NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion

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
NHS Wiltshire	NHS Wiltshire regards eye disease and chronic long term conditions as an important area for commissioning and therefore values innovative interventions for this disease which are proven to be cost effective and affordable in their implementation. NHS Wiltshire welcomes the publication of the Appraisal Committee's recommendations.	Comment noted.
	Whilst we welcome the fact that the proposed patient access scheme would not impose an excessive administrative burden on the NHS, we question the effect such a scheme has on the ability of NHS commissioners to implement NICE Guidance. Such schemes may influence commissioners in such a way that services and technologies are commissioned inequitably.	Comment noted. The manufacturer of ranibizumab (Novartis) has agreed a patient access scheme with the Department of Health, revised in the context of technology appraisal guidance 274, which makes ranibizumab available with a discount applied to all invoices The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS (section 2.4 of the Final Appraisal Determination).
	The clinical trials that assessed the effectiveness of ranibizumab are not fully generalisable to NHS clinical practice The scope for this technology appraisal included people with or without retinal ischaemia. However both the BRAVO trial, which had assessed ranibizumab for macular oedema following BRVO and the CRUISE trial which had assessed ranibizumab for macular oedema following CRVO excluded people with brisk afferent pupillary defect which is severe retinal ischaemia. There is therefore a lack of evidence for the effectiveness of ranibizumab for treatment of RVO in patients with severe ischaemia. Both trials had compared ranibizumab to sham injection rather than treatments used in current clinical practice (bevacizumab and dexamethasone invitreal implants). Although there were differences in the study populations of a study that had assessed dexamethasone (GENEVA), such as time to treatment after emergence of oedema, it was determined that indirect comparisons could be made. Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but no head to head clinical trials comparing these two treatments against each other are yet available.	Comments noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with significant retinal ischaemia and the relative effectiveness between ranibizumab and dexamethasone and are summarized in the FAD (sections 4.9 and 4.20).The Committee also considered the latest evidence relating to the efficacy and safety of bevacizumab (sections 4.4 to 4.8 of the FAD)
	The outcomes in the trial of ranibizumab for branch retinal vein occlusion were confounded.	

Consultee	Comment	Response
	In the BRAVO trial, patients were treated with monthly ranibizumab or sham injections for six months however, after three months the patients could receive grid laser photocoagulation for rescue treatment. This was used in 57.6% of patients in the sham injection group and 21.4% of the ranibizumab group in the first six months. It was noted that the treatment period of the BRAVO trial was insufficient to capture any benefits of grid laser photocoagulation on patient outcomes, which may last longer than three years. Clinical advice to the ERG suggested that concomitant use of ranibizumab and grid laser photocoagulation does not reflect how ranibizumab would be used in clinical practice. Data from the BRAVO trial was treated with caution. Laser photocoagulation is not indicated for people with CRVO.	Comment noted. The issue of confounding in the BRAVO trial was considered by the Committee and is summarized in the FAD (section 4.10, 4.13, 4.23 and 4.24).
	People with macular oedema secondary to RVO will be treated in their 'worse seeing eye' The manufacturer's model had assumed that people would be treated in their better seeing eye. This was considered inappropriate. Clinical specialists confirmed that RVO is a unilateral disease in most patients and therefore the proportions of people treated in the 'worse seeing eye' in the BRAVO and CRUISE trials better reflect clinical practice. Over 90% in the patients in the BRAVO and CRUISE trials were treated in their worse seeing eye.	Comment noted. The Committee accepted the manufacturer's amendment to the economic model which reflected the fact that 90% of patients would be treated in their 'worse-seeing eye', consistent with the BRAVO and CRUISE trials (section 4.14 of the FAD).
	Retinal vein occlusion and a decrease risk in visual acuity both are associated with increased mortality. Data was presented from studies other than the BRAVO and CRUISE trials that suggested that there was an increased risk of mortality both with RVO and with vision impairment as a consequence of RVO.	Comment noted. The Committee concluded that the evidence on the risk of cardiovascular mortality associated with RVO was unclear, and therefore it need not be included in the base-case model to the degree applied in the original ERG report. However it remains an uncertainty in the analysis (section 4.17 of the FAD). With regard to mortality risk associated with visual impairment, the Committee noted that the ERG had accepted the revised approach to applying excess mortality associated with visual impairment (see section 4.21; also
	Innovativeness of the technology. In some cases NICE will take into consideration how innovative an intervention is. For ranibizumab the Committee concluded that ranibizumab is one of a group of innovative anti-VEGF treatments, and does not stand alone in this therapeutic area and its benefits are appropriately captured in the QALY calculation**.**	
	As NHS Commissioners, we welcome the support of NICE in providing the slides, templates, and advice on the implementation of this guidance.	

Consultee	Comment	Response
		discussed in section 3.26 and 3.33). Comment noted. The Committee discussed how innovative ranibizumab was and agreed that anti-VEGF treatments were a substantial improvement over previous treatments, but considered that this improvement applied to the class of drugs, including bevacizumab. The Committee was not aware of any substantial benefits of ranibizumab over its comparators that were not already factored into the QALY estimation in the modelling (section 4.25 of the FAD).
NHS Wirral	NHS Wirral agrees with the ACD that that ranibizumab should not be recommended for the treatment of visual impairment caused by macular oedema secondary to retinal vein occlusion. Wirral PCT does regard eye disease as an important area for commissioning and therefore would value innovative interventions for this disease if they were clearly cost effective and affordable. However, there are other treatment options that are available to treat this disease area which are considerable more cost effective. **Consideration of the clinical evidence** **a) The trials were not comparable to clinical practice:** The two main trials that assessed ranibizumab for macular oedema secondary to retinal vein occlusion were CRUISE and BRAVO. Both of these trials excluded people with brisk afferent pupillary defect which is severe retinal ischaemia. There is therefore a lack of evidence for the effectiveness of ranibizumab for treatment of	Comment noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committee's concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). Comments noted. The Committee considered the approaches taken by the

Consultee	Comment	Response
	RVO in patients with severe ischaemia. The outcomes in the trial of ranibizumab for branch retinal vein occlusion were confounded. In the BRAVO trial, patients were treated with monthly ranibizumab or sham injections for six months however, after three months the patients could receive grid laser photocoagulation for rescue treatment. This was used in 57.6% of patients in the sham injection group and 21.4% of the ranibizumab group in the first six months. It was noted that the treatment period of the BRAVO trial was insufficient to capture any benefits of grid laser photocoagulation on patient outcomes, which may last longer than three years. Clinical advice to the ERG suggested that concomitant use of ranibizumab and grid laser photocoagulation does not reflect how ranibizumab would be used in clinical practice and therefore, data from the BRAVO trial should be treated with caution. **b) The trials did not compare ranibizumab to currently used treatments:** Both trials had compared ranibizumab to sham injection rather than treatments used in current clinical practice (bevacizumab and dexamethasone invitreal implants). Although there were differences in the study populations of a study that had assessed dexamethasone (GENEVA), such as time to treatment after emergence of oedema, it was determined that indirect comparisons could be made. The manufacturer did not compare ranibizumab with bevacizumab which was agreed to be an appropriate comparator in the scope. Bevacizumab (Avastin), like ranibizumab inhibits VEGF. It has marketing authorisation to be used in the treatment of some cancers, but has been used off-license for the treatment of macular oedema at lower doses. Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but because a license has not been sought for the use of bevacizumab in the eye, its safety in the eye is not assured. Additionally concerns were raised from patient experts about the use of unlicensed treatments for which there was no post-marketing surveillance, particularly if there were licensed alternatives. The Committee said that “licensing is not considered a prerequisite for consideration of a comparator in a NICE	manufacturer in relation to the exclusion of people with significant retinal ischaemia and is summarized in the FAD (sections 4.9). The issue of confounding in the BRAVO trial was considered by the Committee and is summarized in the FAD (section 4.10, 4.13, 4.23 and 4.24) Comments noted. The Committee considered the comparators for the appraisal and specifically bevacizumab intravitreal injection. This is summarised in the FAD (sections 4.3 to 4.8). The Committee also considered the relative effectiveness of ranibizumab with dexamethasone intravitreal implant (section 4.20 of the FAD).

