NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion [ID844]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Bayer**
   - **Royal National Institute of Blind People** - *endorsed by patient expert Melba Ryde*
   - **Royal College of Nursing**
   - **Royal College of Ophthalmologists**
   - **Novartis**

   No comment response received from the Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - **Professor S Rajendran – patient expert**, nominated by Royal National Institute of Blind People

   No comments received through the NICE website

4. **Evidence Review Group – revised analysis**

5. **Company response to Evidence Review Group revised analysis –** prepared by Bayer

6. **Evidence Review Group Response to consultation comments**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Aflibercept for treating visual impairment caused by macular oedema after branch 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 companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Bayer	**Issue – there is an error in the calculation of the 'most plausible' ICER. In our analysis we calculate a revised most-plausible ICER of £20,100.** *The ERG made 13 revisions to the company's submitted model (listed on page 129 of ERG report). One of these revisions was a structural change to the model, the stated intent of which was to allow "**antiVEGF dosing for years 6+ of 3.2 annual administrations for 30% of patients for 5 years**". This structural change was a major driver of the ERGs increased ICER relative to that in our submission. The ERG model estimated additional costs of [redacted] in the aflibercept arm as a result of this extra treatment. However, we think there are errors in the ERG model and that the [redacted] figure is a large overestimate:* • *Firstly, the ERG has modelled 100% of patients getting 3.2 injections and not 30% of patients.* • *Secondly, the ERG uses an 'adjustment' factor which appears to reintroduce into the model patients who have previously discontinued. Injections are therefore applied to everyone who is alive in the model* Relevant information from the ERG's model has been extracted and is presented in Table 1. The ERG base case provides the results when all 13 revisions have been implemented (ICER £28,813). Sensitivity analysis 08a (SA08a) provides the results when no treatment from years 6-10 are included in the model but the other 12 ERG	Comment noted. The ERG acknowledged this modelling error and submitted corrected analyses (Committee meeting slides, slide 26). The committee was aware of the modelling error, considered the corrected analyses provided by the ERG and re-examined its original conclusions summarised in the FAD (see sections 4.14 and 4.15).

Consultee	Comment [sic]	Response
	revisions are implemented (ICER £18,355). For this scenario there were no additional QALYs added for the extra 5 years of treatment. Relative to the ERG base case there is a cost increase in the aflibercept arm of [redacted] attributable to the extra treatment (i.e. [redacted]). This is a significant overestimate of the costs that are possible for 30% of patients receiving 3.2 injections annually for years 6-10 (see appendix 1 for details). [Appendix 1 has been received but not reproduced in the table] Bayer analysis We applied in the ERG model 30% of patients getting 3.2 injections in years 6-10 and turned off the adjustment factor (by setting it to 1) so that previously discontinued patients were not reintroduced in to the model. The ICER obtained was £20,100 (see appendix 1 for details). [Appendix 1 has been received but not reproduced in the table] **Table 1. ICERs: based on ERG model**	

Aflibercept first-line		Laser -aflibercept			
Costs	**QALY**	**Costs**	**QALY**	**Δ COSTS**	**Δ QALYs**
ERG base case (i.e. all 13 ERG revisions implemented)					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG SA08a – No antiVEGF yrs 6+ (i.e. 12 non-structural changes implemente					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bayer analysis in ERG model – 0.96 injections applied to patients who have n discontinued					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Consultee	Comment [sic]	Response
	We consider the ICER of £20,100 is still an overestimate because: • The analysis assumes no clinical benefit to the extra 5 years of treatment. Physicians would not treat unless there was a benefit to doing so and the inclusion of treatment benefit in these years, even if small, would reduce the ICER further.	
Bayer	**Issue – Areas of upward uncertainty** *In the ACD it is stated that when the committee's preferred assumptions were implemented the most plausible ICER was £28,813 per QALY. However, two main areas of uncertainty were highlighted which could lead to the ICER being above the range that could be considered a cost-effective use of NHS resources. The two main areas of uncertainty are:* *1) The handling of loss to follow-up data in the company model i.e. LOCF approach* *2) The use of utility values from Brown 1999 instead of those from Czoski-Murray* **<u>Last observation carried forward methodology (LOCF)</u>** *Concerns have been raised regarding the use of the last observation carried forward approach for drop-outs. It was hypothesised in the ERG report that* *"Since many, if not most, will not have resolved by the time they drop out there may be some unobserved rebound among these patients. Given the different immediate treatment effects and the different administration schedules, the size of this rebound may differ between the arms. There are reasons to believe that this rebound among drop outs may be bigger in the*	Comment noted. The committee considered this approach and additional analyses presented by the company. The committee also considered additional analyses presented by the ERG on the impact of LOCF, summarised in *ERG analyses and ACD response* (page 2).

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<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
aflibercept-laser arm than in the laser-aflibercept arm, particularly among patients discontinuing before 6 months
……Any tendency for drop-outs to rebound to baseline might worsen the clinical and cost-effectiveness estimates for aflibercept-laser compared to laser-aflibercept”
To address this uncertainty we have conducted what should be considered an extreme scenario analysis. In this scenario patients who discontinue aflibercept during the first six months have their visual acuity return immediately to baseline. The impact on the ICER of this worst case analysis is minimal i.e. an increase of [redacted] to the cost per QALY (see Appendix 2 for details). A minimal impact on the ICER is to be expected as there are only 6 patients in the aflibercept arm who discontinue in the first six months and the efficacy results are driven by the majority of patients who remain on treatment. Our analysis has been conducted in the ERG model without changes to the adjustment factor or number of injections. [Appendix 2 has been received but not reproduced in the table]
Table 2. Results – LOCF sensitivity analysis
<table>
<tr><th>Change in costs</th><th>Change in QALYs</th><th>ICER</th></tr>
<tr><td colspan="3">ERG base case</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>28,813</td></tr>
<tr><td colspan="3">Scenario analysis – patients who discontinue aflibercept have VA return to baseline value (ERG base case costs)</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>29,560</td></tr>
</table>
</td><td></td></tr>
</table>

Consultee	Comment [sic]	Response
Bayer	**Issue – Areas of upward uncertainty** **<u>Use of Brown 1999 utility values</u>** We used the Czoski-Murray utility values in the base case for this appraisal. However in this appraisal the committee has stated a preference for values from Brown 1999, the use of which would increase the ICER from the most-plausible figure. In the pre-meeting briefing document (section 2 – Relevant Appraisals), two appraisals are listed, both of which were appraised by Committee C (TA283 – ranibizumab in BRVO & TA305 – aflibercept in CRVO). In TA283 the manufacturer used the Brown 1999 utility values in their base case but Committee C preferred the Czoski-Murray values which were described as acceptable for decision-making. In addition, in TA305 Committee C considered the use of Brown utilities to be a "worst-case" scenario. We consider that this committee accepting the use of Czoski-Murray utility values for decision making for ranibizumab in the same disease area, but then using utility values from Brown 1999 to support poorer cost-effectiveness estimates for aflibercept in the same disease area (this appraisal) is difficult to justify.	Comment noted. The committee discussed the preferred source of utilities. The committee examined the source of utilities used in previous visual acuity appraisals. The committee noted that the maximum quality of life gain in the WSE should be 0.1. The committee considered that Czoski-Murray with a 15% WSE proportional impact and Brown with a 30% WSE proportional impact provided estimates closest to 0.1 and agreed that these could be used as a basis for its decision (see FAD section 4.12).

Consultee	Comment [sic]	Response
Bayer	**Issue – Areas of upward uncertainty** ***Use of EQ5D utility values.*** Both the ERG and ourselves appear to be quoting from the same source either in support of the suitability of the EQ5D or its unsuitability i.e. the NICEQol project, funded by the MRC and NIHR (Longworth L et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014;18(9)) The following is from the results section of the report *"Most evidence was found for the EQ-5D. Nearly all studies found significant differences between patients with the condition and a control group without it. Studies comparing EQ-5D scores across severity groups were more mixed, with most finding little or no difference between groups defined by clinical measures of visual impairment."* We therefore agree with the ERG that the EQ5D has been found to have some response according to having a vision-related disease compared to not having vision-related disease. However, the report found that the EQ5D was insensitive to severity of visual impairment. If the EQ5D is unable to show the impact of different health states according to disease severity it is of no use in technology appraisals which are assessing cost-effectiveness of treatments whose impact is on disease severity. We consider that the inclusion of ICERs based on EQ5D utility values are of no relevance.	Comment noted. The committee was aware that the EQ-5D may be insensitive to measuring changes in utility in visual acuity appraisals. The committee noted that Czoski-Murray with 15% WSE proportional impact and Brown 30% WSE proportional impact provided estimates that could be used as a basis for its decision (see FAD section 4.12).

Consultee	Comment [sic]	Response
Bayer	I**ssue – a first-line recommendation would position aflibercept ahead of ranibizumab in the treatment pathway** We believe that another factor that was mentioned in the Appraisal committee meeting (11th May), but not written in the ACD document, may have influenced the draft recommendation i.e. aflibercept as a first line treatment option positions it ahead of ranibizumab in the treatment pathway. We hope that this has not influenced the decision of the committee. NICEs processes are set up to constantly review recommendations in light of new evidence both for single technology appraisals and guidelines. Anti-VEGF treatment was relatively new at the time of the appraisal of ranibizumab in BRVO and the position for ranibizumab was based on the data and prevailing uncertainties at that time. Recent RCO guidelines, based on a maturing evidence base and years of clinical experience, recommend these therapies as first-line treatments. We have presented robust evidence showing the superiority of aflibercept-laser over laser-aflibercept in a trial well designed to investigate first and second line treatment of both laser and aflibercept. In addition, we have shown in an economic model, which for the first time in BRVO considers costs and effects of a pathway of care, that aflibercept is cost-effective as a first-line treatment option. Finally, although not described in the ACD, aflibercept as a first-line treatment was assessed in the company submission against laser followed by ranibizumab (the current pathway of care) and was shown to be cost-effective (table 94 from our submission). These initial analyses were done using the MSM transition tables. We present in Table 3 the cost-effectiveness results of aflibercept first-line versus laser-ranibizumab using shift tables (the ERGs preference) and using an	Comment noted. The committee discussed the proposed position of aflibercept. The committee was aware of the final recommendation made in the appraisal of ranibizumab but made its decision based on the clinical and cost effective evidence presented in this appraisal, summarised in the FAD (sections 4.14 and 4.15).

