NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Novartis	**<u>Has all of the relevant evidence been taken into account?</u>** Novartis do not feel all the relevant evidence has been taken into account, on three grounds: a) Relevant data on the proportion of patients receiving treatment in the better-seeing, worse-seeing and same seeing eye have not been taken into account. In Section A, we set out alternative scenarios for the cost effectiveness of ranibizumab which take into account the impact of patients requiring bilateral treatment. We believe this evidence would have been helpful to the Appraisal Committee's (the Committee's) deliberations in preparation of this ACD and should be considered by the Committee. These scenario analyses clearly demonstrate that the ICERs for the full DMO population discussed in the ACD are likely to be overestimated. This evidence was not submitted as part of its initial submission for rapid review as Novartis had been advised by NICE that the rapid review process is designed to consider the implications of incorporating a PAS within the parameters of existing analyses and that Novartis was not in a position to present new analyses that relied on substantial alterations to the executable model. During a meeting with NICE on 25 January 2012, Novartis was advised against providing new evidence or analyses and, according to NICE, failure by Novartis to comply with such advice could result in rejection of its submission for rapid review. Accordingly, and in line with advice from NICE, Novartis relied on the description of the Committee's considerations in the TAG for direction as to what changes to the economic model would be acceptable within the rapid review process. As noted by the TA237 Committee at its meeting on 4th September 2012, the analysis of the Evidence Review Group (ERG) had gone further than the rapid review process appears to allow, specifically with respect to the modeling of bilateral treatment. Had Novartis been allowed, we would also have welcomed the opportunity to provide additional analysis as detailed as that submitted by the ERG. In order to address this, Novartis have had only one opportunity (during this consultation phase as agreed with the NICE project team) to submit a revised analysis for consideration.	The Committee discussed the manufacturer's approach to estimating the proportion of people who would be treated in the better-seeing eye only, worse-seeing eye only or both eyes. The Committee noted that, as part of these 3 new analyses, the manufacturer presented data on the proportion of patients in RESTORE whom the manufacturer considered as having the same vision in both eyes at the start of treatment. See FAD section 4.16.

Consultee	Comment	Response
Novartis	b) Available evidence suggests there are poorer longer-term outcomes associated with laser photocoagulation (laser) than is inferred in the ACD (ACD, Section 4.18 & 4.21). As clinical experts suggested laser may be more beneficial over time, the ACD concludes that the ICER could be higher than that estimated by the ERG (eg, £27,999+ for scenario 3) and likely to be over the £30,000/QALY threshold. However, evidence presented in section B [Not shown here] refutes the grounds for suggesting the ICER may be higher. c) The impact that the PAS has on use of NHS resources wider than the specific indication of DMO has not been taken into account (ACD, Section 3.45). The Committee's consideration of the significant cost savings arising from the PAS when applied across all existing ranibizumab indications does not appear to have been taken into account in the ACD. We note at paragraph 6.2.13 of the Guide to the Methods of Technology Appraisal June 2008 (the Guide) that: '*The Institute is asked to take account of the overall resources available to the NHS when determining cost effectiveness*.' Further, paragraph 6.2.14 of the Guide provides that: *'... The Committee does take account of how its advice may enable the more efficient use of available healthcare resources..."* We therefore urge the Committee to reconsider the evidence for ranibizumab for the treatment of DMO in light of the significant, positive impact on NHS resources associated with all current and future indications including w-AMD. This is an important feature of the technology in this appraisal that is not captured directly in the cost-effectiveness assessment for DMO alone, and we therefore urge the Committee to reconsider its conclusions at paragraph 4.25 of the ACD in light of this	The Committee also noted that this approach was consistent with previous appraisals. The Committee was aware of the new clinical evidence submitted by consultees in their response to the rapid review appraisal consultation document. The Committee understood that the consideration of such new clinical evidence on the long-term clinical benefits of the comparator treatment laser photocoagulation is beyond the remit of a rapid review, and would require a full review of the appraisal. Therefore the Committee concluded that, although significant uncertainty remains about the long-term benefit of ranibizumab treatment, compared with the manufacturer's original submission, the rapid review model more accurately reflects the duration of benefit that could be expected from treatment with ranibizumab. See FAD section 4.19. In line with the Guide to the Methods of Technology Appraisal June 2008 (section 6.2.14) the potential cost impact of the adoption of a new technology does not determine the Committee's decision. The decision problem that the Committee was faced with was assessing the clinical and cost effectiveness of ranibizumab for diabetic macular oedema and not all indications of ranibizumab.

Consultee	Comment	Response
Novartis	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Novartis do not feel the summary of clinical and cost-effectiveness for the whole DMO patient population considered in the ACD is a reasonable interpretation of the evidence. The main reasons are as follows: a) Non-reference case utility values have been used to influence interpretation of the evidence. Utility values which were derived outside of the NICE Reference Case have greatly influenced the Committee's conclusions regarding the cost effectiveness of ranibizumab (Brown 1999). We expand upon our concerns regarding analyses that do not meet the NICE Reference Case in Section C [Not shown here]. b) The glycaemic characteristics of patients in the RESTORE study are generalisable to clinical practice. We remain concerned with the Committee's conclusion about the implications of the generalisability of the RESTORE study population to patients likely to be seen in routine NHS practice, with respect to glycaemic control. The basis of our concerns are set out in Section D [Not shown here]. c) There is an invalid assessment of the innovation potential of ranibizumab. We also remain concerned about the Committee's interpretation of the evidence with regards to the innovative nature of ranibizumab for the treatment of DMO (further details can be found in Section E [Not shown here]).	At its second committee meeting, the Appraisal Committee gave further consideration to these issues. See FAD sections 4.17, 4.21 and 4.26.