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	technology appraisal as long as it is in routine use or is considered best practice". Clinical specialists said that bevacizumab is currently reasonably widely used in the NHS, but the extent of its use varies between centres. All the clinical specialists involved said they used bevacizumab and NHS Wirral feels it is appropriate that it is considered a relevant comparator for ranibizumab. It is used on Wirral for the treatment of macular oedema secondary to retinal vein occlusion. However, the ERG has carried out indirect comparisons with both bevacizumab and dexamethasone which were considered by the committee therefore, we are happy that all the relevant evidence has been taken into account. For ranibizumab the Committee concluded that ranibizumab is one of a group of innovative anti-VEGF treatments, and does not stand alone in this therapeutic area and its benefits are appropriately captured in the QALY calculation**.** Ranibizumab does not offer patients enough benefits over current treatments at a cost effective price for the NHS. Bevacizumab is considered to have approximately equal effectiveness but at a considerably reduced cost compared to dexamethasone and dexamethasone offers the benefit of reduced dosing – every 6 month as opposed to potentially every month. This is both more appealing to patients who have fewer injections and also from the point of view of service delivery and capacity in the ophthalmology clinics. **Cost effectiveness** Ranibizumab for the treatment of macular oedema secondary to RVO is not a cost effective use of NHS resources and the Committee determined that the most plausible ICERs for ranibizumab compared with alternatives were all above the ranges usually considered cost-effective for NHS use (i.e. £20,000 to £30,000 per QALY gained). For CRVO; Base case estimates produced by the ERG were an ICER of £43,800 per QALY gained for ranibizumab versus best supportive care, and £37,400 per QALY versus dexamethasone. The Committee agreed that ranibizumab and bevacizumab were approximately equally effective and the ERG performed an analysis that concludes "ranibizumab would need to generate 1.7 times more QALYs than bevacizumab (each month between months 2 and 6) in macular oedema secondary to CRVO to give an ICER at the top end of the range usually	Comments noted. The Committee discussed how innovative ranibizumab was and agreed that anti-VEGF treatments were a substantial improvement over previous treatments, but considered that this improvement applied to the class of drugs, including bevacizumab. The Committee was not aware of any substantial benefits of ranibizumab over its comparators that were not already factored into the QALY estimation in the modelling (section 4.25 of the FAD). Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee

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	considered cost effective". Bevacizumab was dominant over ranibizumab in a cost minimization analysis meaning that it is better value for the NHS. Dexamethasone was considered an appropriate comparator as it is currently recommended for use in this indication in the NHS. The ICER for ranibizumab versus dexamethasone intravitreal implant in CRVO was estimated to be in excess of £37,400 per QALY gained. For BRVO, the manufacturer's estimate of £20,500 per QALY gained for ranibizumab versus grid laser photocoagulation was thought to be an underestimation. The ICER for ranibizumab versus dexamethasone for people with BRVO was £31,122. NHS Wirral are satisfied that there are no aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief. Neither do we believe there are any equality -related issues that need special consideration that are not covered in the appraisal consultation document. NHS Wirral feels strongly that the provisional recommendations in the ACD are sound and are a suitable basis for guidance to the NHS. Whilst ranibizumab is an effective treatment for macular oedema secondary to retinal vein occlusion there are other treatment options available to patients and the extremely high cost of ranibizumab compared to the other therapies means that it is just not a cost effective use of NHS resources. Other services (especially eye services) may be withdrawn or stretched if the FAD were to change to recommending ranibizumab for this indication.	considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24).
Novartis	Novartis is very disappointed that the preliminary guidance from NICE does not recommend the use of ranibizumab for the treatment of visual impairment (VI) due to macular oedema (MO) secondary to retinal vein occlusion (referred to hereafter	Comments noted. The Committee considered the amendments to the economic model following consultation, in

Consultee	Comment	Response
	as RVO). We are concerned that the preliminary recommendation may be based on some assumptions and inputs to the cost effectiveness analysis that are not fully evidence-based. Should this recommendation become final guidance, people with visual impairment due to macular oedema secondary to retinal vein occlusion would be denied a sight-restoring treatment that is in fact a cost-effective use of NHS resources. Based on our revised analyses, taking account of the comments of the Appraisal Committee, we believe that ranibizumab is cost-effective well below a £20,000 per Quality Adjusted Life Year (QALY) threshold when compared to dexamethasone implant for the treatment of both Branch and Central RVO (BRVO and CRVO) in the WSE (£6,600 and £11,656 per QALY, in BRVO and CRVO respectively). Ranibizumab is also cost-effective below a £20,000 threshold compared to observation for the treatment of CRVO in the WSE at £18,817 per QALY. We are pleased that the Appraisal Committee has recognised that ranibizumab is a well-tolerated and effective treatment for VI due to MO secondary to both BRVO and CRVO. We are also reassured that the Committee has acknowledged the important impact of ranibizumab on patients' quality of life, when treatment is provided to the worse-seeing eye (WSE). We believe, however, that there are a number of key issues that must be clarified with respect to the evidence submitted by Novartis, the rationale for our assumptions and the implications inherent in alternative assumptions proposed by the Evidence Review Group (ERG). We consider that there are several important areas where elements of the base case we originally submitted were conservative and the ERG's approach results in a significant overestimation of the Incremental Cost Effectiveness Ratios (ICERs). We would therefore be grateful for the Committee's further consideration of the key issues summarised below: ***1. The approach to utility values in the ERG's analysis will significantly underestimate the benefit to patients of treatment*** *a. The ERG's use of the Brazier utilities does not account for a*	conjunction with the critique provided by the Evidence Review Group. The Committee also considered the patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Consultee	Comment	Response
	clinically meaningful change in BCVA of ≥10 letters, which is already accepted by the Committee *b. The source of utility gains from treatment of the WSE does not capture the full impact of visual impairment in the WSE* ***2. There are inconsistencies in the Committee's appraisal of dexamethasone implant for the treatment of RVO and its appraisal of ranibizumab for the treatment of RVO*** *a. Excess mortality associated with RVO was not considered necessary in the dexamethasone implant appraisal* *b. A lifetime time horizon was accepted in the dexamethasone implant base case analysis, and therefore this has been employed for the new ranibizumab analyses* ***3. Best supportive care remains a relevant comparator for CRVO, as defined in the Scope*** ***4. The extent of bias towards ranibizumab in comparison to dexamethasone implant has been overestimated, and bias against ranibizumab has been overlooked*** *a. The indirect comparison at month 3 does not take account of the decline in efficacy of dexamethasone implant after 3 months and is therefore biased against ranibizumab* *b. Dexamethasone implant retreatment frequency was conservative in the original base case, compared to routine clinical practice* *c. Adverse event rates for dexamethasone were included only in year 1, and were therefore conservative in the base case* *d. The mean number of ranibizumab injections is conservative in the base case* *e. Contrary to the ERG's suggestion, the presence of neovascularisation suggests that comparisons to dexamethasone are biased against ranibizumab* ***5. Comparisons to dexamethasone implant in BRVO patients should focus on those with macular haemorrhage for consistency with***	

Consultee	Comment	Response
	recent NICE recommendations ***6. The use of un-pooled transition probabilities based on the sham/0.5 mg ranibizumab-treated patients after 6 months should not be applied to the laser arm of the model, as this attributes the benefit of just starting ranibizumab to laser-treated patients*** ***7. The inclusion of bevacizumab as a comparator in this STA is inappropriate*** ***8. The limitations of the ERG's approach to the comparison versus bevacizumab have not been fully explored*** *a. The studies of bevacizumab in RVO include less than 100 patients, and have important methodological shortcomings* *b. The method of the ERG's indirect comparison appears to be flawed* *c. The interpretation of the indirect comparison result as there being no clinically meaningful difference is not appropriate given the large variance around the point estimate* *d. The reason for assumed bias in the indirect comparison towards ranibizumab is unclear and appears not to be evidence-based* *e. There are important safety considerations that should not be ignored* *f. There is no basis for a cost-minimisation analysis, where equivalent efficacy and safety have not been demonstrated* ***9. Ischaemic disease has not been adequately defined*** These points are discussed in detail in section A of our response below. We urge NICE to reconsider its preliminary guidance in light of our comments.	
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the key questions on which comments were requested is set out below:	