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>assumption of equivalent efficacy for the two anti-VEGF therapies. Please note that this analysis uses the PAS price for aflibercept and the NHS list price for ranibizumab. We have used the ERG model which produces a base case ICER of £28,813 for this analysis.
Table 3. Aflibercept first-line compared to laser followed by ranibizumab
<table>
<tr><th colspan="2">Aflibercept first-line</th><th colspan="2">Laser followed by ranibizumab</th><th></th><th></th></tr>
<tr><th>Costs</th><th>QALY</th><th>Costs</th><th>QALY</th><th>Δ COSTS</th><th>Δ QALYs</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td></td></tr>
</table>

Consultee	Comment [sic]	Response
Bayer	***Summary*** The committee appear to have accepted evidence for the benefit of aflibercept as a first-line treatment and accepted the ERG changes to the model resulting in a most-plausible ICER of £28,813. We believe the ERG model has errors which lead to an overestimation of the costs and consequently the ICER for aflibercept as a first line treatment. In a revised base case, accepting all the ERG changes to the company model, but with modifications to treatment in years 6-10, we estimate an ICER of £20,100. We have shown that the last observation carried forward approach has no meaningful impact on the ICER and that there is minimal upward uncertainty - indeed, there are reasons to believe that the ICER might be better. We do not consider that the current summaries of cost-effectiveness are a reasonable interpretation of the evidence and consequently are not a sound and suitable basis for guidance to the NHS. We hope the committee will give further consideration to the use of aflibercept as a first-line treatment option. We believe it is a cost-effective use of NHS resources.	Comments noted. Responses are detailed above

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Royal National Institute of Blind People: patient expert	It is noted in the consultation report that the committee has carefully considered all the evidences before arriving at conclusions/recommendations. I could see that both the clinical effectiveness and cost implications to NHS were carefully considered but I am not sure that this is a balanced approach. It is important to weigh the additional benefits to patients from using aflibercept over other comparators. The efficacy of aflibercept to bind both VEGF-A and VEGF-B is crucial in the management of macular oedema following BRVO and other comparators, for instance ranibizumab and dexamethasone, do not provide the above benefits of aflibercept but to bind only VEGF-A. The high binding affinity of aflibercept to VEGF-A and VEGF-B has also been published in journals elsewhere. This clearly justifies that aflibercept qualifies for the first-line treatment option instead of the recommended second-line of treatment, which is at par with ranibizumab, after laser photocoagulation.	Comments noted. The committee discussed the placement of aflibercept in the treatment pathway. The committee acknowledged the binding affinity of aflibercept. Based on the clinical and cost-effectiveness evidence, the committee made its recommendation (summarised in the FAD, section 4.14 and 4.15).

Nominating organisation	Comment [sic]	Response
Royal National Institute of Blind People	We welcome the fact that aflibercept has been recommended as an option for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion. However, we are concerned that it has not been recommended as a first line treatment in the ACD. There is a significant amount of evidence showing that laser is inferior to anti-VEGFs in the treatment of BRVO. We also understand that patients who receive laser treatment first, do not fully benefit from anti-VEGF treatments later (if they are switched). We believe that NICE should recommend both aflibercept and ranibizumab as first line treatments for macular oedema due to branch retinal vein occlusion. The guideline must offer patients the superior treatment first â€“ this will give them the best chance of optimal outcomes. We strongly believe that patients in England and Wales should not be denied access to first line treatment with anti-VEGF agents (the superior treatment).	Comments noted. The committee discussed the placement of aflibercept in the treatment pathway. The committee discussed the benefits of receiving aflibercept early (discussed in section 4.6 of the FAD) . Based on the clinical and cost-effectiveness evidence, the committee made its recommendation (summarised in the FAD, section 4.14 and 4.15).
Royal College of Nursing	**Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive	Comment noted
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with visual impairment. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted

Nominating organisation	Comment [sic]	Response
Royal College of Nursing	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and consider that the proposed arrangement will not affect funding arrangements already in situ for this patient group. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted
Royal College of Nursing	**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?** The only group that will be affected is women who are pregnant or thinking of becoming pregnant. In the clinical trials arena, advice on risk of anti-VEGF in pregnancy is also given to male patients who may have plans to start a family. We are not aware of any adverse impact on people with disabilities that may be caused by the technology.	Comment noted
Royal College of Nursing	**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 ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted
Royal College of Ophthalmologists	**Has all of the relevant evidence been taken into account?** We welcome the availability of Aflibercept as another anti-VEGF agent for Macular oedema (MO) due to branch retinal vein occlusion (BRVO). However, The RCOphth	Comments noted. The committee discussed the placement of aflibercept in the treatment pathway. The committee discussed the benefits of receiving aflibercept early and

Nominating organisation	Comment [sic]	Response
	have a major concern in the suggested recommendation of its use in our patients. The Appraisal Consultation Document recommends that Aflibercept is used in eyes where laser photocoagulation has not been beneficial or laser photocoagulation is not suitable because of the extent of macular haemorrhage. This is contrary to the recommendation of the RCOphth that anti-VEGF should be used as first line agent based on the current evidence. The key points from the VIBRANT study show that: 1. Visual outcome following laser photocoagulation is inferior to Aflibercept. 2. If patients are treated with laser photocoagulation as first line, they fail to achieve the outcomes of patients initiated on Aflibercept monotherapy. Therefore, rescuing patients with Aflibercept after providing them with an inferior therapy deprives patients of their maximal visual potential. 3. Laser therapy failed in 74% of the patients and they required Aflibercept therapy later. Therefore, this waiting game with laser treatment should be avoided. 25% benefited from laser but the overall laser outcome was still inferior to Aflibercept therapy. This shows that for the majority of patients, laser was unnecessary and potentially damaging. 4. The inclusion criteria of the BVOS study was very restricted and therefore the outcomes of that study have not been replicated in real-life. Despite choosing the best group for the study, only 40% achieved 6/12 visual acuity outcomes after 36 months. This outcome is far inferior to the outcomes of anti-VEGF therapy, which were not available at the time, and therefore could not be used as a comparator. 5. Similar evidence is available for the higher efficacy of ranibizumab in treatment of macular oedema secondary to BRVO compared to laser photocoagulation (from the BRAVO Study).	noted the clinical efficacy of afilbercept compared with laser photocoagulation in untreated patients (see section 4.6 of the FAD). The committee also noted the proportion of parents in the laser arm that received rescue aflibercept treatment. Based on the clinical and cost-effectiveness evidence, the committee made its recommendation (summarised in the FAD, sections 4.14 and 4.15).

Nominating organisation	Comment [sic]	Response
Royal College of Ophthalmologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The above applies here for clinical effectiveness of aflibercept. Regarding the type of anti-VEGF, we agree with NICE that both ranibizumab and aflibercept are equally clinically effective. For cost-effectiveness, we believe that although the RCOphth guidelines is based on clinical effectiveness only, the guidelines does provide the most economical way of using anti-VEGF agents without compromising patient –level or population level outcomes for this condition. For example, if VA is 6/9 or better, it is best not to initiate anti-VEGF and allow for spontaneous resolution. All the clinical trials have used the visual acuity inclusion criteria of 24 to 73 ETDRS letters. As such this recommendation is backed with RCT evidence. The guidelines also suggest not initiating treatment with severe macular ischaemia. The RCOphth guidelines further suggest that anti-VEGF be stopped if there is no visual acuity gain after 3 injections and that is also based on evidence from BRAVO, VIBRANT, BRIGHTER etc. Therefore, if NICE has to impose restrictions in anti-VEGF use due to cost-effectiveness, the above suggestions will be welcome by patients and clinicians rather than restrict anti-VEGF to after laser photocoagulation.	Comments noted.

Nominating organisation	Comment [sic]	Response
Royal College of Ophthalmologists	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** As above, we would like to stress that the current ACD is not suitable or sound for NHS patients because: 1. NHS patients are offered an inferior treatment as first line when there is strong evidence that anti-VEGF is superior to laser treatment. 2. Patients who can afford anti-VEGF will have to go privately to get the ideal treatment option and this should be strongly discouraged as it raises issues on equity to access. 3. The over-all outcome of BRVO in the NHS will be inferior to those patients in other countries. 4. NICE guidelines is followed around the world and is held in high respect and NICE will be heavily criticised for recommending an obsolete treatment as first line when the world has moved on.	Comments noted.

Comments received from commentators

Commentator	Comment [sic]	Response
Novartis	**ACD, Page 9: Section 4.10** *"The committee understood that the probabilities could instead have been derived directly from patient data and considered that there was no evidence to suggest that these data should not be used in the model. The committee concluded that using real-world data to estimate the probabilities of improving or worsening visual acuity was a preferable approach."* **Novartis comment**: It is unclear what real world data were used to estimate transition probabilities in the economic model. The data appear to be derived from the randomised, controlled VIBRANT trial. The submitting company states under question B15 of the economic clarification document that "*Transition probabilities were derived using the MSM package in R. In this specific case the transitions of patients from the VIBRANT trial were converted to the 4 weekly cycles used in the model*." It is also unclear why the committee concludes that using real world data to estimate the probabilities of improving or worsening visual acuity is preferable when trial data are available. Does this refer to efficacy probabilities in the short or long term?	Comment noted. The committee noted the difference between a probability derived from a model and those taken from patient count data. The committee expressed a preference for those estimated from patient count data. It is acknowledged that the term may be unclear; the wording in the FAD has been amended for clarity (section 4.11).

Commentator	Comment [sic]	Response
Novartis	**ACD, Page 10: Section 4.12** *"It noted that in a sensitivity analysis, the ERG had lowered the proportional impact of a change in the best-seeing eye to 15%..."* **Novartis comment**: The approach undertaken by the ERG appears inconsistent with that used in past appraisals specifically the NICE appraisal of ranibizumab for bRVO (TA283)[1]. In TA283, Novartis made a revised model submission with an assumption of a 0.3 utility gain associated with treating the 'worse-seeing eye' relative to the 'better-seeing eye'. The ERG's base case analysis assumed a 0.1 utility gain derived from Brown (1999)[2]. The analysis highlighted that the assumption of some benefit associated with treating the 'worse-seeing eye' benefit was a key driver of cost-effectiveness. The TA283 final guidance document (Page 42, section 4.16) states *"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 concluded that a utility gain of 0.1 associated with treating the 'worse-seeing eye' was appropriate."* We therefore suggest that the same assumption (i.e. a *0.1 utility gain associated with treating the 'worse-seeing eye)* is made in this review to ensure consistency of the ERG analysis and committee assumptions.	Comment noted. The committee discussed the preferred source of utilities. The committee examined the source of utilities used in previous visual acuity appraisals. The committee noted that the maximum quality of life gain in the WSE should be 0.1. The committee considered that Czoski-Murray with a 15% WSE proportional impact and Brown with a 30% WSE proportional impact provided estimates closest to 0.1 and agreed that these could be used as a basis for its decision (see FAD section 4.12).

