patients with best corrected vision equal to or better than 6/60. As to do so will restrict access for a number of patients, that the evidence base clearly shows benefit in visual and thus improved quality of life outcome if they receive anti-Vegf treatment.</p> <p>It must be noted that objective measurement of visual acuity in the clinical area is only one way of assessing a patient's</p>	<p>Comments noted.</p> <p>The FAD has been amended (see sections 1.1 and 4.3.25).</p>

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		<p>suitability for treatment and can be variable depending on a number of issues that are not always predictable i.e.- patient compliance, anxiety due to stressful situations etc. We understand the need to set a visual limit, but strongly advise that the threshold be reduced. The clinician can then have greater power to decide whether or not individual patients' retina is amenable to treatment and judge whether or not that patient has a chance of benefiting from treatment.</p> <p>From clinical experience we would suggest that no retinal specialist will subject a patient to an interventional procedure unless they thought that it was in the patient's best interests.</p> <p>The Committee needs to clarify the point 'there is no structural damage to the central fovea'. How are we to interpret this? The majority of patients by the fact that they are suffering with Wet ARMD will have some structural damage to the fovea!</p> <p>The recommendation that beyond 14 injections the cost of treatment should be met by the manufacturer is certainly an innovative way of limiting NHS funds to essential treatments. We would support this recommendation but have reservations as to how this will be implemented nationally.</p> <p>It would require very prescriptive rules as to how the funding will</p>	<p>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 document (see also comments from the Royal College of Ophthalmologists above).</p> <p>Comments noted. The Committee discussed a scheme suggested by the manufacturer in which the number of injections paid for by the NHS could be capped, with any remaining injections paid for by the manufacturer. It estimated that ranibizumab was likely to be cost</p>

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		<p>be released to the NHS should the patient require greater number of treatments. We would not want to see a case where the patient was delayed from receiving treatment because NHS and manufactures were in dispute over the funding.</p> <p>Also, what would be the time delay from last NHS injection to the time of requiring further treatment? We could have a scenario that a patient having received 14 injections in the first 24mths then had a recurrence at 30mths and needed additional treatment. Would this be classed as a new course of treatment or failure of existing course?</p> <p>We note that the Committee is not recommending Pegaptanib for patients with ARMD, we would like to suggest that they give the retinal experts the flexibility of offering this treatment to the patients for whom Lucentis may not be an option by making a recommendation in the final guidance that in these circumstances Pegaptanib can be offered on the NHS.</p>	<p>effective if the cost of treatment to the NHS was limited to 14 injections per eye. See FAD sections 1.1, 1.2, 4.3.22, 4.3.25 and 4.3.26.</p> <p>The Committee noted that there could be a long gap between one dose and the need for the next dose and concluded that in this situation treatment should be considered as continuous regardless of whether a patient had been discharged from a clinic between doses (see FAD section 4.3.26).</p> <p>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).</p>
RCN		<p>Conclusion</p> <p>Finally, we would urge the NICE Appraisal Committee to consider the recommendation that anti-VegF treatment be made available on NHS for all Wet AMD patients as a matter of urgency.</p> <p>We consider that limiting the guidance to Lucentis could be problematic in some cases and that ophthalmologists should be</p>	Comments noted

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		<p>allowed to choose the best health technology appropriate for the individual patient.</p> <p>We are already experiencing difficulties with some local providers delaying funding decisions on the premise that they are awaiting NICE recommendations! We are aware of many PCTs with different 'interim' recommendations. This is totally an unmanageable and unethical situation for both clinicians and patients</p>	
<p>Nominated Clinical Specialist 2</p>		<p>Thank you for circulating the second ACD dated December 2007 for the above Health Technology Appraisal and for asking for my comments.</p> <p>I believe that all the relevant evidence has been taken into account in the preparation of this ACD and that the summaries of clinical and cost effectiveness evidence are reasonable.</p> <p>I believe that the recommendations of the Appraisal Committee are sound and do constitute a reasonable basis for the preparation of guidance to the NHS.</p> <p>I believe that there are some additional recommendations that I have previously listed that would greatly benefit patients and the NHS:</p> <ol style="list-style-type: none"> 1. Pegaptanib should be available for the treatment of patients in whom ranibizumab is clinically problematic. In the experience of St. Paul's Eye Unit a small but significant number of patients have problems attending every 4 weeks and in these cases the option to treat with pegaptanib would be beneficial. 	<p>Comments noted</p> <p>The Committee discussed the licensed dosing regimen for ranibizumab (which allows for injections less frequently than monthly. The Committee concluded that there was some uncertainty about the frequency of injections that would be required to achieve the results seen in the MARINA and ANCHOR studies (see FAD section 4.3.4). The Committee considered the</p>

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		<p>2. Treatment should be delivered in dedicated facilities by experts in the management of macular disease supported by ETDRS vision assessment, optical coherence tomography and stereoscopic angiography. This would reduce the risk of patients with inactive disease or no neovascularisation receiving treatment based on inadequate assessment or competence.</p> <p>3. Robust data should be collected on adverse events and outcomes in routine clinical practice. The evidence on safety is limited to phase 3 randomised clinical trials not designed to detect uncommon or rare adverse events. Patients with ischaemic cardiovascular disease were excluded from these RCTs.</p>	<p>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).</p> <p>Comment noted. 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.</p> <p>Comments noted. See FAD section 6.1.</p>