Consultee	Comment	Response
	i) **Has the relevant evidence been taken into account?** The Committee concluded that ranibizumab is an effective treatment for non-ischaemic macular oedema secondary to BRVO and CRVO**.** They state that ranibizumab was associated with statistically significant mean gains in BCVA in the treated eye (for non-ischaemic patients) compared with sham injection for the 6-month treatment phase but we note that they have excluded ischaemic CRVO. The Committee states that patients with RAPD were excluded from the BRAVO and CRUISE studies but such patients are the extreme end of ischaemia. It is known that some non-ischaemic cases may progress to the ischaemic type but are not ischaemic enough to have a RAPD. Thus, all ischaemic patients should not be excluded only those with positive RAPD.	Comment noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with significant retinal ischaemia. This is summarised in the FAD (section 4.9).
	ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In the cost model, the direct comparison of ranibizumab and dexamethasone implant do not take into full account the known side effects of steroids or the unknown re-treatment frequency of dexamethasone implant. It is well documented that the long-term side effects include cataract and glaucoma, so with increased use of steroids there will be an increased financial burden on the NHS in managing these adverse events. This cost, therefore, should be included in the model. Also there are some issues around the lack of discussion related to the independent use of photocoagulation as this is identified as having no cost point (see 3.14). There must be a cost associated to this as healthcare professionals have to undertake the treatment and the machine needs maintenance. We would also like to know how the patient's vision is maintained with just laser as opposed to treatment with both. Further, the information related to the quality of life index does not seem to have been well evaluated. The report indicates that these patients are often younger, so this element is really important as if these individuals cannot	Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committee's concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). Grid laser photocoagulation (BRVO only) was assumed to incur no cost but an administration cost as an outpatient

Consultee	Comment	Response
	work or need care and benefit support for longer, then this is not cost effective (reference to point 3.11 at the end of the page also 3.6). iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We would question the comparison studies used for bevacizumab versus ranibizumab especially Russo (2009). It was a very small, unmasked study so one cannot say that it was unbiased or evidence based. iv) **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 gender, race, disability, age, sexual orientation, religion or belief?** None that we are aware of. v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate. **<u>Conclusion</u>** We would conclude by saying that the current evidence shows that treatment of BRVO and CVRO with ranibizumab offers the greatest promise for patients with a view to improving the management of the condition and vision outcomes. The associated cost of not using this technology should be factored in. In our view, this health technology should be considered for use in the NHS.	procedure was applied (see section 3.14 of the FAD). The Committee noted that the BRAVO and CRUISE trials collected data on the effect of visual impairment on quality of life using the NEI VFQ-25 questionnaire and concluded that treating patients with ranibizumab improved the quality of life of people with macular oedema secondary to RVO (see section 4.12 of the FAD) The Committee considered in detail the comparators for this appraisal, in particular intravitreal bevacizumab injection. This is summarised in the FAD (section 4.4 to 4.8). Comment noted. The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).
Royal College of	The Royal College of Ophthalmologists is disappointed with the Appraisal Committee's preliminary recommendations not to recommend ranibizumab	Since the Appraisal Consultation

Consultee	Comment	Response
Ophthalmologists	intravitreal injection for the treatment of macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The basis of this preliminary opinion is on cost effectiveness and differences between the manufacturer's modelling and the ERG assessment on several key parameters. Specific comments regarding the key assumptions/parameters are outlined below: **i. Use of "worse –seeing eye" rather than "better-seeing eye" in modelling** It is agreed that both in clinical practice and in the pivotal BRAVO and CRUISE trials that the majority of patients present with RVO in their worse seeing eye and that the ERG's assumption to model on this is appropriate. However, the committee has failed to make any specific recommendation on the cost effectiveness for those patients who do actually present with RVO in their better-seeing eye. This could be in up to 10% of cases or 3000 cases per annum in UK. It appears from Table 67 of the ERG report that if a patient does present with CRVO in their better-seeing eye then the use of ranibizumab in this particular cohort is highly cost effective at £9,515 ICER of ranibizumab versus best supportive care. This raises the sensitive ethical issue of whether it is appropriate to not treat a patient when it is their worse seeing eye affected whilst having a highly cost effective treatment if the better seeing is affected. This issue cannot be ignored and must be addressed in any Final Appraisal Document. **ii. Utility values used in model** There are significant uncertainties around the specific utility values used in the modelling. In section 4.15 of the ACD the committee states that they accepted the ERG's recommendations for the use of utility values from Brazier et al (2009) rather than the manufacture's submission of utility scores from Brown et al (1999) based on the need for age adjustment. Further justification for this appears to be that Brazier et al (2009) utility scores assessment was recommended in NICE TA 155 for AMD and that it is generally accepted that it is the level of visual acuity rather than the particular visual disorder that drives the utility score. Although this latter point is accepted it must be pointed out that the Brazier et al paper (2009) used 108 general population volunteers with a mean age of 32 yrs wearing contact lenses to simulate AMD visual states for approx. 1.5 to 2 hours whilst utility scores were estimated through interview. This is in contrast to the Brown et al (1999) utility scores which were	Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD). Comments noted. The Committee considered the manufacturer's revised approach to deriving utilities for the 'better-seeing eye' using Czoski-Murray et al (2009) (formerly referred to as Brazier et al. 2009). The Committee concluded that although uncertain, the use of utilities as applied using the Czoski-Murray equation was acceptable.

Consultee	Comment	Response
	derived from 325 participants with visual disorders (7% had RVO) and a mean age of 67.5 years. It is recognised that reimbursement agencies around the world prefer general population values and that specific patient utility scores may differ from the general population. However, the stark differences in how the utility scores are calculated between these 2 studies raises the significant possibility that utility score benefit from ranibizumab in RVO is underestimated in this appraisal. In section 4.2 the committee acknowledges that "loss of vision caused by macular oedema secondary to retinal vein occlusion seriously impairs health-related quality of life" and yet the analyses used does not appear to appropriately reflect this sentiment. In the ERG updated report and erratum the ERG state that " some simplifying assumptions were made surrounding the application of a smaller set of utility values to a larger number of health states; these assumptions are summarised in Table 54." For better-seeing eye calculations it would appear that the way Brazier utility scores are implemented could underestimate potential benefit. For example, a gain from 56 letters to 75 letters (i.e. 19 letter gain) would not register as an improvement in utility score (a 10 letter gain is often considered clinically relevant and benefit)	This is summarised in the FAD (section 4.15).

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
Table 54. The implementation of utility values from Brazier et al.[40]
<table>
<tr><th>Visual acuity health state</th><th>Base case utility</th><th>Brazier utility</th></tr>
<tr><td>86–100 letters (20/16–20/10)</td><td>0.920</td><td>0.706</td></tr>
<tr><td>76–85 letters (20/32–20/20)</td><td>0.880</td><td>0.706</td></tr>
<tr><td>66–75 letters (20/64–20/40)</td><td>0.770</td><td>0.681</td></tr>
<tr><td>56–65 letters (20/80–20/50)</td><td>0.755</td><td>0.681</td></tr>
<tr><td>46–55 letters (20/125–20/80)</td><td>0.670</td><td>0.511</td></tr>
</table>
iii. Pooling/Unpooling of Transition probabilities
The ERG’s assessment clearly demonstrate that the pooling or unpooling of transition probabilities has a substantial impact on the overall ICER for ranibizumab versus grid laser photocoagulation in BRVO (i.e. raising the ICER from £20,494 to £52,004 per QALY gained).
The ERG report states “The ICER obtained for ranibizumab versus GLP (standard care) in MO secondary to BRVO rose to £52,004 in the first analysis and ranibizumab was dominated in the remaining analyses. This confirmed the supposition that this approach (of pooling transition probabilities) inflated the effect of ranibizumab. However, the impact of this approach on the effect of GLP remains unknown.” Presumably, the unpooled transition probabilities in the Sham/0.5mg column of table 57 of the ERG report may over-estimate the effect of laser due to the concomitant use of ranibizumab over 7-12 mths in this arm. This aspect needs further clarification.