Commentator	Comment [sic]	Response
Novartis	**ACD, Page 11: Section 4.14** *"..ranibizumab was dominated by aflibercept (that is, was both more costly* **ACD, Page 12: Section 4.14** *"In these analyses, ranibizumab remained dominated by aflibercept."* **Novartis comment**: The wording around aflibercept dominating ranibizumab in the various sections of the ACD could be misleading and needs to be contextualised i.e. it should clearly state when the results are based on the ranibizumab list price or PAS price. Regarding the ranibizumab list price, please note that Novartis has reduced the public list price of ranibizumab from £742.00 to £551.00 per vial[3], effective 14th June 2016. The list price alteration does not impact the Patient Access Scheme (PAS), so the NHS purchase price is unchanged. This change will impact the accuracy of the cost-effectiveness comparisons of aflibercept vs. ranibizumab at list price that are reported in the ACD and accompanying documents.	Comment noted. The committee acknowledge that dominance is a technical term. The FAD has been amended to clarify and contextualise the term.
Novartis	**ACD, Page 12: Section 4.14** *"The committee was mindful of its conclusions regarding the clinical effectiveness of aflibercept compared with ranibizumab (see section 4.7), and noted that aflibercept's dominance of ranibizumab would be influenced by the results of the network meta-analysis. The committee considered the cost effectiveness of ranibizumab in the appraisal of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and considered that aflibercept and ranibizumab could be similar in terms of cost effectiveness."*	

Commentator	Comment [sic]	Response
	Novartis comment: We agree with the committee about being mindful of the conclusions regarding the clinical effectiveness of aflibercept compared with ranibizumab and ask that this view be made clear across the entire document. An NMA published by Regnier et al., 2014[4] explored the clinical efficacy of ranibizumab, aflibercept, laser and dexamethasone. The study was based on 8 trials (including trials that the ERG felt should have been in the submitting company's NMA) and showed that the point estimate results for gaining 15 or more letters favour ranibizumab over aflibercept; these results were not significant (median OR: 1.06; 95% CrI 0.16 to 8.94). The ERG comments on page 66 of the ERG report that a series of decisions by the submitting company led to a point estimate of efficacy favouring aflibercept over ranibizumab. It further states *"It is worth noting that if other assumptions had been made (as those made by Novartis), a point estimate favouring ranibizumab could have been obtained, although credible intervals were very wide with considerable overlap with the company's results."* It is also important to note that the base case results presented by the submitting company are based on deterministic analysis and are therefore sensitive to the point estimate of efficacy used. This is validated by some analyses conducted by the manufacturer. • A tornado plot (page 253 of the manufacturer's submission) highlights the uncertainty around this point estimate as when a greater odds of achieving a 15 or greater letter gain is considered, ranibizumab is cost-effective. • The scenario analysis in which all trials were included in the NMA (page	Comment noted.

Commentator	Comment [sic]	Response
	265 of the manufacturer's submission) used a median OR of 1.08 (Crl 0.45-1.45) for achieving a ≥15 letter increase with ranibizumab. This showed that laser followed by aflibercept is associated with a lower cost and a reduced QALY gain compared to ranibizumab after laser.	
Novartis	**ERG report, Page 86: Section 5.2.8** *"The number of 2nd line rescue ranibizumab treatments during the first year is assumed to be equal to that of 2nd line rescue aflibercept."* **Novartis comment**: The assumption of the same number of treatments for ranibizumab and aflibercept based on the VIBRANT trial is inconsistent with the approach taken in previous NICE technology appraisals for related conditions. Specifically: • In the 2013 NICE technology appraisal of ranibizumab in branch retinal vein occlusion (TA283)[1], the injection frequency for ranibizumab was derived from trial data. • In the 2014 NICE technology appraisal of aflibercept in central retinal vein occlusion (TA305)[5], the manufacturer's model derived the number of injections from the respective ranibizumab and aflibercept trials. • In the 2015 NICE technology appraisal of aflibercept for treating diabetic macular oedema (TA346)[6], the injection frequencies are derived separately for aflibercept and ranibizumab. The number of ranibizumab injections was derived from a weighted average based on reported data on the number of injections from the studies included in the NMA. In the FAD (section 3.2.9), the ERG states that the clinical effectiveness evidence for aflibercept	Comment noted. The committee was aware of the frequencies of administration between ranibizumab and aflibercept (committee slides, slide 28) used in previous appraisals and took it into consideration.

Commentator	Comment [sic]	Response
	relates to the dosing frequency used in the aflibercept trials; therefore, the estimate for the number of injections of aflibercept from these trials should be used in the base case because of their alignment to the dosing frequency. The ERG and the committee accepted these approaches in previous appraisals; it is therefore unclear why an alternative assumption of the same dosing is being accepted in this appraisal. We strongly propose that the methodology in this appraisal should be in line with that of the DMO (TA346)[6] appraisal, i.e., the number of ranibizumab injections should be derived from a weighted average of injections from the studies included in the NMA. A recent bRVO cost-effectiveness analysis by Adedokun and Burke (2016)[7] provides the dosing frequency for both aflibercept (9 injections) and ranibizumab (7.8 injections) in the first year based on the trials included in the NMA.	

Comments received from members of the public

Role*	Section	Comment [sic]	Response
		None	

* 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.

Summary of comments received from members of the public

Theme	Response

Bayer response to ACD for aflibercept in BRVO

We welcome the opportunity to respond to the draft guidance for aflibercept in BRVO.

The draft recommendation benefits patients for whom laser photocoagulation has not been beneficial or is unsuitable via the provision of aflibercept as an alternative second-line treatment option. However, it seriously disadvantages those patients who, on clinical presentation, are 'laser-suitable'. The use of laser therapy in this population consigns them permanently to poorer visual outcomes compared to starting treatment with aflibercept.

We present our main issues in the following pages (pages 1-4) with more detail being provided in appendices (pages 5-10). Our response focuses on the use of aflibercept as a first-line treatment option.

Issue – there is an error in the calculation of the 'most plausible' ICER. In our analysis we calculate a revised most-plausible ICER of £20,100.

*The ERG made 13 revisions to the company's submitted model (listed on page 129 of ERG report). One of these revisions was a structural change to the model, the stated intent of which was to allow "**antiVEGF dosing for years 6+ of 3.2 annual administrations for 30% of patients for 5 years**". This structural change was a major driver of the ERGs increased ICER relative to that in our submission. The ERG model estimated additional costs of [redacted] in the aflibercept arm as a result of this extra treatment. However, we think there are errors in the ERG model and that the [redacted] figure is a large overestimate:*

- *Firstly, the ERG has modelled 100% of patients getting 3.2 injections and not 30% of patients.*
- *Secondly, the ERG uses an 'adjustment' factor which appears to reintroduce into the model patients who have previously discontinued. Injections are therefore applied to everyone who is alive in the model*

Relevant information from the ERG's model has been extracted and is presented in Table 1. The ERG base case provides the results when all 13 revisions have been implemented (ICER £28,813). Sensitivity analysis 08a (SA08a) provides the results when no treatment from years 6-10 are included in the model but the other 12 ERG revisions are implemented (ICER £18,355). For this scenario there were no additional QALYs added for the extra 5 years of treatment. Relative to the ERG base case there is a cost increase in the aflibercept arm of [redacted] attributable to the extra treatment (i.e. [redacted] – [redacted]). This is a significant overestimate of the costs that are possible for 30% of patients receiving 3.2 injections annually for years 6-10 (see appendix 1 for details).

Bayer analysis

We applied in the ERG model 30% of patients getting 3.2 injections in years 6-10 and turned off the adjustment factor (by setting it to 1) so that previously discontinued patients were not reintroduced in to the model. The ICER obtained was £20,100 (see appendix 1 for details).

Table 1. ICERs: based on ERG model

Aflibercept first-line		Laser -aflibercept				
Costs	**QALY**	**Costs**	**QALY**	**Δ COSTS**	**Δ QALYs**	**ICER**
ERG base case (i.e. all 13 ERG revisions implemented)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,813
ERG SA08a – No antiVEGF yrs 6+ (i.e. 12 non-structural changes implemented only)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,355
Bayer analysis in ERG model – 0.96 injections applied to patients who have not died or discontinued						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,100

We consider the ICER of £20,100 is still an overestimate because:

- The analysis assumes no clinical benefit to the extra 5 years of treatment. Physicians would not treat unless there was a benefit to doing so and the inclusion of treatment benefit in these years, even if small, would reduce the ICER further.

Issue – Areas of upward uncertainty

In the ACD it is stated that when the committee's preferred assumptions were implemented the most plausible ICER was £28,813 per QALY. However, two main areas of uncertainty were highlighted which could lead to the ICER being above the range that could be considered a cost-effective use of NHS resources. The two main areas of uncertainty are:

1) *The handling of loss to follow-up data in the company model i.e. LOCF approach*
2) *The use of utility values from Brown 1999 instead of those from Czoski-Murray*

<u>Last observation carried forward methodology (LOCF)</u>

Concerns have been raised regarding the use of the last observation carried forward approach for drop-outs. It was hypothesised in the ERG report that

> *"Since many, if not most, will not have resolved by the time they drop out there may be some unobserved rebound among these patients. Given the different immediate treatment effects and the different administration schedules, the size of this rebound may differ between the arms. There are reasons to believe that this rebound among drop outs may be bigger in the aflibercept-laser arm than in the laser-aflibercept arm, particularly among patients discontinuing before 6 months*
>
> *……Any tendency for drop-outs to rebound to baseline might worsen the clinical and cost-effectiveness estimates for aflibercept-laser compared to laser-aflibercept"*

To address this uncertainty we have conducted what should be considered an extreme scenario analysis. In this scenario patients who discontinue aflibercept during the first six months have

their visual acuity return immediately to baseline. The impact on the ICER of this worst case analysis is minimal i.e. an increase of [redacted] to the cost per QALY (see Appendix 2 for details). A minimal impact on the ICER is to be expected as there are only 6 patients in the aflibercept arm who discontinue in the first six months and the efficacy results are driven by the majority of patients who remain on treatment. Our analysis has been conducted in the ERG model without changes to the adjustment factor or number of injections.

Table 2. Results – LOCF sensitivity analysis

Change in costs	Change in QALYs	ICER
ERG base case		
[redacted]	[redacted]	28,813
Scenario analysis – patients who discontinue aflibercept have VA return to baseline value (ERG base case costs)		
[redacted]	[redacted]	29,560

Use of Brown 1999 utility values

We used the Czoski-Murray utility values in the base case for this appraisal. However in this appraisal the committee has stated a preference for values from Brown 1999, the use of which would increase the ICER from the most-plausible figure.

