Comments on the ACD Received from the Public through the NICE Website

Role	NHS Professional
Other role	clinical lead Diabetic Eye Screening programme, Northamptonshire
Location	England
Conflict	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	central retinal thickness should not be the only criteria. Positive cilincal response and the judgement of the clinician should be the guiding factor
Section 2 (The technology)	I agree with the above comments
Section 3 (The manufacturer's submission)	there is ample evidence of the clinical effectivness in treatment in macular oedema
Section 4 (Consideration of the evidence)	I strongly agree with the consnderation of the evidence
Section 5 (Implementation)	I agree with the comments in this section
Section 6 (Proposed recommendations for further research)	Agreed with the comments
Section 7 (Related NICE guidance)	agreed with the comments
Section 8 (Proposed date of review of guidance)	agree with the comments

Role	NHS Professional
Location	England
Conflict	Yes
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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.
Section 4 (Consideration of the evidence)	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 soley at the OCT measurements.

Role	NHS Professional
Other role	Lead Pharmacist, NHS Hertfordshire
Location	England
Conflict	No
Notes	This response is made on behalf of NHS Hertfordshire as the current commissioning organisation for the 1.12m population of Hertfordshire as well as on behalf of East and North Herts and Herts Valley Clinical Commissioning Groups, as the future receiving organisations for commissioning ophthalmology service.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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 a wider use privately.
Section 2 (The technology)	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
Section 3 (The manufacturer's submission)	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 paients need on-going treatment to control oedema and to optimise VA. Therefore, we do not agree with reduction in number of injections estimated.

Section 4 (Consideration of the evidence)	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.
Section 5 (Implementation)	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 thcikness 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.
Section 6 (Proposed recommendations for further research)	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.
Section 7 (Related NICE guidance)	A MTA comparing anti-veGFs to steroids for DMO would be helpful.

Role	NHS Professional
Location	England
Conflict	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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
Section 3 (The manufacturer's submission)	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 plausable" treatment group, tests of statistical significance for 3 catagories of CFT are done but the tests are not presented, why not? Differences in clinical outcome for a the recommendation would be key.
Section 4 (Consideration of the evidence)	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.
Section 6 (Proposed recommendations for further research)	Absolutely agree that ranibizumab and bevacizumab should be directly compared, and consideration may be given to aflibercept in such analysis.

Role	NHS Professional
Location	England
Conflict	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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 greatley 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.
Section 2 (The technology)	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 bu 4x the amount required is neccessary, this is not the case for other injectables. Adverse reactions are as expected.
Section 3 (The manufacturer's submission)	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 belive 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.
Section 4 (Consideration of the evidence)	We note that this is an additional treatment following laser and thus it imposes an additional financial burden on the NHS.
Section 6 (Proposed recommendations for further research)	We concur and think this is of great importance.

Role	NHS Professional
Other role	Head of Medicines Management
Location	England
Conflict	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Feedback from local consultant opthalmologists indicate that the reference to central retinal thickness is too vague, and this needs to be defined. Local Gloucestershire consultant opthalmoloist is working with leading retinal experts to develop an algorithim 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.
Section 3 (The manufacturer's	Patient Access Schemes have been found to be problematic to administer by the NHS. This is further compounded when there

submission)	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 cental 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?
Section 4 (Consideration of the evidence)	Safety - The included studies have not assessed safety outcomes, but did not find any differenece 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.
Section 6 (Proposed recommendations for further research)	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 relaesing resource for use in other advanced technologies.

Role	NHS Professional
Location	England
Conflict	Yes
Notes	Have worked on a clinical trial and recieved education support from Novartis.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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.
Section 3 (The manufacturer's submission)	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.
Section 4 (Consideration of the evidence)	Good - see previous comment in section3.
Section 5 (Implementation)	This would be very helpful. I have already made a draft business case but it will need modification once the full guidance is givven. I think it will be important to give clinicians a guide for expected numbers to treat, numbers of treatments and visits etc.
Section 8 (Proposed date of review of guidance)	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 alot of difficult conversations with patients about why they can't receive treatment with ranibizumab. February 2015 would be a better date.

Role	NHS Professional
Location	England
Conflict	No
Comments on individual sections of the ACD:	
Section 3 (The manufacturer's submission)	● 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.
Section 4 (Consideration of the evidence)	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 flucinolone 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.
Section 6 (Proposed recommendations for further research)	Who will fund this research? It is needed urgently.
Section 8 (Proposed date of review of guidance)	Should be earlier as new drugs are coming on the market for DMO

Role	NHS Professional
Location	England
Conflict	No
Notes	involvement in the the TANDEM trial
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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 sigificantly under estimated. Each of these has a bearing on the deliberations of the committee.
Section 2 (The technology)	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 effectivness 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.
Section 3 (The manufacturer's submission)	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.
Section 4 (Consideration of the evidence)	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 manufacturers 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 rabibizumab 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 optomise visual acuity.
Section 5 (Implementation)	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.

Role	NHS Professional
Location	England
Conflict	Yes
Notes	I work in NHS practice but have undertaken national and international research studies as principal investigator funded by the manufacturer. I have previously undertaken consultancy work within advisory boards funded by the manufacturer Novartis and also other manufacturers; Allergan, Bayer, Alimera and Alcon. I have accepted travel grants previously from the manufacturer Novartis and other pharmaceutical companies. The opinions expressed in this document are my personal opinions and are not expressed on behalf on the NHS Trust at which I am employed.
Comments on individual sections of the ACD:	
Section 4 (Consideration of the evidence)	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.

Role	NHS Professional
Other role	Consultant Ophthalmologist
Location	England
Conflict	Yes
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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.

Role	NHS Professional
Location	England
Conflict	No
Notes	I am lead clinican diabetic eye service at Hillingdon and Western Eye hospitals.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I like the simple guidelines. I approve of this. Also the fact it can be first line treament is good.
Section 2 (The technology)	Agree with this.
Section 3 (The manufacturer's submission)	Very good summary

Section 4 (Consideration of the evidence)	Very good.
Section 5 (Implementation)	All very good and with Medisfot audit program will be possible
Section 6 (Proposed recommendations for further research)	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.
Section 7 (Related NICE guidance)	I would not favour steriods in Diabetic eye disease due to the side effects. Pegaptanib is similar drug so is encourabintg
Section 8 (Proposed date of review of guidance)	Verg good.

Role	NHS Professional
Location	England
Conflict	No
Notes	I am involved with a clinical trial of ranibizumab for vein occlusions
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	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.
Section 2 (The technology)	Visual acuity does not correlate well to retinal thickness and so a better indication for re treatment is recurring retinal fluid seen on OCT.