The ERG are concerned that the sham arm of BRAVO 0-6mths does not represent a true reflection of a GLP laser treated cohort as only 57.6% of patients in this arm actually received laser. In section 5.4.6 of the ERG report it is stated that “ The use of GLP in the sham arm does not represent the use of GLP in
</td><td>Comments noted. The Committee’s consideration of the manufacturer’s revised approach to address the concerns regarding the use of pooled transition probabilities is summarised in the FAD (section 4.18)</td></tr>
</table>

Consultee	Comment	Response
	clinical practice as all patients in the sham arm would have been eligible for GLP after having MO for 3 months". This not completely accurate and misleading. In the BRAVO study it was at the clinician's discretion whether to treat with laser based on assessment as to whether haemorrhage had cleared sufficiently to allow safe laser treatment and certain anatomical and functional criteria were met. The criteria used in BRAVO is consistent with how patients would be treated in the NHS with the standard of care and thus the sham arm of BRAVO should be considered a true representation of standard of care in BRVO. As there is no true direct comparative study of ranibizumab versus laser it is noted that the ERG have attempted to do further indirect modelling of ranibizumab versus laser by using the sham arm of the Moradian et al study. In the report the ERG state "The direction of bias in this analysis was likely to be towards ranibizumab and the result was an improvement of 8 letters for ranibizumab at month 3 compared with GLP." It must be stated that although there is undoubtedly some improvement with time in GLP treated patients and that a 3 month timeline may not capture this the clinical experience of the benefit of using ranibizumab far exceeds any potential benefit seen in laser treated patients. **iv. ICER of Ranibizumab versus Dexamethasone Implant** It is agreed that the committee's decision to consider an indirect comparison with dexamethasone intravitreal implant for CRVO and BRVO was acceptable. However, due to the significant difference in duration of macular oedema, presenting level of visual acuity and retinal thickness of the pivotal studies (BRAVO/CRUISE versus GENEVA) then any comparison must be considered with caution. The Committee conclude that these differences between the studies would bias ranibizumab and thus the ERG's exploratory assessment of the ICERs for CRVO of £37,400 per QALY and £31,100 for BRVO are likely to be higher. However, it is not clear whether the ERG or the Committee have adequately taken into account the adverse event rate of cataract development of 30% and the raised intraocular pressure event rate requiring glaucoma topical medication of 25% in the dexamethasone treated group after just 2 injections. Presumably, if these adverse events rates are considered then the calculated ICERs may be lower and potentially bias against ranibizumab.	Comments noted. The Committee's consideration of the updated estimate of the rate of cataract development for dexamethasone is discussed in section 4.19 of the FAD.

Consultee	Comment	Response
	It must be stated that there are many patients who present with RVO but who have relative contra-indications to dexamethasone implant such as uncontrolled raised intraocular pressure (IOP) or past history of difficult to control IOP. In such patients then dexamethasone would not be considered best practice and the strong clinical evidence would be to recommend ranibizumab in preference to dexamethasone. A further group of patients that would be relatively contraindicated for dexamethasone implant are younger patients who would not normally be at risk of developing cataract but may have a 30% risk after only 2 implant injections over the period of 1 year. **v. Use of bevacizumab as a comparator** In section 4.7 the ACD states "The Committee noted that licensing is not a prerequisite for consideration of a comparator in a NICE technology appraisal as long as it is in routine use or is considered to be best practice." It is important to state that the use of bevacizumab in RVO cannot be considered routine in the NHS and certainly not considered best practice as 2 licensed products are indicated in RCOphth Interim RVO guidelines (Dec 2010). Although many ophthalmologists throughout the UK have used bevacizumab in selected RVO cases, at present the majority of RVO patients do not receive anti-VEGF treatment, and the practice varies widely from unit to unit dependent on local NHS Trust pharmacy approvals. In addition there is significant variation in dosing schedules and no universally agreed treatment protocols. Although indirect comparisons can be made between ranibizumab and bevacizumab in RVO the analyses must be viewed with caution. The long-term benefit and need for repeated treatment for both ranibizumab and bevacizumab are unknown. The Royal College of Ophthalmologists has recently issued a statement (14th December 2011) regarding the use of anti-VEGF agents in the treatment of neovascular age-related macular degeneration (AMD) and is of the view that, in the case of neovascular AMD, the current published literature is consistent with the conclusion that bevacizumab and ranibizumab are equally effective and there is no convincing evidence of a clinically significant difference in the incidence of serious adverse events between the two groups. However, it remains unknown whether similar conclusions will be reached when studies comparing directly between the two agents in RVO are available. It is likely that between 5 and 9 repeated treatments with bevacizumab will be required over the	Comment noted. The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in visual impairment caused by macular oedema secondary to retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8).

Consultee	Comment	Response
	first 12 months. The clinical effect of bevacizumab probably lasts for 6-12 weeks. Patients are likely to need review 6-8 weekly over the first 12 months. The ancillary investigations for each of these visits such as vision assessment and OCT measurement are anticipated to be the same at each visit. It would be anticipated that the injection procedure and associated costs would be identical for ranibizumab and bevacizumab In reply to specific questions the answers are outlined below: **Has all of the relevant evidence been taken into account?** All relevant evidence has been taken into account except for the 12month papers from BRAVO and CRUISE which give significant p values for the 12 month data : Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG, Murahashi WY. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion:12-month outcomes of a phase III study. Ophthalmology. 2011 Aug;118(8):1594-602. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology. 2011 Oct;118(10):2041-9. In addition it is not clear whether the 12 month GENEVA data paper was used for AE rate in the comparison ICER calculations of ranibizumab versus dexamethasone : Julia A. Haller, Francesco Bandello, Rubens Belfort Jr, Mark S. Blumenkranz, Mark Gillies, Jeffrey Heier, Anat Loewenstein, Young Hee Yoon, Jenny Jiao, Xiao-Yan Li, Scott M. Whitcup for the Ozurdex GENEVA Study Group. Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion: Twelve-Month Study Results. Ophthalmology. 2011 Dec;118(12):2453-60	Comments noted. The Committee considered the 12-month open-label extension of both trials, the HORIZON study. See section 4.9 and 4.10 of the FAD.

Consultee	Comment	Response
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Summary of clinical effectiveness is fair except that in section 4.5 of the ACD it states " It also noted that ranibizumab provided sustained gains in BCVA at 12 months in both BRAVO and CRUISE, but that these were not statistically significant." This is incorrect as stated above the p values in the papers cited above are highly significant for benefit in BRAVO and CRUISE at 12 months (p=<0.01 and p=<0.001 respectively). There are particular concerns regarding interpretation of the evidence with regards to cost effectiveness as outlined in sections i) to v) above. The issue of better-seeing eye analysis versus worse-seeing eye seems appropriate but there are significant uncertainties regarding other key parameters such as source of utility scores used and ICER analysis of ranibizumab versus GLP. The cost effectiveness if a patient presents with CRVO in their better-seeing eye (10% of patients) needs a clearer statement. It appears from Table 67 of the ERG report that if a patient does present with CRVO in their better-seeing eye then the use of ranibizumab in this particular cohort is highly cost effective at £9,515 ICER of ranibizumab versus best supportive care. The ICER calculation for ranibizumab versus dexamethasone for both BRVO and CRVO appears to underestimate the cost of adverse events for dexamethasone implant. The cost of AEs for ranibizumab is calculated at £61.00 (see tables 69 and 74 of ERG report) whilst for dexamethasone implant is only £152.00 (see tables 72 and 75 of ERG report). It is not clear what rate of IOP medication or cataract rate is used for these analyses. Previously, the 6 month cataract rate of 7.3% from the original Geneva trial has been used to estimate the extrapolated cataract rate at 12mths or after 2 injections. However, a recent update of the GENEVA trial shows that the cataract rate after 2 dexamethasone implant injections at 12 mths is as high as 29.8% (90/302 phakic eyes : Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion Twelve-Month Study Results : Haller et al Ophthalmology. 2011 Dec;118(12):2453-60). It is possible that the cataract rate for repeated dexamethasone injections has been underestimated and that this could lead to an	Comment noted. The FAD has been amended to reflect this (section 4.10). Comment noted. The Committee considered the manufacturer's revised approach to deriving utilities for the 'better-seeing eye' using Czoski-Murray et al (2009) (formerly referred to as Brazier et al. 2009). The Committee concluded that although uncertain, the use of utilities as applied using the Czoski-Murray equation was acceptable. This is summarised in the FAD (section 4.15). Comment noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of