In the pre-meeting briefing document (section 2 – Relevant Appraisals), two appraisals are listed, both of which were appraised by Committee C (TA283 – ranibizumab in BRVO & TA305 – aflibercept in CRVO). In TA283 the manufacturer used the Brown 1999 utility values in their base case but Committee C preferred the Czoski-Murray values which were described as acceptable for decision-making. In addition, in TA305 Committee C considered the use of Brown utilities to be a "worst-case" scenario.

We consider that this committee accepting the use of Czoski-Murray utility values for decision making for ranibizumab in the same disease area, but then using utility values from Brown 1999 to support poorer cost-effectiveness estimates for aflibercept in the same disease area (this appraisal) is difficult to justify.

Use of EQ5D utility values.

Both the ERG and ourselves appear to be quoting from the same source either in support of the suitability of the EQ5D or its unsuitability i.e. the NICEQol project, funded by the MRC and NIHR (Longworth L et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014;18(9))

The following is from the results section of the report

> *"Most evidence was found for the EQ-5D. Nearly all studies found significant differences between patients with the condition and a control group without it. Studies comparing EQ-5D scores across severity groups were more mixed, with most finding little or no difference between groups defined by clinical measures of visual impairment."*

We therefore agree with the ERG that the EQ5D has been found to have some response according to having a vision-related disease compared to not having vision-related disease.

However, the report found that the EQ5D was insensitive to severity of visual impairment. If the EQ5D is unable to show the impact of different health states according to disease severity it is of no use in technology appraisals which are assessing cost-effectiveness of treatments whose impact is on disease severity. We consider that the inclusion of ICERs based on EQ5D utility values are of no relevance.

Issue – a first-line recommendation would position aflibercept ahead of ranibizumab in the treatment pathway

We believe that another factor that was mentioned in the Appraisal committee meeting (11th May), but not written in the ACD document, may have influenced the draft recommendation i.e. aflibercept as a first line treatment option positions it ahead of ranibizumab in the treatment pathway.

We hope that this has not influenced the decision of the committee. NICEs processes are set up to constantly review recommendations in light of new evidence both for single technology appraisals and guidelines. Anti-VEGF treatment was relatively new at the time of the appraisal of ranibizumab in BRVO and the position for ranibizumab was based on the data and prevailing uncertainties at that time. Recent RCO guidelines, based on a maturing evidence base and years of clinical experience, recommend these therapies as first-line treatments.

We have presented robust evidence showing the superiority of aflibercept-laser over laser-aflibercept in a trial well designed to investigate first and second line treatment of both laser and aflibercept. In addition, we have shown in an economic model, which for the first time in BRVO considers costs and effects of a pathway of care, that aflibercept is cost-effective as a first-line treatment option.

Finally, although not described in the ACD, aflibercept as a first-line treatment was assessed in the company submission against laser followed by ranibizumab (the current pathway of care) and was shown to be cost-effective (table 94 from our submission). These initial analyses were done using the MSM transition tables. We present in Table 3 the cost-effectiveness results of aflibercept first-line versus laser-ranibizumab using shift tables (the ERGs preference) and using an assumption of equivalent efficacy for the two anti-VEGF therapies. Please note that this analysis uses the PAS price for aflibercept and the NHS list price for ranibizumab. We have used the ERG model which produces a base case ICER of £28,813 for this analysis.

Table 3. Aflibercept first-line compared to laser followed by ranibizumab

Aflibercept first-line		Laser followed by ranibizumab				
Costs	**QALY**	**Costs**	**QALY**	**Δ COSTS**	**Δ QALYs**	**ICER**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6,873

Summary

The committee appear to have accepted evidence for the benefit of aflibercept as a first-line treatment and accepted the ERG changes to the model resulting in a most-plausible ICER of £28,813. We believe the ERG model has errors which lead to an overestimation of the costs and consequently the ICER for aflibercept as a first line treatment. In a revised base case,

accepting all the ERG changes to the company model, but with modifications to treatment in years 6-10, we estimate an ICER of £20,100.

We have shown that the last observation carried forward approach has no meaningful impact on the ICER and that there is minimal upward uncertainty - indeed, there are reasons to believe that the ICER might be better.

We do not consider that the current summaries of cost-effectiveness are a reasonable interpretation of the evidence and consequently are not a sound and suitable basis for guidance to the NHS. We hope the committee will give further consideration to the use of aflibercept as a first-line treatment option. We believe it is a cost-effective use of NHS resources.

Appendix 1 – Overestimation of treatment costs for years 6-10

ERG modelling approach

As the company's originally submitted model was not structured for treatment beyond year 5 the ERG made some modifications to estimate the impact on the ICER of continued treatment. According to the ERG report they "had to construct a second, simple cohort flow at the end of the company's model". This cohort flow (Markov-aflibercept tab) was used to estimate the costs of treating patients beyond year 5.

Adjustment factor

The ERG apply an adjustment factor from the end of year 5 (cell RN173: Markov-Aflibercept tab). We do not understand this adjustment factor which increases the number of patients who will receive treatment (0.94 after isolating it from the formula in eg. cell RR173 : Markov-Aflibercept tab) relative to the prior cycle (eg. cell RQ172 : Markov-Aflibercept tab = 0.529). The result of the adjustment factor is that no patients are allowed to discontinue from the model and therefore treatment is applied to all patients who are alive.

The use of the adjustment factor is intentional and although we are not sure we consider that it might be related to the injection rates sourced from the physician survey. In this respect the ERG were of the opinion that the respondents, when asked about the average number of treatments, interpreted "this average as being for the initially treated patient body as a whole rather than among those remaining on treatment at the start of the year". The ERG might have sought to inflate the survey responses in light of this thought process and this inflation has continued to be applied even though a different source of injection rate is now used i.e. the RETAIN study.

The rate of 3.2 annual injections comes from the RETAIN study and represents the number of injections required in unresolved patients in year 4. The RETAIN publication reports on 34 patients who had completed both the BRAVO study and its extension, the HORIZON study. By definition this paper does not consider those patients who had discontinued treatment prior to the start of the RETAIN study but only reports on those 34 patients who are still being monitored. Some, but not all of these patients receive treatment.

The population followed in the RETAIN study relates to an equivalent population in the model i.e. patients who are alive and have not discontinued treatment but are still being monitored.

The proportion of patients requiring treatment

From the RETAIN study the 3.2 annual injections are for unresolved patients i.e. 30% of the population. However, in the ERG model all patients receive 3.2 injections.

Bayer analysis

We have undertaken our own analysis (Table 4) using the ERG model (base case ICER 28,813). In this analysis we have

1) entered 0.96 (30% x 3.2 injections) in cell C44 of the 'ERG' tab (from a modelling perspective entering 0.96 for all patients is equivalent to 30% of patients getting 3.2 injections), and

2) we have set the ERGs adjustment factor to 1.

These changes reduce the ICER to £20,100.

Table 4. Results

Aflibercept first-line		Laser -aflibercept				
Costs	**QALY**	**Costs**	**QALY**	**Δ COSTS**	**Δ QALYs**	**ICER**
ERG base case (i.e. all 13 ERG revisions implemented)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,813
ERG SA08a – No antiVEGF yrs 6+ (i.e. 12 non-structural changes implemented only)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,355
Bayer analysis in ERG model – 0.96 injections applied to patients who have not died or discontinued						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,100

Appendix 2 – Last observation carried forward methodology (LOCF)

Concerns have been raised regarding the use of the last observation carried forward approach for drop-outs. It was hypothesised in the ERG report that

> *"Since many, if not most, will not have resolved by the time they drop out there may be some unobserved rebound among these patients. Given the different immediate treatment effects and the different administration schedules, the size of this rebound may differ between the arms. There are reasons to believe that this rebound among drop outs may be bigger in the aflibercept-laser arm than in the laser-aflibercept arm, particularly among patients discontinuing before 6 months*
>
> *…Any tendency for drop-outs to rebound to baseline might worsen the clinical and cost-effectiveness estimates for aflibercept-laser compared to laser-aflibercept"*

We have concerns from a process perspective that this issue was only raised at the ERG report stage where manufacturers are restricted to identifying factual inaccuracies only. As this concern is hypothetical, and the outcomes of patients who have discontinued from the study can never be known, overemphasis has been given to this uncertainty.

We have conducted a scenario analysis of the impact of LOCF on the cost-effectiveness of treatment (see below). In addition, Table 5 (table 21 from the companies submission) shows that the findings of the primary outcome (proportion gaining 15 or more letters from baseline) were confirmed by all supportive/sensitivity analyses (PPS, OC, multiple imputation).

Table 5. Proportion of patients gaining ≥15 letters in BCVA at week 24 from baseline

	Laser n (%)	Aflibercept n (%)
Primary analysis (FAS, LOCF)	**N=90**	**N=91**
Patients who gained at least 15 letters in BCVA	24 (26.7)	48 (52.7)
Difference (aflibercept vs. laser)		26.1%
Adjusted difference (%) (95% CI) [a]		26.6 (13.0, 40.1)
p-value b		0.0003
Per protocol set (PPS; LOCF) Patients who gained at least 15 letters in BCVA	**N=85** 24 (28.2)	**N=90** 48 (53.3)
Difference (aflibercept vs. laser)		25.1%
Adjusted difference (%) (95% CI) [a]		25.2 (11.3, 39.1)
p-value [b]		0.0007
Observed values (OC analysis)	**N=90**	**N=91**
Patients who gained at least 15 letters in BCVA	23/83 (27.7)	43/84 (51.2)
Difference (aflibercept vs. laser)		23.5%
Adjusted difference (%) (95% CI) [a]		24.8 (10.7, 38.9)
p-value [b]		0.0011
Multiple imputation analysis	**N=90**	**N=91**
Patients who gained at least 15 letters in BCVA [c]	24 (27)	48 (52.8)
Difference (aflibercept vs. laser)		25.8%
Adjusted difference (%) (95% CI) [d]		26.3 (12.8, 39.8)
p-value [e]		0.0005

LOCF=last observation carried forward method (used to impute missing data)

[a] Difference was aflibercept group minus laser [+ aflibercept] group; confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200).

[b] P-value using 2-sided Cochran-Mantel-Haenszel test adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200).

[c] Calculated from the average of 100-multiple imputed data i.e.mean number of responses in a 100 imputed datasets

[d] Calculated using Mantel-Haenszel weighting scheme adjusted by regions (Japan vs. North America) and baseline

BCVA (BCVA ≤ 20/200 and BCVA > 20/200) for each imputed data, then obtained the average of the results.
[e] Calculated from CMH test adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤20/200 and BCVA >20/200) for each imputed data, then calculated the p-value after Wilson Hilferty transformation.