Consultee	Comment	Response
Novartis	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Novartis do not believe this to be the case. The provisional guidance fails to recommend ranibizumab for all patients with DMO which does not fully take into account the evidence base. Furthermore, feedback from clinical experts suggests that the preliminary recommendation may be misinterpreted. We expand on our concern in section F [Not shown here].	The guidance statement in the FAD states that: Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if: • the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and** • the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). See FAD section 1.1
Royal College of Ophthalmologists	**Has all of the relevant evidence been taken into account?** The RESTORE study and the DRCR.net study both use a PRN protocol which is the most appropriate treatment regimen. As mentioned above, month 36 results from DRCR.net study have been published since the rapid review process. As these results provide the longest follow-up data for DMO patients treated with ranibizumab, their relevance is significant.	The Committee was aware that additional clinical data, including 3-year results from the DRCR.net study, had become available since the publication of NICE technology appraisal guidance 237, but that these data could not be considered as part of the rapid review process. See FAD section 4.27.

Consultee	Comment	Response
Royal College of Ophthalmologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Appropriate modelling using the available data on treatment outcomes and subgroup analyses were used. The use of two subgroups of CRT is appropriate as this has evidence base, is pragmatic and also differentiates patients in terms of treatment response in terms of mean change in vision. The method of modelling, however, does not take into account the ceiling effect in the subgroup with less oedema at baseline and better baseline acuities. The ceiling effect basically reduced the difference in treatment effect between ranibizumab and laser. When modelling is done based on the difference between the new technology and comparator in terms of change in health state from poor to better rather than maintenance of good health state, the advantage of treating early disease is not demonstrated well resulting in a worse ICER value when there is a ceiling effect. Early feedback from ophthalmologists indicates a strong desire to treat DMO earlier when vision is still good. Such treatment maintains vision, i.e. prevents any further vision loss. The impact of treating WSE was judged to be 30% only (scenario 3). For reasons given above, a higher impact may be more representative i.e. scenario 4. Changing this may help to justify cost effectiveness of treating an additional group of patients with DMO less than 400 microns in thickness.	The Committee noted that, although there is little evidence of the impact of vision in the worse-seeing eye on health-related quality of life, the Brown study suggested that among people who had good vision in their better-seeing eye, the worse-seeing-eye contributed little to health-related quality of life. The Committee therefore considered scenario analysis 3 to be consistent with previous appraisals, which suggested that changes in vision for people treated in their worse-seeing eye had 30% of the health-related quality of life impact of the same change in vision from treating the better-seeing eye. In response to the rapid review appraisal consultation document, the Royal College of Ophthalmologists commented that the ERG's approach seemed logical, but that scenario 4 might be more appropriate. However, in the absence of new empirical evidence to suggest otherwise, the Committee accepted that scenario 3 reasonably reflected the clinical situation for people with diabetic macular oedema. See FAD section 4.15.

Consultee	Comment	Response
Royal College of Ophthalmologists	**<u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>** It is acknowledged that original comments in 2011 by the RCOphth following the first ACD were mainly based on the subgroup with thicker retina of greater than 400 microns. This was based on the evidence that the greatest relative difference between ranibizumab and laser in visual outcome was seen in this subgroup of DMO patients. Following this second ACD, the College recently released a statement calling for more evidence to support the ranibizumab in patients with DMO less than 400 microns. Given the availability of new evidence in year 3 data from DRCR.net showing that in the deferred laser group, 54% of patients did not require any laser in the entire 3 year period and 86% did not require laser in the third year, there seems to be good supporting evidence to use ranibizumab as a first line therapy for patients with DMO less than 400 microns. Another argument for using ranibizumab to treat DMO of less than 400 microns thickness, is that the central retinal thickness reduced quickly in most patients in this group (75th centile thicknesses were 268-274microns) and continued to stay stable out to month 36. This suggests that in the long term there is unlikely to be any difference in recurrence of severe oedema and long term stability, or requirement for repeat injections whether the baseline thickness was greater or less than 400 microns. In further consideration of ranibizumab as first line therapy for patients with DMO of less than 400 microns, these patients tend to have better vision when the retina is not severely thickened. Given the new finding for the first time that deferring laser in 54% of patients results in better visual outcome for that group (p=0.02), it may be become increasingly difficult to justify using laser as initial therapy as laser may have a detrimental effect on visual acuity. The beneficial effect of laser on reducing number of injections, however, will also have to be borne in mind. Given these recent observations, it would be reasonable at this stage to produce recommendation which promotes some use of initial laser, but apply the DRCR.net criterion for laser failure early and switch to ranibizumab in these patients before central retinal thickness worsens to 400 microns.	The Committee was aware of the new clinical evidence submitted by consultees in their response to the rapid review appraisal consultation document. The Committee understood that the consideration of such new clinical evidence on the long-term clinical benefits of the comparator treatment laser photocoagulation is beyond the remit of a rapid review, and would require a full review of the appraisal. Therefore the Committee concluded that, although significant uncertainty remains about the long-term benefit of ranibizumab treatment, compared with the manufacturer's original submission, the rapid review model more accurately reflects the duration of benefit that could be expected from treatment with ranibizumab. See FAD section 4.19.