Consultee	Comment	Response
	increased cost of AEs for dexamethasone and a subsequent reduction in the ICER. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Further clarification over the issue of the cohort of patients presenting with RVO in their better-seeing eye and ICER calculations is required. In the case of CRVO, the committee agree that "It was aware that current standard treatment in the UK (for CRVO) is dexamethasone or anti-VEGF drugs and therefore comparing ranibizumab with best supportive care in CRVO was not relevant to UK clinical practice." This is an appropriate statement and consistent with the RCOphth interim guidelines on RVO management (Dec 2010). Thus comparing ranibizumab with dexamethasone the committee state the most plausible ICER is £37,400 per QALY. The RCOphth are concerned that the AE cost for dexamethasone may have been underestimated and that the ICER value may be lower. In the case of BRVO, the committee state that "… the most plausible ICER for ranibizumab versus dexamethasone in BRVO was £31,100 per QALY gained while ranibizumab versus grid laser photocoagulation in BRVO was likely to be in excess of £20,500 per QALY gained." As with CRVO there may have been an underestimate of the AE cost of dexamethasone. **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 gender, race, disability, age, sexual orientation, religion or belief?** No **Matters of factual nature** In section 3.5 the ACD states "…..At month 12 of the BRAVO trial (that is, at the end of the 6-month observation period, during which all patients could receive ranibizumab as needed), the 0.5 mg ranibizumab group reported an average gain in BCVA baseline score of 18.3 letters (95% CI 15.8 to 20.9) compared with the sham (plus ranibizumab) group that had gained 12.1 letters (95% CI 9.6 to 14.6, **p**	amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD). .

Consultee	Comment	Response
	value not reported)." The p value is reported in the full published paper as p = <0.01 (Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG, Murahashi WY. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion:12-month outcomes of a phase III study. Ophthalmology. 2011 Aug;118(8):1594-602.)	Comment noted.
	In section 3.6 the ACD states "… in the CRUISE trial … The manufacturer reported that the improvements in visual acuity in the ranibizumab group at month 6 were generally maintained, through to month 12 with treatment as needed (13.9 letters [95% CI 11.5 to 16.4] for ranibizumab; 7.3 letters [95% CI 4.5 to 10.0] for sham (plus ranibizumab) group; **p value not reported**)." The p value is reported in the full published paper as p = <0.001 (Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology. 2011 Oct;118(10):2041-9.)	Comment noted. This has been amended in the FAD to reflect this (sections 3.5)
	In section 4.5 the ACD states "It also noted that ranibizumab provided sustained gains in BCVA at 12 months in both BRAVO and CRUISE, but that these were not statistically significant." This is incorrect as stated above the p values are highly significant for benefit in BRAVO and CRUISE at 12 months (p=<0.01 and p=<0.001 respectively).	Comment noted. The FAD has been amended to reflect this (section 3.6).
	In section 3.18 the ACD states "Furthermore, clinical advice to the ERG suggested that concomitant use of ranibizumab and grid laser photocoagulation does not represent how ranibizumab would be used in clinical practice." It is likely that in the majority of patients ranibizumab would be used as monotherapy. However, there will be a proportion of patients who may be considered for combination therapy with laser. In the BRAVO study 21.4% of patients received concomitant laser in the initial 6 month treatment period of ranibizumab. This would be a reasonable estimate for practice in the NHS with the available evidence.	Comment noted. The FAD has been updated to reflect this (section 4.10).
		Comment noted. This paragraph reflects

Consultee	Comment	Response
		the evidence reported by the ERG.
RNIB	**Section 1** Appraisal Committee's preliminary recommendations : We believe that NICE should approve ranibizumab for the treatment of macular oedema secondary to retinal vein occlusion (RVO). This is essential for RVO patients where dexamethasone (Ozurdex) is contra-indicated, which includes those with: • advanced glaucoma which cannot be adequately controlled by medicinal products alone • previous raised intraocular pressure with steroids • hypersensitivity to dexamethasone • active or suspected ocular or periocular infection Ranibizumab is an important treatment option for patients with macular oedema secondary to central retinal vein occlusion (CRVO). This type of RVO is the most severe and grid laser photocoagulation is not effective in this subgroup **Section 4** Consideration of the evidence: Comment on the comparator: We are concerned that Avastin is being used as a comparator in this appraisal. There is still insufficient data to draw firm conclusions on the comparative safety of this drug in the treatment of wet AMD. Like the Royal College of Ophthalmologists, we feel the Medicines and Healthcare Products Regulatory Agency and NICE must review the use of Avastin in the treatment of this condition. We also believe it is vital that a national body is identified to take responsibility for risk management and pharmacovigilance to monitor the ongoing usage of Avastin in the eye. (b) Comment on the Committee's quality of life assumption:	Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Consultee	Comment	Response
	The Evidence Review Group and Committee both assume that a patient's quality of life only improves if their best corrected visual acuity (BCVA) improves by 20 letters or more. However, patients and experts tell us that a gain of 10 letters or more is significant and clinically meaningful. Therefore, we believe the quality of life benefits have been underestimated	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal National Institute for the Blind (RNIB) – (Prof Gibson)	I am writing to you regarding the above appraisal which I attended on behalf of the RNIB as a consultee expert. I would like to comment under the following heading: **"Are the provisional recommendations sound and a suitable basis for guidance to the NHS?"** It is important that ophthalmologists are able to treat patients with RVO for which Dexamethasone (Ozurdex) may be contra-indicated and it is that we are able to offer a licensed anti-VEGF drug in these situations. Contraindications to Ozurdex would be cases with existing glaucoma, previous raised intraocular pressure with steroids, known adverse reactions to dexamethasone and cases where large needle intraocular injections may be inadvisable (Ozurdex is 22 gauge compared to 30 gauge for ranibizumab) i.e. needle phobia, recent intraocular surgery. For these patients an alternative to Ozurdex is required, and ranibizumab should be approved for these special cases, which will represent limited numbers.	Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Nominating organisation	Comment	Response
Sobha Sivaprasad	It is disappointing that the use of ranibizumab is not recommended for this condition based on this ACD. I have noted my comments under 3 of your suggested headings below: **<u>Has all of the relevant evidence been taken into account?</u>** ***Mortality*** I refer the Committee to the NHS Evidence Review in 2010, which summarises the published evidence for an excess mortality risk associated with RVO. This review notes that 'the body of evidence from observational studies on this subject are conflicting'. Whilst there is some evidence suggesting an increased risk of cerebrovascular mortality, there are other studies suggesting no increased risk. It is of concern that the Tsaloumas study has been selected, whilst the wider body of evidence has been ignored. In addition this study suggests an increased risk of myocardial infarction rather than overall mortality; as may have been interpreted in this appraisal. All the evidence regarding overall mortality in RVO patients must be taken into account in order to reach a balanced view. Based on all the published evidence, it is not reasonable to conclude that there is an increased overall mortality risk for these patients. Furthermore cardiovascular assessment and management of cardiovascular risk factors, as recommended by the Royal College of Ophthalmologists, is likely to have improved the risk of mortality in patients with RVO since the Tsaloumas study, which begun in the 1980s. ***10 letter changes in BCVA*** As my clinical colleagues and I confirmed at the Committee Meeting, a change in BCVA of at least 10 letters is considered clinically meaningful. This level of improvement can be of significant benefit to	Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD). Comment noted. The Committee concluded that the evidence on the risk of cardiovascular mortality associated with RVO was unclear, and therefore it need not be included in the base-case model to the degree applied in the original ERG report. However it remains an uncertainty in the analysis (section 4.17 of the FAD). With regard to mortality risk associated with visual impairment, the Committee noted that the ERG had accepted the revised approach to applying excess mortality