Scenario analysis

Under LOCF, if a patient discontinues treatment, their last observation is used to estimate the efficacy of treatment. To understand the impact of this approach on cost-effectiveness a worst-case scenario was implemented. In this scenario any patient who discontinued aflibercept treatment prior to the six-month timepoint had their visual acuity return immediately to baseline. The model has been provided separately.

The results are shown in Table 6. In this scenario analysis there was a very small decrease in QALYs which is to be expected given the small number of drop-outs. There was also a decrease in costs compared to the ERG base case which requires explanation. In our original submission the MSM transition matrices were used in the base case with the shift tables being presented as a scenario analysis. When the shift tables were applied as part of the originally submitted model there was no discontinuation applied in the first 12 months (this is different to when the MSM package was used where patients could discontinue at any time). In the analyses presented here discontinuation in the first 12 months has been applied. The decrease in costs offsets the decrease in QALYs leading to an improved ICER. We also present the result if the decrease in QALYs are applied to the ERG base case costs. In this instance the ICER worsens but by only [redacted].

Table 6. Results: aflibercept first line versus laser followed by aflibercept (drops outs return to baseline)

Aflibercept-laser		**Laser-aflibercept**				
Cost	QALY	Cost	QALY	Δ COSTS	Δ QALYs	ICER
ERG base case						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,812
Scenario analysis A – patients who discontinue return to baseline						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,967
Scenario analysis B – QALYs from Scenario B but using ERG base case costs						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,560

Received via email by Royal National Institute of Blind People:

“We welcome the fact that aflibercept has been recommended as an option for treating visual impairment in adults caused by macular oedema after branch retinal vein occlusion.

However, we are concerned that it has not been recommended as a first line treatment in the ACD. There is a significant amount of evidence showing that laser is inferior to anti-VEGFs in the treatment of BRVO. We also understand that patients who receive laser treatment upfront do not fully benefit from anti-VEGF treatments later (if they are switched).

We believe that NICE should recommend both aflibercept and ranibizumab as first line treatments for macular oedema due to branch retinal vein occlusion. The guideline must offer patients the superior treatment first – this will give them the best chance of optimal outcomes. We strongly believe that patients in England and Wales should not be denied access to first line treatment with anti-VEGF agents (the superior treatment)”.

National Institute for Health and Care Excellence

Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion [ID844]

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion [ID844].

Nurses caring for people with visual impairment were invited to review the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The reviewers' response to the questions on which comments were requested is set out below:

i) **Has the relevant evidence has been taken into account?**

The evidence considered seems comprehensive.

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with visual impairment. The preliminary views on resource impact and implications should be in line with established standard clinical practice.

iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and consider that the proposed arrangement will not affect funding arrangements already in situ for this patient group.

The RCN would welcome guidance to the NHS on the use of this health technology.

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?**

The only group that will be affected is women who are pregnant or thinking of becoming pregnant. In the clinical trials arena, advice on risk of anti-VEGF in pregnancy is also given to male patients who may have plans to start a family.

We are not aware of any adverse impact on people with disabilities that may be caused by the technology.

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 ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.

The ROYAL COLLEGE of OPHTHALMOLOGISTS

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28 June 2016

Meindert Boysen
Programme Director
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Dear Meindert

Re: Single Technology Appraisal (STA), Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion [ID844] Appraisal consultation document

Please find below the response from The Royal College of Ophthalmologists in response to your email of 1 June 2016 requesting comments on this Technology Appraisal. There did not seem to be a specific response template so we have attempted to list our responses in relation the questions in your email.

Has all of the relevant evidence been taken into account?

We welcome the availability of Aflibercept as another anti-VEGF agent for Macular oedema (MO) due to branch retinal vein occlusion (BRVO). However, The RCOphth have a major concern in the suggested recommendation of its use in our patients. The Appraisal Consultation Document recommends that Aflibercept is used in eyes where laser photocoagulation has not been beneficial or laser photocoagulation is not suitable because of the extent of macular haemorrhage. This is contrary to the recommendation of the RCOphth that anti-VEGF should be used as first line agent based on the current evidence.

The key points from the VIBRANT study show that:

1. Visual outcome following laser photocoagulation is inferior to Aflibercept.
2. If patients are treated with laser photocoagulation as first line, they fail to achieve the outcomes of patients initiated on Aflibercept monotherapy. Therefore, rescuing patients

with Aflibercept after providing them with an inferior therapy deprives patients of their maximal visual potential.

3. Laser therapy failed in 74% of the patients and they required Aflibercept therapy later. Therefore, this waiting game with laser treatment should be avoided. 25% benefited from laser but the overall laser outcome was still inferior to Aflibercept therapy. This shows that for the majority of patients, laser was unnecessary and potentially damaging.
4. The inclusion criteria of the BVOS study was very restricted and therefore the outcomes of that study have not been replicated in real-life. Despite choosing the best group for the study, only 40% achieved 6/12 visual acuity outcomes after 36 months. This outcome is far inferior to the outcomes of anti-VEGF therapy, which were not available at the time, and therefore could not be used as a comparator.
5. Similar evidence is available for the higher efficacy of ranibizumab in treatment of macular oedema secondary to BRVO compared to laser photocoagulation (from the BRAVO Study).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The above applies here for clinical effectiveness of aflibercept. Regarding the type of anti-VEGF, we agree with NICE that both ranibizumab and aflibercept are equally clinically effective.
For cost-effectiveness, we believe that although the RCOphth guidelines is based on clinical effectiveness only, the guidelines does provide the most economical way of using anti-VEGF agents without compromising patient –level or population level outcomes for this condition.

For example, if VA is 6/9 or better, it is best not to initiate anti-VEGF and allow for spontaneous resolution. All the clinical trials have used the visual acuity inclusion criteria of 24 to 73 ETDRS letters. As such this recommendation is backed with RCT evidence.

The guidelines also suggest not initiating treatment with severe macular ischaemia. The RCOphth guidelines further suggest that anti-VEGF be stopped if there is no visual acuity gain after 3 injections and that is also based on evidence from BRAVO, VIBRANT, BRIGHTER etc.

Therefore, if NICE has to impose restrictions in anti-VEGF use due to cost-effectiveness, the above suggestions will be welcome by patients and clinicians rather than restrict anti-VEGF to after laser photocoagulation.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

As above, we would like to stress that the current ACD is not suitable or sound for NHS patients because:

1. NHS patients are offered an inferior treatment as first line when there is strong evidence that anti-VEGF is superior to laser treatment.
2. Patients who can afford anti-VEGF will have to go privately to get the ideal treatment option and this should be strongly discouraged as it raises issues on equity to access.
3. The over-all outcome of BRVO in the NHS will be inferior to those patients in other countries.
4. NICE guidelines is followed around the world and is held in high respect and NICE will be heavily criticised for recommending an obsolete treatment as first line when the world has moved on.

Yours sincerely

[redacted]

Pp

[redacted]

On behalf of The Royal College of Ophthalmologists

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29th June 2016

Dear Mr Boysen,

Re: NICE Single Technology Appraisal (STA), Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion [ID844] - Appraisal Consultation Document

Thank you for the opportunity to provide comments on the above appraisal where Novartis is a registered commentator.

The following pages contain comments on the ACD and accompanying documents in response to the question posed by NICE - Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?.

If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]
Novartis Pharmaceuticals UK Limited

ACD, Page 9: Section 4.10

"The committee understood that the probabilities could instead have been derived directly from patient data and considered that there was no evidence to suggest that these data should not be used in the model. The committee concluded that using real-world data to estimate the probabilities of improving or worsening visual acuity was a preferable approach."

Novartis comment: It is unclear what real world data were used to estimate transition probabilities in the economic model. The data appear to be derived from the randomised, controlled VIBRANT trial. The submitting company states under question B15 of the economic clarification document that "*Transition probabilities were derived using the MSM package in R. In this specific case the transitions of patients from the VIBRANT trial were converted to the 4 weekly cycles used in the model*."

It is also unclear why the committee concludes that using real world data to estimate the probabilities of improving or worsening visual acuity is preferable when trial data are available. Does this refer to efficacy probabilities in the short or long term?

ACD, Page 10: Section 4.12

"It noted that in a sensitivity analysis, the ERG had lowered the proportional impact of a change in the best-seeing eye to 15%..."

Novartis comment: The approach undertaken by the ERG appears inconsistent with that used in past appraisals specifically the NICE appraisal of ranibizumab for bRVO (TA283)[1].

In TA283, Novartis made a revised model submission with an assumption of a 0.3 utility gain associated with treating the 'worse-seeing eye' relative to the 'better-seeing eye'. The ERG's base case analysis assumed a 0.1 utility gain derived from Brown (1999)[2]. The analysis highlighted that the assumption of some benefit associated with treating the 'worse-seeing eye' benefit was a key driver of cost-effectiveness.

The TA283 final guidance document (Page 42, section 4.16) states *"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 concluded that a utility gain of 0.1 associated with treating the 'worse-seeing eye' was appropriate."*

We therefore suggest that the same assumption (i.e. a *0.1 utility gain associated with treating the 'worse-seeing eye)* is made in this review to ensure consistency of the ERG analysis and committee assumptions.

ACD, Page 11: Section 4.14
"..ranibizumab was dominated by aflibercept (that is, was both more costly and less effective)."
ACD, Page 12: Section 4.14
"In these analyses, ranibizumab remained dominated by aflibercept."

Novartis comment: The wording around aflibercept dominating ranibizumab in the various sections of the ACD could be misleading and needs to be contextualised i.e. it should clearly state when the results are based on the ranibizumab list price or PAS price.

Regarding the ranibizumab list price, please note that Novartis has reduced the public list price of ranibizumab from £742.00 to £551.00 per vial[3], effective 14th June 2016. The list price alteration does not impact the Patient Access Scheme (PAS), so the NHS purchase price is unchanged. This change will impact the accuracy of the cost-effectiveness comparisons of aflibercept vs. ranibizumab at list price that are reported in the ACD and accompanying documents.

ACD, Page 12: Section 4.14
"The committee was mindful of its conclusions regarding the clinical effectiveness of aflibercept compared with ranibizumab (see section 4.7), and noted that aflibercept's dominance of ranibizumab would be influenced by the results of the network meta-analysis. The committee considered the cost effectiveness of ranibizumab in the appraisal of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and considered that aflibercept and ranibizumab could be similar in terms of cost effectiveness."