Consultee	Comment	Response
Diabetes UK	Diabetes UK agrees that the relevant evidence has been taken into account and therefore also with the preliminary recommendation of the rapid review (paragraphs 1.1 and 1.2); that ranibizumab will be available as a treatment option for visual impairment due to diabetic macular oedema (DMO) if the person has a central retinal thickness of 400 micrometers or more and the manufacturer provides ranibizumab at a discounted price as part of the Patient Access Scheme. The relevant evidence in terms of the importance of vision to people with DMO is partially acknowledged in paragraph 4.2; that visual impairment has a substantial negative impact on quality of life, the ability of the person to manage their own condition and on their emotional wellbeing. Further to this, the likely effect of the negative impact on patients' ability to self-manage their condition and the worsening of diabetic complications is described by Williams *et al*: "Visual impairment as a result of diabetic retinopathy has a significant impact on patients' quality of life, and can compromise their ability to manage successfully their disease, which in turn can have a negative impact on the incidence of other diabetic complications and overall life expectancy."(Ref 1) We note in paragraph 4.11 the Committee's acknowledgment that the manufacturer's revised subgroup analysis of central retinal thickness is based on a post-hoc analysis of the RESTORE trial but also that this analysis was provided in response to comments from clinical experts that laser photocoagulation may be less effective in thicker, more oedematous retinas. The Committee's acknowledgement in paragraph 4.22 of the clinical plausibility of 'a greater relative efficacy of ranibizumab in such people [CRT > 400µm], because it understood that laser photocoagulation may be less effective when used on a thicker retina' and the conclusion that it has received robust evidence demonstrating a subgroup effect in favour of people with thicker retinas are to be welcomed for people with DMO who are less likely to respond to laser photocoagulation. The provisional recommendations are therefore sound and a suitable basis for guidance to the NHS. As the Committee could not consider a comparison with bevacizumab (paragraph 4.24) the guidance offers consistent access to a subgroup of patients across England and Wales to an anti-vascular endothelial growth factor A drug. This is because, and as stated in paragraph 4.24, bevacizumab is not in routine use throughout the NHS. No issues of unlawful discrimination were recognised. 1) Williams *et al* (2004) Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye*, 18, 963-983.	Comments noted.

Consultee	Comment	Response
Association of British Clinical Diabetologists (ABCD) and the Royal College of Physicians	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** As given, ABCD/RCP have some concerns around a blanket recommendation to use ranibizumab in the treatment of diabetic macular oedema and would suggest some limitations are included. The committee commented on the lack of clarity surrounding the effectiveness of treatment in those with poor glycaemic control. That treatment may not be as effective in those with high blood glucose levels can be inferred from the higher ICERs in those with an HbA1c greater than 64mmol/mol (8%). Although RESPOND included patients with an HbA1c up to 10% and RESOLVE up to 12%, the data as published seems to suggest that most patients included were very well controlled. As commented by the committee, this may not be typical of those selected for treatment in clinical practice. The trial data do not comment in any detail on blood pressure control. This is an expensive treatment. While ABCD/RCP would not like to deprive individuals of what will be a valuable treatment, it would seem reasonable to suggest that nobody should receive this treatment unless they have been adequately assessed and treated by a specialist physician to optimise their risk factors prior to treatment.	Comments noted.

Consultee	Comment	Response
Royal National Institute of Blind People	We are delighted that NICE has issued positive draft guidance recommending Lucentis for the treatment of Diabetic Macular Oedema (DMO) in patients with a central retinal thickness of 400 micrometres or more. RNIB is also pleased that it states patients currently receiving Lucentis who do not have a central retinal thickness of 400 micrometres will be able to continue treatment until they and their clinician consider it appropriate to stop. We remain concerned, however, that patients with a central retinal thickness of less than 400 micrometres will not be able to access Lucentis for DMO. Clinicians tell us that there will be situations where standard care is not appropriate for patients in this group and that Lucentis would provide an alternative treatment option. Overall the decision is a step in the right direction and a decision that we hope will eventually be extended to reach all patients with DMO. **Has all of the relevant evidence been taken into account?** RNIB is not aware of any new evidence. We welcome the fact that the Committee recognises the substantial negative impact DMO has on quality of life, especially in relation to loss of independence and employment. We are also pleased that the Committee acknowledges that diabetes is managed with self-care and that visual impairment can affect a person's ability to manage their own condition. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We are not aware of any discrimination caused by NICE's draft recommendations.	The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisals Service	• We are in agreement with the recommendation in the ACD to recommend ranibizumab for this indication only if the person has a central retinal thickness of 400 micrometres or more and the manufacturer provides ranibizumab with the discount agreed as part of the patient access scheme (as revised in 2012). On the basis of the evidence considered it is likely that this treatment can be considered clinically and cost effective in real life clinical practice. • Ranibizumab gave the greatest improvement in people with thicker retinas and more severe visual impairment at baseline. In one large trial (RESTORE), gains in BCVA with ranibizumab were greatest in the subgroup of people with central foveal thickness greater than 300 micrometres. • Ranibizumab improves visual acuity compared to laser photocoagulation alone, but there is no additional benefit of adding laser to ranibizumab. The two larger of four trials (RESTORE and DRCR.net) found that, for the whole treatment population, ranibizumab improved BCVA over 2 years, but there was no evidence for a benefit in adding laser to ranibizumab. • Uncertainties remain over whether the trial data is relevant to the eligible UK population. There were uncertainties over whether the glycaemic control and use of laser photocoagulation in the trials accurately reflected what would be seen in UK clinical practice. • Ranibizumab could be considered a cost effective use of NHS resources in the subgroup of people with thicker retinas. The ICER when accounting for treatment in both eyes had been estimated at between £27,999 and £36,089 per QALY depending on the utility values used, but the Committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be below £25,000 per QALY. • The manufacturer's revised model used more plausible assumptions than those used in the economic model submitted for TA237. The manufacturer's revised model produced an ICER of £13,322 per QALY for treating both eyes in people with thicker retinas. This ICER would be likely to increase depending on characteristics of the treatment population but it still expected to be below £25,000 per QALY.	Comments noted.