Nominating organisation	Comment	Response
	patients, even when vision in the other eye is unaffected. Using the Brazier utilities presented in the ERG's report (page 108) would not capture these important benefits to patients of 10 letter change in BCVA. These suggest that patients with 20/80 (6/30) BCVA and 20/400 (6/120) BCVA have the same utility value applied. This difference is equivalent to 35 letters, whereas our comments to the Committee were that much smaller changes in vision are of benefit to patients. To set this in context, 6/30 snellen metres is moderately impaired vision, whereas 6/120 is likely to be a blind eye. Therefore, I do not feel that the evidence about a clinically meaningful difference of 10 letters has been taken into account. ***Utilities for worse-seeing eye*** The evidence for the 0.1 estimate of overall utility gain in the worse-seeing eye is not clear. I am aware of the study by Brown and colleagues in which a difference of around 0.1 was suggested for patients with good bilateral vision and good vision in only one eye; the second eye having vision less than 6/12. This implies that more than 0.1 could be derived from improving vision in a worse seeing eye that has very poor vision or is blind. The Brown study was a small sample of patients, which means it should be interpreted cautiously, but it is noteworthy that some patients with unilateral visual impairment had utility values as low as 0.33. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** ***Patients with Ischaemia*** The ACD implies that the evidence for ranibizumab cannot be applied to patients with any degree of ischaemia. I would like to clarify that brisk afferent pupillary defect is clinical sign of irreversible ischaemic vision loss and is equivalent to severe retinal ischaemia. Therefore, RCO guidelines do not recommend any treatment for this group of patients. Patients with less severe forms of ischaemia are likely to	associated with visual impairment (see section 4.21; also discussed in section 3.26 and 3.33). Comment noted. Comment noted. The Committee considered that a 0.3 utility gain associated with treating the 'worse-seeing eye' seems high given that utility is driven primarily by the 'better-seeing eye', and therefore lacked face validity. The Committee was also aware of the results of an analysis from NICE technology appraisal guidance 229 (Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion) the details of which are commercial in confidence. The Committee concluded that a utility gain of 0.1 associated with treating the 'worse-seeing eye' was appropriate. See section 4.16 of the FAD. Comment noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with

Nominating organisation	Comment	Response
	benefit from treatment, including with ranibizumab. It is important to ensure the summary of clinical effectiveness is clear on this point, to avoid an unnecessary restriction of treatment in patients who could benefit. As it stands, the ACD is slightly misleading on this issue. ***Assumptions about the effectiveness of laser*** The Committee notes that the unpooled estimates for the sham group in BRVO during months 7-12 were higher than the pooled estimates. It is important to remember that the BRAVO study introduced ranibizumab to the sham arm from month 7. Therefore the outcomes in the sham arm from month 7 are actually representative of patients treated with ranibizumab for the first time, not sham injections. It seems to me to be quite unreasonable to conclude that ranibizumab is not cost-effective compared to laser, when it is actually being compared to ranibizumab. ***Bevacizumab*** There are very few evidence based studies on bevacizumab for RVO and Novartis presented data from observational studies in wet AMD that suggest systemic safety concerns might be associated with bevacizumab in the eye. Due to these reasons and given that bevacizumab is not routinely used in the NHS for eye conditions, it is prudent that provision to monitor and review its safety when used in the eye is established in the NHS. ***Dexamethasone implant*** The Committee has concluded that all the ICERs for ranibizumab compared to dexamethasone are underestimated. However, the summary of cost effectiveness evidence does not take account of the increased frequency of retreatments in clinical practice, compared to the frequency studied in GENEVA. As noted in the NICE appraisal of dexamethasone implant, it is likely that patients would be treated every 4 months (rather than every 6 months) and this would increase the number of clinic visits as well as the cost of drug. Importantly, there is also uncertainty about the adverse events of treatment – both	significant retinal ischaemia. This is summarised in the FAD (section 4.9). Comment noted. The Committee's consideration of the manufacturer's revised approach to address the concerns regarding the use of pooled transition probabilities is summarised in the FAD (section 4.18). Comment noted. The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in visual impairment caused by macular oedema secondary to retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8). Comment noted. The Committee was aware of remaining uncertainties regarding the possible confounding in the data resulting from both groups in the CRUISE trial receiving ranibizumab as needed from month 7 (section 4.10). It was also aware of the remaining uncertainty because of the absence of a direct

Nominating organisation	Comment	Response
	in relation to an increased retreatment regimen than studied in the trials and in relation to the long term efficacy beyond the 12 month data currently available. I also note that an increased mortality rate for RVO was not applied during the dexamethasone appraisal. **<u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>** For the reasons set out above, I do not believe that the provisional recommendations can be considered are appropriate guidance. I am confident that further review of the evidence will ensure that a sound decision is reached.	comparison with dexamethasone, however on balance the Committee considered that the most plausible ICER for ranibizumab for visual impairment caused by macular oedema secondary to CRVO was between the £20,000 and £30,000 per QALY gained thresholds. However, there remained uncertainties because of the absence of a direct comparison with dexamethasone. It could therefore be considered a cost-effective use of NHS resources. Comment noted. The Committee has now recommended ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion.

Comments received from commentators

Commentator	Comment	Response
Allergan	***Has all of the relevant evidence been taken into account?*** Yes ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** Allegan would like to endorse and reiterate the points made by the ERG with regard to the indirect comparison of Ozurdex to ranibizumab. Allergan agrees that the exploratory indirect comparisons conducted by the ERG and provided by the manufacturer in its economic comparison are biased to favour ranibizumab efficacy because of differing patient characteristics in the RCTs informing the comparison (namely GENEVA for Ozurdex and BRAVO	Comments noted. The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD). The Committee was aware of remaining uncertainties regarding the possible confounding in the data resulting from both groups in the CRUISE trial receiving ranibizumab as needed from month 7 (section 4.10). It was also aware of the remaining uncertainty because of the absence of a direct

Commentator	Comment	Response
	& CRUISE for ranibizumab). These differences included: • greater duration of macular oedema in both the BRVO and CRVO patient populations of GENEVA versus BRAVO and CRUISE, respectively, • lower baseline best-corrected visual acuity and larger central retinal thickness measures in both BRAVO and CRUISE versus GENEVA, and • lack of specific criteria to exclude ischaemic patients in the GENEVA study. As a result, the ERG cautions (and Allergan agrees) that any differences in efficacy between Ozurdex and ranibizumab presented in the ACD and ERG report should be interpreted with caution. The most appropriate manner to assess the relative efficacy of these two products would be a head to head clinical study. ***Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*** Yes ***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 gender, race, disability, age, sexual orientation, religion or belief?*** No ***Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?*** No	comparison with dexamethasone, however on balance the Committee considered that the most plausible ICER for ranibizumab for visual impairment caused by macular oedema secondary to CRVO was between the £20,000 and £30,000 per QALY gained thresholds. However, there remained uncertainties because of the absence of a direct comparison with dexamethasone. It could therefore be considered a cost-effective use of NHS resources.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	We agree with this recommendation as, based on the available information, this treatment would not be cost-effective use of NHS resources, compared to other treatment options for the same condition. Ranibizumab for the treatment of macular oedema secondary to RVO is not a cost effective use of NHS resources The Committee determined that the most plausible ICERs for ranibizumab compared with alternatives were all above the ranges usually considered cost-effective for NHS use (i.e. Â£20,000 to Â£30,000 per QALY gained).	Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committee's concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