Novartis comment: We agree with the committee about being mindful of the conclusions regarding the clinical effectiveness of aflibercept compared with ranibizumab and ask that this view be made clear across the entire document.

An NMA published by Regnier et al., 2014[4] explored the clinical efficacy of ranibizumab, aflibercept, laser and dexamethasone. The study was based on 8 trials (including trials that the ERG felt should have been in the submitting company's NMA) and showed that the point estimate results for gaining 15 or more letters favour ranibizumab over aflibercept; these results were not significant (median OR: 1.06; 95% CrI 0.16 to 8.94).

The ERG comments on page 66 of the ERG report that a series of decisions by the submitting company led to a point estimate of efficacy favouring aflibercept over ranibizumab. It further states *"It is worth noting that if other assumptions had been made (as those made by Novartis), a point estimate favouring ranibizumab could have been obtained, although credible intervals were very wide with considerable overlap with the company's results."*

It is also important to note that the base case results presented by the submitting company are based on deterministic analysis and are therefore sensitive to the point estimate of efficacy used. This is validated by some analyses conducted by the manufacturer.

- A tornado plot (page 253 of the manufacturer's submission) highlights the uncertainty around this point estimate as when a greater odds of achieving a 15 or greater letter gain is considered, ranibizumab is cost-effective.
- The scenario analysis in which all trials were included in the NMA (page 265 of the manufacturer's submission) used a median OR of 1.08 (Crl 0.45-1.45) for achieving a ≥15 letter increase with ranibizumab. This showed that laser followed by aflibercept is associated with a lower cost and a reduced QALY gain compared to ranibizumab after laser.

ERG report, Page 86: Section 5.2.8

"The number of 2nd line rescue ranibizumab treatments during the first year is assumed to be equal to that of 2nd line rescue aflibercept."

Novartis comment: The assumption of the same number of treatments for ranibizumab and aflibercept based on the VIBRANT trial is inconsistent with the approach taken in previous NICE technology appraisals for related conditions.
Specifically:

- In the 2013 NICE technology appraisal of ranibizumab in branch retinal vein occlusion (TA283)[1], the injection frequency for ranibizumab was derived from trial data.
- In the 2014 NICE technology appraisal of aflibercept in central retinal vein occlusion (TA305)[5], the manufacturer's model derived the number of injections from the respective ranibizumab and aflibercept trials.
- In the 2015 NICE technology appraisal of aflibercept for treating diabetic macular oedema (TA346)[6], the injection frequencies are derived separately for aflibercept and ranibizumab. The number of ranibizumab injections was derived from a weighted average based on reported data on the number of injections from the studies included in the NMA. In the FAD (section 3.2.9), the ERG states that the clinical effectiveness evidence for aflibercept relates to the dosing frequency used in the aflibercept trials; therefore, the estimate for the number of injections of aflibercept from these trials should be used in the base case because of their alignment to the dosing frequency.

The ERG and the committee accepted these approaches in previous appraisals; it is therefore unclear why an alternative assumption of the same dosing is being accepted in this appraisal. We strongly propose that the methodology in this appraisal should be in line with that of the DMO (TA346)[6] appraisal, i.e., the number of ranibizumab injections should be derived from a weighted average of injections from the studies included in the NMA.

A recent bRVO cost-effectiveness analysis by Adedokun and Burke (2016)[7] provides the dosing frequency for both aflibercept (9 injections) and ranibizumab (7.8 injections) in the first year based on the trials included in the NMA.

References

1) NICE Technology Appraisal No. 283, May 2013, 'Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion'.

2) Brown GC. Vision and quality-of-life*. Trans Am Ophthalmol Soc* 1999;97**:**473-511.

3) Monthly Index of Medical Specialities (MIMS) (2016). Available at: http://www.mims.co.uk Accessed: 29 June 2016.

4) Regnier SA, Larsen M, Bezlyak V, Allen F. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: A network meta-analysis. BMJ Open 2015;5 (6).

5) NICE Technology Appraisal No. 305, Feb 2014, 'Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion'.

6) NICE Technology Appraisal No. 346, Jul 2015 'Aflibercept for treating diabetic macular oedema'.

7) Adedokun L, Burke C. Cost-Effectiveness of Ranibizumab Versus Aflibercept for Macular Edema Secondary to Branch Retinal Vein Occlusion: A UK Healthcare Perspective*. Adv Therap* 2016;33**:**116-28.

Professor S Rajendran – patient expert, nominated by Royal National Institute of Blind People

It is noted in the consultation report that the committee has carefully considered all the evidences before arriving at conclusions/recommendations. I could see that both the clinical effectiveness and cost implications to NHS were carefully considered but I am not sure that this is a balanced approach. It is important to weigh the additional benefits to patients from using aflibercept over other comparators. The efficacy of aflibercept to bind both VEGF-A and VEGF-B is crucial in the management of macular oedema following BRVO and other comparators, for instance ranibizumab and dexamethasone, do not provide the above benefits of aflibercept but to bind only VEGF-A. The high binding affinity of aflibercept to VEGF-A and VEGF-B has also been published in journals elsewhere. This clearly justifies that aflibercept qualifies for the first-line treatment option instead of the recommended second-line of treatment, which is at par with ranibizumab, after laser photocoagulation.

Aflibercept for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion

Revised analyses in light of the company's error check of ERG model revisions

Produced by Aberdeen HTA Group

Date completed 29 June 2016

Contains CIC/AIC

The company has queried whether the ERG cohort flows to account for dosing in years 6+ should multiply or divide by the variable *ERG_Afli_6yrplus_adjustment*. This variable is employed as an approximate correction for discontinuations within the model during the first six year so that the ongoing dosing for years 6+ is as a proportion of the original cohort rather than the of the cohort remaining on treatment at year 6. The ERG is of the opinion that the ERG division is correct as outlined in the arithmetic below. In terms of the company thoughts these are most easily explored by examining cell RR173 of the *Markov – Aflibercept* worksheet, which is intended to be the number of additional doses in cycle 61.

RR173 = RQ173*ERG_Dosing_AFLI_yr6plus/12*$KT173*(1/ERG_Afli_6yrplus_adjustment)
Where:

- RQ173 = Patient number remaining alive of the original cohort conditioned by mortality and discontinuation
- ERG_Dosing_AFLI_yr6plus/12 = monthly dose = DOSE
- $KT173 = Discount factor = DF
- ERG_Afli_6yrplus_adjustment = RQ173/RO173 hence 1/ERG_Afli_6yrplus_adjustment = RO173/ RQ173

So more compactly:
RR173 = RQ173 * DOSE * DF * RO173 / RQ173
= DOSE * DF * RO173
where RO173 is the proportion of the original cohort surviving not adjusted for discontinuations. So it seems to be correct to divide by *ERG_Afli_6yrplus_adjustment*.

However, there is a serious error in the above in that it is not conditioned by the 30% proportion of the original cohort who are being assumed to receive aflibercept during Yr6+: the *ERG_Tx_Perc_AFLI_yr6plus* in the ERG revised model. This error is most easily identified by changing this variable in the *ERG* worksheet and noting that it has no effect on the model outputs when it clearly should have an effect.

1. Correction of model error: Proportion of population receiving ongoing treatment

This error is easily remedied by conditioning cells SC111:SD111 by *ERG_Tx_Perc_AFLI_yr6plus*.

The tables below show the revised ICERs.

Table 1. ICERs: ERG error corrected: Aflibercept-laser versus laser-aflibercept

	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	£21,492
SA01: R MSM TPMs	[redacted]	[redacted]	£19,197
SA02: 8 study NMA	[redacted]	[redacted]	n.a.
SA03: 15% WSE QoL	[redacted]	[redacted]	£24,899
SA04: 43% WSE QoL	[redacted]	[redacted]	£19,625
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£27,324
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£37,727
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£55,501
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	£18,355
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	£22,801
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	£20,134
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	n.a.
SA11: VA2 shift tables	[redacted]	[redacted]	£35,553
SA12: VA3, VA4 + VA5 shift tables	[redacted]	[redacted]	£18,428
SA03, and SA05 combined	[redacted]	[redacted]	£32,520
SA03, SA05 and SA08c combined	[redacted]	[redacted]	£34,502

Table 2. ICERs: ERG error corrected: laser-aflibercept versus laser-ranibizumab

	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	DOM
SA01: R MSM TPMs	[redacted]	[redacted]	n.a.
SA02: 8 study NMA	[redacted]	[redacted]	£298k
SA03: 15% WSE QoL	[redacted]	[redacted]	DOM
SA04: 43% WSE QoL	[redacted]	[redacted]	DOM
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	DOM
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	DOM
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	DOM
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	DOM
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	DOM
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	DOM
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	DOM
SA11: VA2 shift tables	[redacted]	[redacted]	n.a.
SA12: VA3, VA4 + VA5 shift tables	[redacted]	[redacted]	n.a.
SA03, and SA05 combined	[redacted]	[redacted]	DOM
SA03, SA05 and SA08c combined	[redacted]	[redacted]	DOM

2. Exploratory analysis for laser-aflibercept v laser-dexamethasone: Dosing assumptions

Note that for table 3 due to no data being identified no ongoing dosing for either aflibercept or for dexamethasone in years 6+ has been applied. But the ICERs differ from those of the original ERG report due to the revised dosing for aflibercept in years 3, 4 and 5 in the light of the revised dosing schedule given the original company error check; i.e. 3.2 anti-VEGF doses per patient on treatment. Recall that the assumed dosing for dexamethasone is of 1.69, 0.93, 0.21 and 0.10 for years 2, 3, 4 and 5 is still based upon the company expert survey. The parallel figures from the original company model or aflibercept based upon the expert responses for ranibizumab were 4.15, 2.61, 1.12 and 0.58. The following retains the expert survey data for dexamethasone but sets a floor of 3.2 for aflibercept.

Table 3. ICERs: ERG error corrected: laser-aflibercept versus laser-dexamethasone

	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	£29,152
SA01: R MSM TPMs	[redacted]	[redacted]	n.a.
SA02: 8 study NMA	[redacted]	[redacted]	£32,959
SA03: 15% WSE QoL	[redacted]	[redacted]	£33,752
SA04: 43% WSE QoL	[redacted]	[redacted]	£26,982
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£36,976
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£51,641

SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£76,749
SA03, and SA05 combined	[redacted]	[redacted]	£43,558

The dosing for dexamethasone in the above is based upon the company expert survey. The ERG was critical of this as it appeared that respondents to the survey may have been interpreting this as asking about dosing as a percentage of the original cohort rather than of those remaining on treatment which is what the model needs. This would help explain, at least in part, why the estimated dosing was rather low compared to what was suggested by the actual follow up data for ranibizumab. The reliability of the survey was also called into question by the responses suggesting a somewhat lower dosing schedule for aflibercept than for ranibizumab. This is why the ERG revised the anti-VEGF dosing schedule to reflect the RETAIN study as reported by Campochiaro et al and the data of Sophie et al.