Commentator	Comment	Response
	• The manufacturer has agreed a patient access scheme. The scheme will make ranibizumab available with a discount, the details of which are commercial in confidence. • The Committee had no concerns regarding the safety of ranibizumab. The included studies have not assessed safety outcomes, but found no difference in the rate of adverse events. • Bevacizumab was not compared to ranibizumab. Bevacizumab was listed as a comparator in the scope but the manufacturer did not compare clinical effectiveness despite the ERG noting that a recent head-to-head trial of ranibizumab and bevacizumab for age-related macular degeneration (CATT) showed equivalent efficacy between the two technologies. The committee agreed with the manufacturer that a cost effectiveness analysis was not possible as the costs associated with preparing and administering bevacizumab, (e.g. dose and number of injections required) was not readily available. The committee proposed that further research directly comparing the clinical and cost effectiveness of ranibizumab and bevacizumab in people with DMO should be conducted.	
Department of Health	"My first comment concerns the simulated population used for the health economic modelling. The population has a mean age of 63 years. Whilst this is probably reflective of the population with diabetic maculopathy in general, I wonder whether there would be additional benefit in quality of life for younger individuals with the condition. Secondly, is there any differential benefit for people with type 1 or type 2 diabetes, or are the studies too small to detect any discernable differences? Thirdly, whilst no restriction is placed on the use of this agent in terms of HbA1c, I think it is important to point out that the HbA1c at the time of the decision to treat with this agent is of only modest value in determining whether an individual has good glycaemic control, as the development of retinopathy reflects glycaemic control over a very prolonged period".	Comments noted. No further clinical evidence was provided by the manufacturer in its rapid review submission in regard to these issues in line with the rapid review process.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	This guidance assumes that patients with significant macular oedema but less than 400 micrometres should be treated with laser. It therefore excludes a significant number of patients for who laser would be harmful because of the position close to the central retina at which the laser would need to be applied. It also makes no allowance for cases in which laser has failed and thickness is less than 400 micrometers.	The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.
NHS Professional	4	NICE needs to look at three year data of the large trials which indicates progressively diminishing requirement for injections in subsequent years. Patients who may benefit most are those with vision better than driving in order to maintain their ability to work. These patients are unlikely to be included in criteria that look solely at the OCT measurements.	The Committee was also aware that additional clinical data, including 3-year results from the DRCR.net study, had become available since the publication of NICE technology appraisal guidance 237, but that these data could not be considered as part of the rapid review process. See FAD section 4.27

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional	1	We cannot agree with the recommendations for the following reasons: (1) we are not convinced that true charges for activity have been taken into account to work out cost-effectiveness (2) size of population eligible for treatment under these criteria is not known (size can be affected by type of OCT machine used, if subgroups excluded from trials are treated - these are more likely to have complications and (3) comparison with bevacizumab has not been undertaken despite this being part of the scope, a large body of evidence supports the use of bevacizumab for this indication, there are comparative trials CATT and Ivan, comparing the two anti-VEGFs and RCO accept the clinical efficacy and safety of bevacizumab. Some NHS commissioners commission bevacizumab for unlicensed indications and for indications not approved by NICE. Therefore, there is use of bevacizumab in the NHS and a wider use privately.	The Committee discussed whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible. The Committee recognised that a formal comparison of the 2 drugs would need evidence not only of all aspects of clinical effectiveness and safety, but also of the costs associated with preparing and administering bevacizumab, including the dose and number of injections needed. The Committee agreed that such evidence, in particular about the balance of harms and benefits associated with bevacizumab, was not readily available for people with diabetic macular oedema. The Committee also noted that it was unaware of any evidence of the effectiveness of intravitreal bevacizumab compared with ranibizumab in the subgroup of patients with thicker retinas. The Committee agreed that, taking into account all these uncertainties, it could not consider a comparison of ranibizumab with bevacizumab. See FAD section 4.25.
NHS Professional	2	Without full scrutiny of the PAS scheme by NHS commissioner to ensure assumptions feeding into it are robust, we are not able to agree with the last 2 sentences in para 2.3	NICE considers it essential that patient access schemes can be received and considered in confidence. NICE also understands that manufacturers may experience commercial and other harm if information on the detail of proposed schemes were made publically available at this point. Therefore, NICE will treat all details of proposed schemes as confidential and will not release any information relating to it under the Freedom of Information Act or in any other circumstance, unless the manufacturer has agreed to the release.

Role*	Section	Comment	Response
NHS Professional	3	The key question here is the need to compare this technology to bevacizumab as per the scope of the TA. We agree with ERG views in para 3.19 and are aware of the Sheffield DSU being commissioned to undertake a comparison of the two anti-VEGFs for TA for RVO. The CATT and IVAN study also provide comparative evidence. We note that RCO also accept the efficacy and safety of bevacizumab in RVO. Without transparency in the PAS scheme, NHS commissioners are not able to assess the robustness of the scheme, and therefore, we cannot comment on the calculation of QALY. As commissioners we ask NICE to note that the procedure cost to the NHS is about £300 per eye and NOT £150. In clinical practice, the use of this product will not be limited to better-seeing eye, in patients with good glycaemic control etc. Also, 3-year data on ranibizumab in DMO (Diana V et al. Arch Ophthalmol.2012;(1-7.doi:10.1001/2013.jamaophthalmol.91) highlights many patients need on-going treatment to control oedema and to optimise VA. Therefore, we do not agree with reduction in number of injections estimated.	The Appraisal Committee gave further consideration as to whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible in its second meeting. See FAD section 4.25. NICE considers it essential that patient access schemes can be received and considered in confidence. NICE also understands that manufacturers may experience commercial and other harm if information on the detail of proposed schemes were made publically available at this point. Therefore, NICE will treat all details of proposed schemes as confidential and will not release any information relating to it under the Freedom of Information Act or in any other circumstance, unless the manufacturer has agreed to the release. The clinical specialists suggested that ranibizumab treatment would need an ophthalmologist and would be provided on an outpatient basis. See FAD section 4.6. The Committee for NICE technology appraisal guidance 237 concluded that the outpatient tariff of £150 per injection provided a fair estimate of reasonable costs. The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. See FAD section 4.18.