* 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
	3	The clinical trials that assessed the effectiveness of ranibizumab are not fully generalisable to NHS clinical practice. There is therefore a lack of evidence for the effectiveness of ranibizumab for treatment of RVO in patients with severe ischaemia. The outcomes in the trial of ranibizumab for branch retinal vein occlusion were confounded. In the BRAVO trial, patients were treated with monthly ranibizumab or sham injections for six months however, after three months the patients could receive grid laser photocoagulation for rescue treatment. Â This was used in 57.6% of patients in the sham injection group and 21.4% of the ranibizumab group in the first six months. Â It was noted that the treatment period of the BRAVO trial was insufficient to capture any benefits of grid laser photocoagulation on patient outcomes, which may last longer than three years. Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but no head to head clinical trials comparing these two treatments against each other are yet available. Neither BRAVO or CRUISE trial compare ranibizumab with dexamethasone implant (current practice).	Comments noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with significant retinal ischaemia and is summarized in the FAD (sections 4.9). The issue of confounding in the BRAVO trial was considered by the Committee and is summarized in the FAD (section 4.10, 4.13, 4.23 and 4.24) The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8).

Role*	Section	Comment	Response
	4	The manufacturer had not compared ranibizumab against bevacizumab as specified in the scope.For CRVO Base case estimates produced by the ERG were an ICER of Â£43,800 / QALY gained for ranibizumab vsbest supportive care, and Â£37,400 / QALY vs dexamethasone. The ERG performed an analysis that concludes ?ranibizumab would need to generate 1.7 times more QALYs than bevacizumab (each month between months 2 and 6) in macular oedema secondary to CRVO to give an ICER at the top end of the range usually considered cost effective?. Bevacizumab was dominant over ranibizumab in a cost minimization analysis meaning that it is better value for the NHS. Dexamethasone was considered an appropriate comparator as it is currently recommended for use in this indication in the NHS. The Committee said that ?licensing is not considered a prerequisite for consideration of a comparator in a NICE technology appraisal as long as it is in routine use or is considered best practice?. Clinical specialists said that bevacizumab is currently reasonably widely used in the NHS, but the extent of its use varies between centres.	Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to the economic model to address the Committee's concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD). The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8).

Role*	Section	Comment	Response
	5	This is a condition for which there have been few treatment options in the past however, recently a number of treatments have become available. These treatments need to be incorporated into a care pathway, with clear selection criteria to ensure cost-effective use of resources. This is difficult when there is limited local experience and no head-to-head evidence comparing the different treatment options.	Comment noted.
NHS Professional	1	North Yorkshire & York are supportive of the decision on the basis of the evidence presented Health ecomonic evaluation presented	Comment noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Role*	Section	Comment	Response
	2	We are satisfied that a discount represents the most realistic patient access scheme and hope that any discount will represent a direct discount on the list price meaning any NHS business transactions ane straightforward. Â Any other scenario (e.g. Paying list price and provider reimbursed a discount as Novartis stock) is not preferred by the commissioner on the basis that this is unnecessarily complex necessitating admin staff to process any discounts in various departments, savings may not be realised.	Comment noted. The manufacturer of ranibizumab (Novartis) has agreed a patient access scheme (revised in the context of NICE technology appraisal 274) with the Department of Health which makes ranibizumab available with a discount applied to all invoices (section 2.4 of the FAD).
	3	We are disheartened by the lack of manufacturer comparison with bevacizumab, knowing NICE would accept Â this agent for comparison as license not a prerequisite for a comparator. We would consider bevacizumab is used in clinical practice to varying degrees across the NHS. This organisation is receiving requests for both these anti VEGFs for ophthalmic indications.We note the view of the clinical specialists indicating approximate equal efficacy and in the ERG analysis, bevacizumab would appear to offer more eye health for equivalent investment overall representing better value when resources are scarce. Â We would wish to clarify admin costs in 3.14, locally admin of Lucentis currently average cost approx Â£500, this is likely to be similar for other commissioners. Â Dexamethasone implant should equally be considered as a comparator within the analysis, this is formally now within treatment pathway, realistically as a bridge until NICE determines its position on Lucentis/antiVEGF for RVO. Locally clinicians have proposed there are some patients with glaucoma and retinal haemorrhage in whom laser and dexamethasone are not appropriate , whether cost effective for this group? Uncertain.	The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8).

Role*	Section	Comment	Response
	4	Consider that the relevant clinical trials have been included noting the lack of evidence for severe ischaemia and outcomes in BRAVO were confounded by rescue laser, and consider a correction to worse seeing eye with corrected utility values appropriate. Whilst accepting the PAS is in commercial confidence, it is difficult to comment on direct costs without detail.	Comments noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with significant retinal ischaemia and is summarized in the FAD (sections 4.9). Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Role*	Section	Comment	Response
	5	The drug administration schedule and follow up of patients for this service requires significant staffing not only of ophthalmologists to inject but also optometrists and other staff who run the service. Whilst patient numbers are less than DMO or ARMD, it is not clear how much capacity is available within the existing infrastructure to extend the service within provider organisations. In terms of the costing template, it is recognised that this can be delivered as an outpatient service. Commissioners would therefore ask that if this is agreed that costs are presented to reflect this.	Comment noted.
	6	Commissioner organisations recognise that NICE did undertake a scoping exercise to evaluate bevacizumab in eye conditions some time ago subject to referral from the Secretary of State to progress with this. It is our belief that the NHS commissioners would Â wish to see this evaluation undertaken.	Comment noted.

Role*	Section	Comment	Response
NHS Professional	1	We strongly concur wit the Committees preliminary recomendations. This is not a cost effective use of exceptionally scarce resources, there are significant flaws and weaknesses in the manufacturers case. It is entirely inappropriate that the manufacturer did not consider avastin as a comparator (though we understand the commercial reasons for not doing so), but from the perspective of the NHS at local level it is an entirely acceptable comparator. Were the committee to change their preliminary recomendation there would be significnant opportunity cost at local level, with disinvesmtnet in other opthalmology services being seen as necessary should clinicians start to use lucentis in this indication following a positive TA recomendation.	Comment noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).
	2	Without knowing the details of the price agreed with DH, it seems utterly ludicrous to expect the NHS locally to make any detailed plans for the introduction of this technology. Commissioners must know the price of this medicine in this indication and should be a part of the negotiations on price.	Comment noted. Upon publication of the final guidance, there will be a contact for the NHS to gain access to the discount (see section 5.3 of the FAD)

Role*	Section	Comment	Response
	3	The manufacturer had not compared ranibizumab against bevacizumab as specified in the scope. A drug currently used in the NHS for this indication, but this was considered by the committee based on analysis done by the ERG. We understand the obvbious commercial reasons for this, given the nature of the corporate chain between Roche, Genentech and Novartis. However, there is consensus and indeed reasonable evidence that VEGFs are superior to steroids, and that there is no compelling evidence that lucentis is any better than avastin (a conclusion also reached by the ERG). It also seems there is reasonable consensus that avastin is an acceptable alternative were lucentis not available to opthalmologists. Therefore we contend strongly that avastin IS a relevant comparator. The clinical trials that assessed the effectiveness of ranibizumab are not fully generalisable to NHS clinical practice! The scope for this technology appraisal included people with or without retinal ischaemia. However both the BRAVO trial, which had assessed RBZ for macular oedema following BRVO and the CRUISE trial which had assessed RBZ for macular oedema following CRVO excluded brisk afferent pupillary defect	Comment noted. The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8). Comment noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with significant retinal ischaemia and is summarized in the FAD (sections 4.9).