The ERG did not identify a parallel source in the literature for dexamethasone dosing, the estimates for which are still based upon the company expert survey. In the light of this it may be more sensible or at least consistent for the comparison of laser-aflibercept with laser-dexamethasone to retain the dosing estimates of the company expert survey. This results cost effectiveness estimates of table 4.

Table 4. ICERs: Original ERG report: laser-aflibercept versus laser-dexamethasone

	ΔCosts	**ΔQALYs**	**ICER**
Base case	[redacted]	[redacted]	£18,542
SA01: R MSM TPMs	[redacted]	[redacted]	n.a.
SA02: 8 study NMA	[redacted]	[redacted]	£20,969
SA03: 15% WSE QoL	[redacted]	[redacted]	£21,468
SA04: 43% WSE QoL	[redacted]	[redacted]	£17,162
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£23,518
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£32,846
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£48,815
SA03 and SA05 combined	[redacted]	[redacted]	£27,706

In short, there remains uncertainty around the dosing that should be assumed for dexamethasone.

References

Campochiaro PA, Sophie R, Pearlman J, Brown DM, Boyer DS, Heier JS, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: The RETAIN study. *Ophthalmology* 2014;**121:**209-19.

Sophie R, Hafiz G, Scott AW, Zimmer-Galler I, Nguyen QD, Ying H, et al. Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion. *Am J Ophthalmol* 2013;**156:**693-705.

Bayer comment on ERG document titled "Revised analyses in light of the company's error check of ERG model revisions"

As stated in the Appraisal Consultation Document, the committee considered the most plausible ICER for aflibercept in patients with untreated visual impairment compared with aflibercept after laser photocoagulation. When its preferred assumptions had been incorporated the base case ICER was £28,813.

However, as detailed in the ERGs revised analyses there was a calculation error in the ERG's model. Correction of the error results in an ICER of £21,492. Please note that this ICER still includes the committees preferred assumptions. We believe that if the committee accepted the previous ICER, then this corrected ICER would now be considered the 'most-plausible'.

In respect of this corrected 'most-plausible' ICER Bayer still considers it to be conservative. In the ERGs base case they extended the treatment duration out to year 10 (previously 5 years in the company's model). The cost of this extra treatment is included but additional benefit isn't. Inclusion of benefit for the extra years of treatment would improve the ICER.

We believe that the ICER supports aflibercept as a cost-effective use of NHS resources when used as a first-line treatment option.

Aflibercept for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion

Analyses in light of the ACD and the company response to ERG analyses

Produced by Aberdeen HTA Group

Date completed 8 July 2016

Contains CIC/AIC

Multivariate scenario analyses suggested by the ACD

The ACD suggested a number of scenario analyses. The figures in the ACD also reflected the ERG error of assuming that 100% of those alive at year 6 would receive ongoing anti-VEGF treatment rather than 30%. Retaining this error yields the following multivariate sensitivity analyses for the comparison of aflibercept-laser with laser aflibercept.

Table 01: Multivariate sensitivity analyses retaining ERG year 6+ dosing error

	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	£28,812
SA03, and SA05 combined	[redacted]	[redacted]	£43,597
SA03, SA05 and SA08c combined	[redacted]	[redacted]	£50,202

LOCF scenario analysis

Within the aflibercept-laser arm of VIBRANT during the first six months 6 patients discontinued, and during the second six months another 12 patients discontinued. The company has explored assuming that discontinuations during the first six months rebounded to baseline rather than remained at their LOCF.

For this the company has very reasonably provided a scenario analysis that assumes that this only affects QALYs and not costs. It could alternatively assume that those lost to follow-up also ceased treatment so reducing costs in the aflibercept arm but this would then beg a number of questions, not least among them how to assess costs and lost to follow-up with LOCF in the laser-aflibercept arm.

Table 02: Bayer 1st 6 months LOCF revisions analysis

	Δ Costs	Δ QALYs	ICER
ERG	[redacted]	[redacted]	£28,812
LOCF revised costs and QALYs	[redacted]	[redacted]	£26,966
LOCF revised QALYs	[redacted]	[redacted]	£29,504

Within the model those lost to follow-up cross over to the ceased treatment part of the cohort flow. There is an error within the revised patient count TPMs in that these patients are not conditioned by mortality in the same manner as those remaining on treatment[1]. This causes slightly fewer to be modelled as having died in the first year in the aflibercept-laser arm than in the laser aflibercept arm.

[1]It appears that the raw patient counts for those having withdrawn from VIBRANT should be modelled elsewhere accounting for SE_Decline but not accounting for mortality, with this data the being treated as raw patient counts for entry into the shift table TPM. This can then be conditioned by mortality in the same way as those remaining on treatment; e.g. condition this patient count data by (1-mortality!$I20)*(1-T48) for the entries in cells M49:P49 of the *Shift_tables* worksheet. This results in the same number being modelled as dead during the first 13 cycles of the model for aflibercept-laser as laser-aflibercept.

This additional survival at the end of the first year provides ongoing benefits in the aflibercept arm over the 35 year time horizon of the model. The effects of correcting this are as below.

Table 03: Bayer 1st 6 months LOCF revisions analysis: Bayer error corrected

	Δ Costs	Δ QALYs	ICER
ERG	[redacted]	[redacted]	£28,812
LOCF revised costs and QALYs	[redacted]	[redacted]	£28,292
LOCF revised QALYs	[redacted]	[redacted]	£31,003

But these estimates retain the ERG error of not conditioning the year 6+ dosing by 30%.

Table 04: Bayer 1st 6 months LOCF revisions analysis: Bayer and ERG errors corrected

	Δ Costs	Δ QALYs	ICER
ERG	[redacted]	[redacted]	£21,492
LOCF revised costs and QALYs	[redacted]	[redacted]	£20,415
LOCF revised QALYs	[redacted]	[redacted]	£23,126

With both corrections made the revised handling of LOCF for the first six months of the aflibercept-laser arm causes the ICER to worsen by around £1,600 per QALY. Adopting the LOCF revised QALYs approach to the ERG sensitivity analyses corrected both errors results in the following.

Table 05: Bayer 1st 6 months LOCF revisions analysis: ERG sensitivity analyses

		Original		LOCF adjusted	
	ΔCosts	ΔQALYs	ICER	ΔQALYs	ICER
Base case	[redacted]	[redacted]	£21,492	[redacted]	£23,126
SA01: R MSM TPMs	[redacted]	[redacted]	£19,197	[redacted]	n.a.
SA02: 8 study NMA	[redacted]	[redacted]	n.a.	[redacted]	n.a.
SA03: 15% WSE QoL	[redacted]	[redacted]	£24,899	[redacted]	£26,670
SA04: 43% WSE QoL	[redacted]	[redacted]	£19,625	[redacted]	£21,160
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£27,324	[redacted]	£29,429
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£37,727	[redacted]	£40,795
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£55,501	[redacted]	£59,649
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	£18,355	[redacted]	£19,750
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	£22,801	[redacted]	£24,535
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	£20,134	[redacted]	£21,665
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	n.a.	[redacted]	n.a.
SA11: VA2 shift tables	[redacted]	[redacted]	£35,553	[redacted]	n.a.
SA12: VA3, VA4 + VA5 shift tables	[redacted]	[redacted]	£18,428	[redacted]	n.a.
SA03, and SA05 combined	[redacted]	[redacted]	£32,520	[redacted]	£34,833
SA03, SA05 and SA08c combined	[redacted]	[redacted]	£34,502	[redacted]	£36,955

Year 6+ dosing benefits of treatment

The company notes that the ERG additional anti-VEGF dosing for years 6+ does not allow for any benefits of treatment. The company model has a placeholder for year 6+ dosing but this is not implemented in the model. Implementing this would require quite substantial revisions to the model structure.

The model assumes a common 2% annual worsening by one health state for those not on treatment. For SA08a of no dosing for years 6+ not adjusted for LOCF of £18,355 setting this worsening to 0% worsens the ICER to £19,589 per QALY or by around 6.7%. While very crude, the benefits for the 30% receiving ongoing dosing could be seen as being about a 2.0% reduction in the ICER. The effects of discounting might further reduce this to around a 1.8% improvement in the ICER: around £350 at £20,000, £500 at £30,000 and £700 at £40,000. But it should be stressed that this is a very crude indication of what not applying the 2% annual worsening among those receiving ongoing anti-VEGF dosing for five years from year 6+ may be.

Quality of life in previous assessments in RVO: Dexamethasone [TA229]

The STA of dexamethasone for RVO used a two stage process:

- A TTO study among 607 members of the general public of the UK, Canada and the US that used the six item VFQ-UI subset of the NEI-VFQ-25 to define 8 binocular health states which enabled HRQoL to be modelled as a function of the six item VFQ-UI subset.
- The trial patient HRQoL as implied by their day 180 six item VFQ-UI subset scores being regressed on their presumably study eye BCVA differentiated by whether it was their WSE or BSE at baseline.

This resulted in the HRQoL as a function of the BCVA in letters of the study eye estimated:

- HRQoL (BSE) = [redacted]
- HRQoL (WSE) = [redacted]

It should be noted that no confidence intervals or standard errors were supplied by the company or asked for by the ERG at clarification. In terms of the reliability of this function it appears that 97% of eyes in the trial were the WSE.

There are six BCVA health states within the model based upon 15 letter bands as below, with the associated quality of life values depending upon whether the BSE or the WSE is being treated.

Table 06: Dexamethasone RVO STA [TA229] QoL values

BCVA Health State	HS0	HS1	HS2	HS3	HS4	HS5
ETDRS range	≥ 69	59-68	54-58	44-53	39-43	≤ 38
Assumed mean ETDRS	75.0	63.5	56.0	48.5	41.0	33.0
HRQoL BSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HRQoL WSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Quality of life in previous assessments in RVO: Ranibizumab [TA283]

The company submission was a model of treatment of the BSE. The company used Brown et al 1999 as its source for quality of life values.

Table 07: Brown et al 1999 BSE TTO QoL values

	N	TTO QoL
20/20	32	0.92
20/25	50	0.87
20/30	44	0.84
20/40	54	0.80
20/50	31	0.77
20/70	40	0.74
20/100	18	0.67
20/200	16	0.66
20/300	13	0.63
20/400	9	0.54
CF	12	0.52
HM-NLP	6	0.35
CF – Counting fingers HM-NLP – Hand movement, no light perception		

There are eight 10 letter health states within the ranibizumab model with the company deriving the following quality of life values for the BSE from Brown et al. The company derives the following BSE quality of life values, often by averaging across two of the Brown et al values.