Role*	Section	Comment	Response
NHS Professional	4	We note that para 3.47 uses 7 injections in year 1, para 4.4 states 7-9 and states in clinical practice, patients with more advanced disease than clinical trials would be seen and these would require more frequent treatment and observation - therefore costs used in model will not apply to real practice; from funding requests we receive, we believe that the treatment will be used in combination with laser or in patients who have progressed on laser, in patients with poor glycaemic control and in both good and worse seeing eye. We agree with the committee that the generalisability of clinical trials to real life practice is uncertain and therefore, would expect to see more patients treated for longer.	The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. See FAD section 4.18.
NHS Professional	5	Our experience with use of ranibizumab for wet AMD suggests that this treatment will be needed more frequently in 2nd and 3rd year compared to what the manufacturer has modelled and for longer than 3 years. In practice, the NHS does not have resources to audit the use to be limited to patients with retinal thickness of 400 microns or more; limited to better seeing eye and use in patients with HBA1c <10. The NICE is urged to consider the implications to the NHS for recommending very restricted criteria.	The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. See FAD section 4.18.
NHS Professional	6	Following on from Ford et al paper in BMJ (doi:10.1136/bmj.e5182), we recommend that the NHS should support a larger study comparing ranibizumab with bevacizumab for this indication.	Comment noted.
NHS Professional	7	A MTA comparing anti-veGFs to steroids for DMO would be helpful.	Comment noted.

Role*	Section	Comment	Response
NHS Professional	1	Given the relative absence of detail regarding the PAS and the potential eligible population with DMO and a CRT of 400 micrometers, it is not possible to advise CCGs regarding the patient numbers and thus service capacity and cost issues. What is clear however is that there are not savings to be made through the recent changes to the NICE ARMD PAS and this TA will offer an additional treatment at significant additional service and drug cost therefore affordability cannot be concluded	NICE considers it essential that patient access schemes can be received and considered in confidence. NICE also understands that manufacturers may experience commercial and other harm if information on the detail of proposed schemes were made publically available at this point. Therefore, NICE will treat all details of proposed schemes as confidential and will not release any information relating to it under the Freedom of Information Act or in any other circumstance, unless the manufacturer has agreed to the release.

Role*	Section	Comment	Response
NHS Professional	3	There must be a comparison between bevacizumab & ranibizumab. Bevacizumab is a treatment option as per RCO statement for bevacizumab in medical retina therefore this appears to support the principle this is clinically effective and a valid comparator. It is noted that additional work was commissioned by DSU related to bevacizumab for RVO and it appears illogical that such an evaluation would not be considered for this indication. We acknowledge that ranibizumab can be administered in the out-patient setting pending clean room facilities, however, whilst we recognise that the model presented by the manufacturer demonstrates that it is feasibly possible to deliver this under the proposed £150 costs, we know that this is not reflective of the actual costs routinely the NHS incur when the drug is administered in this setting. Attendance costs vary but are of the order locally of £300, which is double that which the manufacturer has modelled. Section 3.30 "clinically plausible" treatment group, tests of statistical significance for 3 categories of CFT are done but the tests are not presented, why not? Differences in clinical outcome for the recommendation would be key.	The Appraisal Committee gave further consideration as to whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible in its second meeting. See FAD section 4.25. The clinical specialists suggested that ranibizumab treatment would need an ophthalmologist and would be provided on an outpatient basis. See FAD section 4.6. The Committee for NICE technology appraisal guidance 237 concluded that the outpatient tariff of £150 per injection provided a fair estimate of reasonable costs. For the rapid review, the manufacturer presented subgroup analyses based on central retinal (rather than foveal) thickness, arguing that this more reliably measures retinal thickness than central foveal thickness. The manufacturer acknowledged that the pattern of cost-effectiveness estimates for the 3 subgroups defined by central foveal thickness had been erratic, and may have been influenced by small sample sizes. Therefore, the manufacturer combined the 2 subgroups with lower values of central retinal thickness to create 2 subgroups (less than 400 micrometres and 400 micrometres or greater) of similar size. The manufacturer presented post hoc tests of the statistical significance of differences in clinical outcome according to baseline central retinal thickness, which suggested that laser photocoagulation was less effective in people with central retinal thickness of 400 micrometres or more ($p<0.01$) than in people with thicker retinas. See FAD section 3.49.

Role*	Section	Comment	Response
NHS Professional	4	Noted 4.4 clinical specialists are proposing 7-9 ranibizumab injections in the 1st year of treatment. This is likely to reflect true NHS clinical practice and proposes a greater number of injections than that modelled in the manufacturers submission, commissioners would seek clarification of the implications of the administration/costing uncertainty. We agree that outwith the clinical trial setting, it is likely that there will be greater variance in HbA1c within the whole DMO population and are concerned given uncertainty of the eligible population and subsequent overall cost/cost effectiveness. There remains concern regarding the clinical trial population with HbA1c < 10% versus the real DMO population who would could be eligible for treatment despite far worse diabetic control. The relative benefits/additional complications and its effect on the cost effectiveness analysis is uncertain and this is seen as an additional financial risk to commissioners.	The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. See FAD section 4.18. Based on the evidence provided in the manufacturer's original submission, the Committee agreed that uncertainty remained about the cost effectiveness of ranibizumab in people with poorer glycaemic control. Therefore, the Committee concluded that the manufacturer's model would probably generate a higher ICER if it was more reflective of the population seen in routine clinical practice. See FAD section 4.21.
NHS Professional	6	Absolutely agree that ranibizumab and bevacizumab should be directly compared, and consideration may be given to aflibercept in such analysis.	Comment noted.