Role*	Section	Comment	Response
	4	we concur the the ERGs analysis that avastin is dominant over lucentis, and this should have a strong bearing on the eventual TA recomendation. for BRVO, we agree the manufacturers estimate of £20,500 per QALY gained for ranibizumab versus grid laser photocoagulation seems an underestimation. The ICER for ranibizumab versus dexamethasone for people with BRVO was Â£31,122.	Comment noted. The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8). Comments noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Role*	Section	Comment	Response
	5	The NICE costing template TA229 estimates that there are 18 patients with BRVO and 17 patients with CRVO who will be eligible for treatment per 100,000 population. For Bradford and Airedale this equates to approximately 100 patients per year. The costs of lucentis in this indication are not known precisely as there is a confidential PAS and PCTs do not know the price that has been agreed. It is assumed the price will be CONSIDERABLY more expensive than current treatments, thus representing a signficiant incremental net cost for the NHS locally, when considering current treatments. Whislt it is accepted that TA committees are precluded from considering affordability, we would wish to bring to the attention of the committee the not inconsiderable opoortunity cost of sight years forgone as a result of investment in this technology. Commissioners increasingly think in terms of programme budgets, and investment in one area of the eye programme budget must be met by explicit disinvestment elsewhere. There seems to be a reasonable consensus that VEGFs are superior to steroid treatment, and that avastin would be an acceptable alternative.	Comment noted. Since the Appraisal Consultation Document was published, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. The manufacturer has also made a number of amendments to the economic model. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).
	6	Innovativeness of the technology is an important consideration in taking into account considering related technology. In some cases NICE will take into consideration how innovative an intervention is. For ranibizumab the Committee concluded that ranibizumab is one of a group of innovative anti-VEGF treatments, and does not stand alone in this therapeutic area and its benefits are appropriately captured in the QALY calculation.	Comment noted. The Committee discussed how innovative ranibizumab was and agreed that anti-VEGF treatments were a substantial improvement over previous treatments, but considered that this improvement applied to the class of drugs, including bevacizumab. The Committee was not aware of any substantial benefits of ranibizumab over its comparators that were not already factored into the QALY estimation in the modelling (section 4.25 of the FAD).

Role*	Section	Comment	Response
NHS Professional	3	The clinical trials that assessed the effectiveness of ranibizumab are not fully generalisable to NHS clinical practice The scope for this technology appraisal included people with or without retinal ischaemia. However both the BRAVO trial, which had assessed ranibizumab for macular oedema following BRVO and the CRUISE trial which had assessed ranibizumab for macular oedema following CRVO excluded people with brisk afferent pupillary defect which is severe retinal ischaemia. There is therefore a lack of evidence for the effectiveness of ranibizumab for treatment of RVO in patients with severe ischaemia. Both trials had compared ranibizumab to sham injection rather than treatments used in current clinical practice (bevacizumab and dexamethasone invitreal implants). Although there were differences in the study populations of a study that had assessed dexamethasone (GENEVA), such as time to treatment after emergence of oedema, it was determined that indirect comparisons could be made. Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but no head to head clinical trials comparing these two treatments against each other	Comments noted. The Committee considered the approaches taken by the manufacturer in relation to the exclusion of people with significant retinal ischaemia and the relative effectiveness between ranibizumab and dexamethasone and are summarized in the FAD (sections 4.9 and 4.13). The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8).

Role*	Section	Comment	Response
	4	Ranibizumab for the treatment of macular oedema secondary to RVO is not a cost effective use of NHS resources The Committee determined that the most plausible ICERs for ranibizumab compared with alternatives were all above the ranges usually considered cost-effective for NHS use (i.e. Â£20,000 to Â£30,000 per QALY gained).The manufacturer did not compare its drug against bevacizumab. Bevacizumab (Avastin), like ranibizumab inhibits VEGF. It has marketing authorisation to be used in the treatment of some cancers, but has been used off-license for the treatment of macular oedema at lower doses. Comments from clinical specialists were that ranibizumab had approximately equal effectiveness to bevacizumab but because a license has not been sought for the use of bevacizumab in the eye, its safety in the eye is not assured. Additionally Â concerns were raised from patient experts about the use of unlicensed treatments for which there was no post-marketing surveillance, particularly if there were licensed alternatives. The Committee said that ?licensing is not considered a prerequisite for consideration of a comparator in a NICE technology appraisal as long as it is in routine use or is c	Comment noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD). The Committee considered the report by the NICE Decision Support Unit relating to the evidence on intravitreal bevacizumab injection in retinal vein occlusion. The Committee concluded that bevacizumab is an appropriate comparator but that the current evidence base is not sufficient for a reliable comparison between ranibizumab and bevacizumab. This is summarised in the FAD (section 4.4 to 4.8).

Role*	Section	Comment	Response
NHS Professional	1	It is deeply disappointing that Â we do not have access to Lucentis for retinal vein conclusions or diabetic retinopathy. Â The additional time taken by consultants to fill in individual funding requests for all those patients for whom ozurdex is not suitable (glaucoma, ocular hypertension etc) and the cost of the IFR panel sitting has not been costed. There is also the additional time needed in clinic with each patient as we have to explain that the best treatment (safety and efficacy) is Lucentis but they cant have that unless I put in an IFR but they may be able to have ozurdex as an option but our PCT is quibbling about whether an option means it is obliged to pay or not. In addition there is triamcinolone which we have used for years but the manufacturer says we shouldnt use in the eye and then again there is Avastin which NICE reported as being as effective as ozurdex with a better safety profile and probably cheaper but didnt recommend even as an option. There is also a loss of choice here. Some patients may prefer the injection in to their eye to have a small needle(unlike ozurdex) and not to run the risk of cataract and a 25% chance of ending up on glaucoma drops.	Comment noted. Since the Appraisal Consultation Document was published, the manufacturer has made a number of amendments to their economic model to address the Committees concerns relating to several assumptions used in the original model. The Committee considered these amendments in conjunction with the critique provided by the Evidence Review Group. In addition, the manufacturer submitted a patient access scheme, revised in the context of NICE technology appraisal 274. These amendments and revised cost effective estimates are summarised in the FAD (see sections 4.13 to 4.24). The Committee has now recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or is not suitable because of the extent of macular haemorrhage (see section 1.1 of the FAD).

Summary of comments received from members of the public

Theme	Response
Dear sir/madam A family member has this condition - hence my interest from semi-retirement. While it does seem that this agent is not an appropriate use of NHS resources - the documentation available is perhaps not presented in a manner that can allow accessible feedback Namely - the issuing of an erratum document alongside the main	Thank you for your comments. Following the consideration of a revised economic model by the manufacturer (including a patient access scheme submitted in 2013) and consideration of the critique by the Evidence Review Group, the Committee has recommended ranibizumab as an option for people with CRVO and for people with BRVO for whom grid laser photocoagulation has not been beneficial or

Theme	Response
evidence review group means I have found it difficult to work out what is what vis a vis changes/errors etc - SURELY it would be fairer and clearer to issue one finalised AND ACCURATE document - especially as both seem to have been made available for comment at the same time. IS this normal practice? On a more pedantic matter - the erratum document highlights changes made to tables RE sham amended to sham/0.5mg. What does this 0.5 mg mean - I assume volume of sham product injected - if so - this seems too detailed as this would be a natural assumption in such a study Im told. However, I have also been told that it may be that this means sham OR the agent - if so this really should be made clear! I am grateful for this opportunity to comment - a wonderful process	is not suitable because of the extent of macular haemorrhage. In line with NICE processes for an open and transparent consultation, all the documentation that Committee receives in order to make its decisions is shared in exactly the same form as Committee receives them. Please refer to the NICE guide to the STA process for further information. Comment noted. The terminology and abbreviations are sometimes confusing and through our guidance documents we aim to make these as understandable as possible. The amendment to 'sham/0.5 mg' refers to those people who were randomised to the 'sham'-injection arm of the trial, but because of the trial protocol set out at the beginning of the study, these patients were also allowed to receive 0.5 mg of ranibizumab after 6 months of the trial starting. Therefore in some of the source documents (the manufacturer's evidence submission and the Evidence Review Group's report) this is then abbreviated to the 'sham/0.5 mg (ranibizumab) group. Section 3.2 of the Final appraisal determination document explains the protocol in a bit more detail.