Role*	Section	Comment	Response
NHS Professional	1	We are concerned that it is not possible for us to comment upon cost effectiveness when the cost details are redacted. We would prefer it to be made clear if treatment should be offered to both eyes or to the worse or best. 1.2 could include patients treated privately and greatly expand the number of patients treated. This PCT is likely to have to withdraw services from other areas to afford this treatment. We would want to see stopping criteria.	NICE considers it essential that patient access schemes can be received and considered in confidence. NICE also understands that manufacturers may experience commercial and other harm if information on the detail of proposed schemes were made publically available at this point. Therefore, NICE will treat all details of proposed schemes as confidential and will not release any information relating to it under the Freedom of Information Act or in any other circumstance, unless the manufacturer has agreed to the release.
NHS Professional	2	All PAS schemes impose administrative burdens, which are cumulative and should not be taken alone. A single PAS may be easy to deal with but having many require additional staff to deal with. We have seen no reason to believe that overfilling of a vial by 4x the amount required is necessary, this is not the case for other injectables. Adverse reactions are as expected.	The Department of Health considered that the patient access scheme for ranibizumab does not constitute an excessive administrative burden on the NHS. See FAD section 2.4.
NHS Professional	3	We agree with the ERG comments in this section. We would point out that patients will continue to be treated for a number of years beyond that in the evidence. We agree that scenarios 2 and 3 are the most likely. We believe that it remains uncertain if the patients reflect UK population. We are also concerned that there was no comparison with bevacizumab which is frequently used for this patient group. We believe that bevacizumab costs could have been obtained for use in analysis.	The Appraisal Committee gave further consideration as to whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible in its second meeting. See FAD section 4.25.
NHS Professional	4	We note that this is an additional treatment following laser and thus it imposes an additional financial burden on the NHS.	Comment noted.
NHS Professional	6	We concur and think this is of great importance.	Comment noted.

Role*	Section	Comment	Response
NHS Professional	1	Feedback from local consultant ophthalmologists indicate that the reference to central retinal thickness is too vague, and this needs to be defined. Local Gloucestershire consultant ophthalmologist is working with leading retinal experts to develop an algorithm for treatment based on a combination of retinal thickness and visual acuity. Use of ranibizumab in the treatment of DMO at this degree of retinal thickness is not best use of clinically effective resource, as at this stage of retinal thickness, vision is significantly compromised. The ICER when accounting for treatment in both eyes was estimated between £27,999 and £36,089 per QALY depending on the utility values used. However the committee concluded that the most plausible ICER for the subgroup of people with thicker retinas was likely to be below £25K per QALY.	The guidance statement in the FAD states that: Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if: • the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and** • the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). See FAD section 1.1

Role*	Section	Comment	Response
NHS Professional	3	Patient Access Schemes have been found to be problematic to administer by the NHS. This is further compounded when there is a commissioning and a provider organisation involved. The provider organisation is the organisation with the contract with the manufacturer and through contracting arrangements will pass the cost onto the commissioner. Why was the guidance for use in patients with central retina thickness of 400 micrometres, when RESTORE demonstrated improvement of BCVA was greatest in the sub group of patients with central retina thickness of 300 micrometres?	The Department of Health considered that the patient access scheme for ranibizumab does not constitute an excessive administrative burden on the NHS. See FAD section 2.4. For the rapid review, the manufacturer presented subgroup analyses based on central retinal (rather than foveal) thickness, arguing that this more reliably measures retinal thickness than central foveal thickness. The manufacturer acknowledged that the pattern of cost-effectiveness estimates for the 3 subgroups defined by central foveal thickness had been erratic, and may have been influenced by small sample sizes. Therefore, the manufacturer combined the 2 subgroups with lower values of central retinal thickness to create 2 subgroups (less than 400 micrometres and 400 micrometres or greater) of similar size. The manufacturer presented post hoc tests of the statistical significance of differences in clinical outcome according to baseline central retinal thickness, which suggested that laser photocoagulation was less effective in people with central retinal thickness of 400 micrometres or more ($p<0.01$) than in people with thicker retinas. See FAD section 3.49.

Role*	Section	Comment	Response
NHS Professional	4	Safety - The included studies have not assessed safety outcomes, but did not find any difference in the rate of adverse events. The manufacturer's revised model produced an ICER of £13,322 per QALY for treating both eyes in people with thicker retinas. This ICER would be likely to increase depending on characteristics of the treatment population but is still expected to be below £25K per QALY. There were uncertainties over whether the glycaemic control and use of laser photocoagulation in the trials accurately reflected what would be seen in UK clinical practice. It is noted that the proportion of better seeing eyes that were treated were not reported and designated as academic interest in confidence, by the manufacturer.	Comment noted.
NHS Professional	6	Bevacizumab was listed as a comparator in the scope but the manufacturer did not compare clinical effectiveness despite the ERG noting that a recent head to head trial of ranibizumab and bevacizumab for age-related macular degeneration (CATT) showed equivalent efficacy between the two technologies. The notion of undertaking a cost and clinical effectiveness comparison analysis in DMO should be conducted urgently. A positive outcome would significantly reduce the cost of treatment and resultant costs to the NHS and the public purse, thus releasing resource for use in other advanced technologies.	The Appraisal Committee gave further consideration as to whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible in its second meeting. See FAD section 4.25.

Role*	Section	Comment	Response
NHS Professional	1	1.1 Our internal audit shows that the 400micron cut off excludes treatment for between 70-80% of patients with centre involving DMO. The three yearDRCR.net study results show those with prompt laser have poorer visual outcomes compared with those in the deferred laser group. This cut off of 400 microns means that we will be giving laser treatment to patients and potentially giving them poorer long term outcomes. 1.2 Some patients have been started on bevacizumab as that is the drug the PCTs will fund. It would be appropriate to state that any patient who is currently on anti-VEGF treatment (bevacizumab or ranibizumab) for DMO for CRT>400 microns should be able to continue treatment with ranibizumab. This guidance does however exclude situations where laser is not possible or would worsen vision such as 1) macular ischaemia where laser would damage the foveal avascular zone, 2) leakage from microaneuryms at the fovea only, 3) cataracts preventing view for laser, 4) proliferative diabetic retinopathy where PRP can worsen maculopathy.	The Committee was aware that additional clinical data, including 3-year results from the DRCR.net study, had become available since the publication of NICE technology appraisal guidance 237, but that these data could not be considered as part of the rapid review process. The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.
NHS Professional	3	The only comment is that in real life our patients have much poorer diabetic control than in the trials, and may have concomitant proliferative retinopathy (an exclusion criteria in the trials) so the DRCR net finding of 9 injections in year 1 may be more realistic.	The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. See FAD section 4.18.

Role*	Section	Comment	Response
NHS Professional	5	This would be very helpful. I have already made a draft business case but it will need modification once the full guidance is given. I think it will be important to give clinicians a guide for expected numbers to treat, numbers of treatments and visits etc.	NICE Implementation will produce a costing template to estimate the financial cost and the health benefits of implementing the guidance.
NHS Professional	8	If the guidance is going to be so restrictive that only 20-30% of patients will be eligible for treatment the review should come sooner. As clinicians we are going to have a lot of difficult conversations with patients about why they can't receive treatment with ranibizumab. February 2015 would be a better date.	The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.
NHS Professional	3	Ranibizumab improves visual acuity compared to laser photocoagulation alone, but there is no additional benefit of adding laser to ranibizumab. The two larger of four trials (RESTORE and DRCR.net) found that, for the whole treatment population, ranibizumab improved BCVA over 2 years, but there was no evidence for a benefit in adding laser to ranibizumab.	Comment noted.
NHS Professional	4	We disagree with the Committee's opinion that bevacizumab should not be used as a comparator. There are several trials looking at bevacizumab in DMO. It is used within our local healthcare economy therefore is a relevant comparator for us. The cost-effectiveness compared to bevacizumab will depend on local discounts rather than the agreed PAS. This approach rewards high users of Lucentis and encourages out-of-NICE use. We also believe that fluocinolone and aflibercept are relevant comparators. Uncertainties remain over whether the trial data is relevant to the eligible UK population. There were uncertainties over whether the glycaemic control and use of laser photocoagulation in the trials accurately reflected what would be seen in UK clinical practice.	The Appraisal Committee discussed a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible in its second meeting. See FAD section 4.25. Fluocinolone and aflibercept were not listed as relevant comparators at the time the scope for NICE technology appraisal guidance 237 was issued. The Appraisal Committee discussed the generalisability of the RESTORE trial population in its second meeting. See FAD section 4.21.

Role*	Section	Comment	Response
NHS Professional	6	Who will fund this research? It is needed urgently.	Comment noted.
NHS Professional	8	Should be earlier as new drugs are coming on the market for DMO	The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.
NHS Professional	1	There would seem some flaws in the decision making process. The DSU report on Bev as a comparator does not appear to have been considered in scope nor by the committee. There would seem to be some "rather optimistic" assumptions in the PAS. These certainly have an impact on the implementation, they may have an impact on the ICER also. The cost of intra vitreal injection is significantly under estimated. Each of these has a bearing on the deliberations of the committee.	The Committee was aware of the emerging evidence on the effectiveness and safety of bevacizumab as a treatment option for diabetic macular oedema, including work undertaken by NICE's Decision Support Unit and ongoing clinical trials comparing bevacizumab with ranibizumab in diabetic macular oedema and other eye diseases. See FAD section 4.27. The clinical specialists suggested that ranibizumab treatment would need an ophthalmologist (rather than a nurse) and would be provided on an outpatient basis. See FAD section 4.6. The Committee for NICE technology appraisal guidance 237 concluded that the outpatient tariff of £150 per injection provided a fair estimate of reasonable costs.

Role*	Section	Comment	Response
NHS Professional	2	In a separate TA process (ranibizumab in Retinal Vein Occlusion - RVO), the institute has commissioned Sheffield University (Decision Support Unit - DSU) to undertake a substantial piece of work on whether bevacizumab is a valid comparator. My understanding is that the DSU work is now complete. Given the Institute asked DSU to undertake this work in one ophthalmic indication it seems illogical for the principle to not be carried into the DMO indication. In our view this DSU report should be considered by the committee. On the likely effectiveness and safety of bevacizumab, in their 2011 guidance for clinicians on this matter, the Royal College of Ophthalmologists recommended Bevacizumab in DMO, in the absence of an NICE TA. Given that RCO are principally concerned with clinical effectiveness and safety (and that cost considerations are entirely secondary to this) it must follow that RCO are satisfied that Bevacizumab is a medicine that is effective and safe in this indication.	The Committee was aware of the emerging evidence on the effectiveness and safety of bevacizumab as a treatment option for diabetic macular oedema, including work undertaken by NICE's Decision Support Unit and ongoing clinical trials comparing bevacizumab with ranibizumab in diabetic macular oedema and other eye diseases. See FAD section 4.27. The Appraisal Committee gave further consideration as to whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible in its second meeting. See FAD section 4.25.
NHS Professional	3	I would wish to draw to your attention the Ford et al paper in BMJ (doi: 10.1136/bmj.e5182) highlighting no apparent differences between the effectiveness of ranibizumab and bevacizumab in this indication. The authors did point out the wide confidence intervals, suggesting that a larger study would be needed. It would seem this study will not be industry sponsored, principally for commercial reasons.	Comment noted.

Role*	Section	Comment	Response
NHS Professional	4	We note (para 3.47 of ACD) the manufacturer assumed that people receiving ranibizumab alone would require a total of 14 ranibizumab injections over 4 years: 7 injections in the first year, 4 injections in the second year, and 3 injections in the third year. These assumptions were based on a 2-year extension of the RESTORE study, which showed trial participants needed a decreasing number of ranibizumab injections from the first year to the third year. The manufacturer assumed that no injections were required in the fourth year This is set against, para 4.4 of the ACD notes that "The clinical specialists anticipated that people with diabetic macular oedema would require between 7 and 9 treatments in the first year." This is more than seems to have been modelled into the economics (referenced against the manufacturer's model). We also noted that the committee heard from clinical specialists that it was likely that "treatment would not be for a predefined period. Instead, clinicians would discontinue treatment if a person's vision stopped improving, and would restart treatment in the event that the person's vision worsened." This obviously is easy to say in theory, hard to implement in practice (both from the perspective of a clinician stopping a patient on active treatment and from the perspective of the commissioner). We fear that the net effect will be very few patients are stopped, and an ever growing cohort of patients remain on long courses of treatment (as seems to have happened in the AMD cohort). Our fear is further heightened by the publication of the 3 year data on ranibizumab in DMO (Diana V et al. *Arch Ophthalmol.* 2012;():1-7. doi:10.1001/2013.jamaophthalmol.91) highlighting that many patients need on-going treatment to control oedema and to optimise visual acuity.	The Committee was aware that some consultees had suggested that people with diabetic macular oedema would need more frequent treatment with ranibizumab than was assumed by the manufacturer. The Committee also noted that uncertainty remained about whether people would need ranibizumab beyond 4 years and, if they did, what the costs of ongoing treatment would be. However, the Committee acknowledged that the manufacturer had attempted to address this uncertainty by conducting a threshold analysis to assess the maximum number of injections per person that could be administered while maintaining an ICER below £30,000 per QALY gained. See FAD section 4.18.

Role*	Section	Comment	Response
NHS Professional	5	With respect to the revised PAS, there are many seemingly overly optimistic assumptions that have a bearing on implementation and maybe on ICER Early indications from some PCTs is the reduced price when combined with the removal of the 14 injection cap results in a significant net cost increase for the PCT. Thus it would appear a fallacy to make the assumption that "savings in AMD will free up resources to pay for introduction in DMO". Our initial understanding (based on work undertaken in two PCTs in Yorkshire) is the new PAS price (both the removal of the 14 injection cap and the lower price per injection) for ranibizumab will result in an approximate net cost of £60,000 per £100,000. For the Bradford and Airedale economy this new price equates to a net cost of £300,000. Thus it is simply not true to suggest that savings from a lower price will result in freed up expenditure to provide optimal treatment for the DMO population. A lower price will, however, make the medicine more cost effective. We would encourage the PAS to be considered in more detail by the ERG, with active input from NHS Commissioners.	Comments noted. The Department of Health considered that the patient access scheme for ranibizumab does not constitute an excessive administrative burden on the NHS. See FAD section 2.4.

Role*	Section	Comment	Response
NHS Professional	4	As a Consultant Ophthalmologist with particular expertise in Diabetic retinopathy I frequently see patients who are under long term review with gradual loss of vision due to diabetic maculopathy despite argon laser treatments. These patients are usually of working age and have disease centred at the fovea. They would welcome the opportunity to receive Ranibizumab injections following a protocol as described of 3 loading doses as the evidence would suggest that they would gain superior visual acuity outcomes and would avoid further laser treatments destructive to the retinal pigment epithelium. Clinical scenarios where the patient has diffuse macular oedema (>400um) are particularly refractory to laser. In addition this degree of maculopathy in an eye with advanced media opacities eg cataract would also benefit from Ranibizumab as laser treatment is then difficult without a clear view of the fundus whereas Ranibizumab injections can be performed safely in this scenario. Real life effective argon laser therapy requires significant skill and audit data suggests sub-optimal results (Jyothi Eye 2011), whereas Ranibizumab injections are less skill dependant.	The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.

Role*	Section	Comment	Response
NHS Professional	1	To prevent us from treating "hopeless" cases with 400 micrometres thickness there should be a recommendation e.g. "frank macular ischemia should be ruled out by fluorescein angiography (FFA) prior to starting treatment". This is important as ischemic maculae tend to have more pronounced oedema. On the other hand it would make clinical sense to link the criterion of 400 micrometres retinal thickness to the 3 standard definitions of clinical significant macular oedema (CSMO), i.e. 1. Retinal oedema within 500 micrometres of centre of fovea 2. Hard exsudates within 500 micrometres of centre of fovea with adjacent oedema which may be outside 500 micrometres limit 3. Retinal oedema one disc area or larger, any parts of which is within one disc diameter (1500 micrometres) of centre of fovea --- i.e. the clinician is only allowed to treat if the essential criterion of retinal thickness of 400 micrometres is found in any of the above 3 locations.	The Committee noted that, in its rapid review submission, the manufacturer provided additional subgroup analyses that showed that ranibizumab has a lower ICER in people with thicker retinas (central retinal thickness of 400 micrometres or more) than in people with thinner retinas (central retinal thickness of less than 400 micrometres) at the start of treatment. See FAD section 4.23.
NHS Professional	6	Main issue is implementation. Capacity in already over burned service. Time lines from diagnosis of Odema to treatment should be stated otherwise trusts could delay starting treatment for months. Additional funding for doctors and nurses to do the treatment and the reviews will be needed.	The guidance statement in the FAD states that: Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if: • the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and** • the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012). See FAD section 1.1

Role*	Section	Comment	Response
NHS Professional	1	I agree the trials comparing laser to ranibizumab suggest a better outcome of ranibizumab compared to laser only in the thicker groups however there are some patients who have localised central leak which is not safe to laser and so would not have been included in such a trial. All the trials show improvement in vision with ranibizumab so I think this group should be included. The judgement on central leak could be based on FFA. In some cases laser will have been tried 3 or 4 times and there may still be fluid. Such laser failures should also be allowed to be treated.	The Committee heard that some commentators suggested that the proposed date for review should be earlier than February 2016, because the guidance would exclude ranibizumab as a treatment option for a significant proportion of people with diabetic macular oedema. Therefore, the Committee agreed that the proposed date for review of the guidance should be brought forward to February 2015. See FAD section 4.27.
NHS Professional	2	Visual acuity does not correlate well to retinal thickness and so a better indication for re treatment is recurring retinal fluid seen on OCT.	Comment noted.