Table 08: Company BSE TTO QoL values from Brown et al

	ETDRS	Snellen	Brown states	Average
HS1	86–100	>20/16	20/20	0.920
HS2	76–85	20/32-20/20	20/20, 20/30	0.880
HS3	66–75	20/64-20/40	20/40, 20/70	0.770
HS4	56–65	20/80-20/50	20/50, 20/70	0.755
HS5	46–55	20/125-20/80	20/100	0.670
HS6	36–45	20/200-20/125	20/100, 20/200	0.665
HS7	26–35	20/320-20/200	20/200, 20/300	0.645
HS8	<25	<20/320	20/300, 20/400, CF, HM-NLP	0.510

The ranibizumab ERG report cites the HTA monograph of TA155, which assessed treatments for wet AMD, as the source for the 0.1 difference between good binocular vision and good vision in one eye and reduced vision in the other. The current ERG has not been able to find this within the HTA monograph for this assessment. The HTA monograph includes appendix 15 which outlines NICE requesting a number of additional analyses including "*Can sensitivity analyses be presented around the assumptions for utility gain from treating one or the worst-seeing, as opposed to the better-seeing, eye only?*" but as far as the ERG can see the HTA monograph does not attempt to answer this question. But the FAD to TA155 does note that "the manufacturer argued that the relative benefits of binocular and monocular vision should be taken into account, citing a study which showed a difference in utility value of approximately 0.1 between people with good visual acuity in both eyes and people with good vision in only one eye". The ERG has not been able to find an explicit reference for this but on the advice of NICE assumes it to be Brown et al 2001. The Brown et al 2001 data for TTO quality of life values for the WSE is very similar to the parallel Brown et al 1999 data presented in table 51 of the ERG report for the current assessment.

The Brown et al data for the WSE in the ranibizumab STA submission is as presented in the ERG report for the current assessment which in turn is near identical to the more recent data of Brown et al 2001. This provides the TTO values for those with good vision of at least 20/20 in their BSE and visual impairment in the other.

Table 09: Brown et al 2001 WSE QoL values

Vision in the WSE	n	QoL	95% CI
20/40–20/50	24	0.87	0.81–0.93
20/70–20/100	12	0.90	0.81–0.99
20/200–20/400	14	0.94	0.81–1.00
CF	25	0.88	0.81–0.95
HM-NLP	6	0.81	0.65–0.97

Across these patients the mean quality of life is 0.89. Among the 66 patients who had good vision in both eyes the mean quality of life was 0.97, suggesting a difference of 0.08. This rounded up to 0.1 appears to be the basis for the ranibizumab STA ERG estimate.

If the bottom group is thought to be of limited relevance to the current assessment there is no relationship between the BCVA in the WSE and the quality of life values of Brown. A caveat to this is that this data only relates to patients with good vision in their BSE. If the BCVA of the BSE worsens it is possible to imagine that preserving the BCVA of the WSE may become more important.

The company noted that:

> *"This lack of correlation between VA in the WSE and utility reported by Brown and colleagues is not corroborated by studies that report on the quality of life. Deramo 2003 found that for the majority of VFQ-25 subscales, the HRQL scores were significantly lower in the CRVO group, where the affected eyes were the WSEs, than in the reference group, indicating that loss of vision in the WSE does have a negative impact upon HRQL. Awdeh 2010 found that HRQL scores for BRVO patients were associated with the level of VA in the affected eye, even if the other eye had good vision. These findings are corroborated by the BRAVO and CRUISE studies for ranibizumab, where approximately 90% of the patients were affected in the WSE. In these studies treatment with ranibizumab was associated with a significantly greater improvement at month 6 on the VFQ-25 than that observed in the sham injection-treated group for both BRVO and CRVO patients. Therefore the WSE utilities from Brown 1999 do not seem to be representative of the true quality of life loss caused by vision impairment in the worse-seeing eye due to RVO."*

The company submission to the ranibizumab STA does not compare the absolute changes in the NEI-VFQ for the BRAVO and CRUISE patients with estimates from the literature for the WSE and the BSE. There is also no assessment of the magnitude of the changes in the NEI-VFQ for changes in the BCVA of the BSE and the WSE.

With regards the above the HTA monograph for TA155 notes:

> *"Differences in overall score on NEI-VFQ (and in subscales such as near activities, dependency, driving, role difficulties, distance activities, mental health and general vision) were shown to be significantly related to differences in visual acuity of better-seeing eyes. Berdeaux and colleagues also reported that these scores were also significantly related to visual acuity of the worse-seeing eye. However, NEI-VFQ has been shown to be sensitive to differences in general health, therefore adjustment for general health should be considered when comparing scores between patient groups."*

A mapping function from the NEI-VFQ to EQ-5D utility scores has been estimated by Payakachat et al from data from 151 AMD patients. The ERG has not reviewed this but it raises the possibility of mapping WSE trial data to HRQoL and comparing this with the Brown et al TTO estimates. IT should be borne in mind that the dexamethasone submission also used a mapping function based upon a subset of the NEI-VFQ.

The ranibizumab ERG preferred Czoski-Murray as the source of quality of life values. Rather than using the regression equation of Czoski-Murray they used the mean TTO over the four groups to infer values for the quality of life associated with the BSE.

Table 10: Mean TTO QoL by group from Czoski-Murray

BCVA	TTO value
≥20/40	0.706
20/40 to 20/80	0.681
20/80 to 20/400	0.511
≤20/400	0.314

The ranibizumab ERG conducted several scenario analyses one of which assumed that "*the utility associated with visual acuity of 86–100 in the WSE is equivalent to the utility associated with visual acuity of 86–100 in the BSE and that the slope of the WSE utility curve of 0.014 thereafter (equivalent to an overall utility loss of 0.1, listed in Table 55)*". Table 55 does not list the 0.1 utility loss. But a slope of 0.016, which is similar to the stated 0.014, when applied to the health state midpoints converted to LogMAR values results in a quality of life of 0.82 for the worst health state as outlined below.

Table 11: Ranibizumab RVO STA QoL values

	ETDRS	ETDRS mid	Brown	ERG CM	ERG WSE
HS1	86–100	93.0	0.920	0.706	0.920
HS2	76–85	80.5	0.880	0.706	0.916
HS3	66–75	70.5	0.770	0.681	0.909
HS4	56–65	60.5	0.755	0.681	0.898
HS5	46–55	50.5	0.670	0.511	0.885
HS6	36–45	40.5	0.665	0.511	0.868
HS7	26–35	30.5	0.645	0.511	0.848
HS8	<25	12.5	0.510	0.314	0.822

Quality of life in current AFLI assessment

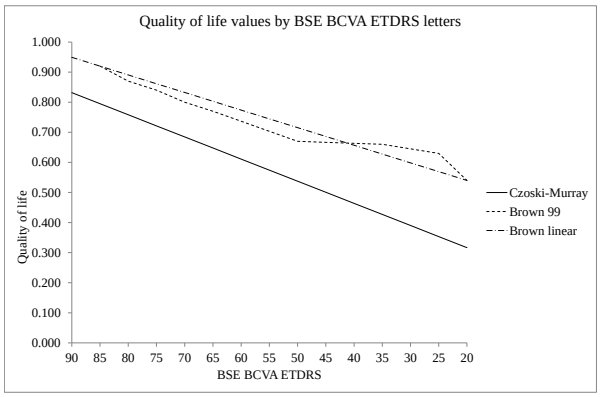
The company estimated various binocular quality of life functions from the VIBRANT EQ-5D data but these explained little of the overall variation in the data and the coefficients on not just the WSE but also the BSE were quite low. These are not reconsidered here. Instead the company concentrated upon the Czoski-Murray regression equation that models HRQoL as a function of the BCVA of the BSE based upon the TTO values of the experimental lens study. The ERG noted that the company had in previous assessments also presented values based upon Brown et al 1999. Given the five health states of the model that were typically 15 letters wide this resulted in the following values and figure within the ERG report. The crudely derived ERG function resulted in a slope of -0.292 compared with -0.396 of Czoski Murray. Note that for this the ERG ignored the two worst health states of Brown of counting fingers and hand movement/no light perception due to the mid-point of the worst health state

being 20 letters and it being likely that the distribution of any eyes falling into this health state would be left skewed.

Table 12: BSE QoL from Czoski and Brown 1999 current assessment

ETDRS	Snellen	LogMAR	Czoski linear	Brown values	Brown linear
90	20/15	-0.10	0.832		0.949
85	20/20	0.00	0.795	0.920	0.920
80	20/25	0.10	0.758	0.870	0.891
75	20/32	0.20	0.721	0.840	0.862
70	20/40	0.30	0.685	0.800	0.832
65	20/50	0.40	0.648	0.770	0.803
60	20/63	0.50	0.611		0.774
55	20/80	0.60	0.574		0.745
50	20/100	0.70	0.537	0.670	0.715
45	20/125	0.80	0.501		0.686
40	20/160	0.90	0.464		0.657
35	20/200	1.00	0.427	0.660	0.628
30	20/250	1.10	0.390		0.598
25	20/320	1.20	0.353	0.630	0.569
20	20/400	1.30	0.317	0.540	0.540

Figure 01: Company and ERG BSE quality of life functions of current assessment



The values for the WSE effectively reduced the slope parameters by a given percentage according to the company equation.

A comparison of QoL values across assessments

Only the ranibizumab assessment uses values for given VA subgroup health states from the published literature. The dexamethasone assessment and the current assessment apply smooth functions based upon patients' BCVA. As a consequence, comparison across the assessments is facilitated by using the health states of the ranibizumab assessment and assuming that these quality of life values apply to

the mid points of the health states. The smooth functions of the other assessments can then be applied to these mid-points.

Note that in what follows the ERG implementation of the Brown calculation revises the Czoski-Murray slope coefficient from -0.396 to -0.292. This alters the vertical position of the function due to it also applying the Czoski-Murray Age and intercept term. But it does not affect the decrements associated with visual loss. But given the 1.23 mortality multiplier for having one eye in the worst health state there is a small survival difference within the aflibercept model and the vertical movement of the quality of life function might have an impact. The discounted survival difference between aflibercept-laser and laser-aflibercept is 0.004 years. The vertical shift in the Brown function is between 0.10 and 0.15. As a consequence, any QALY bias arising from this source seems likely to be small and perhaps somewhere between 0.0004 QALYs and 0.0006 QALYs.

Since in the current assessment the worst health state ranges from 0 to 35 letters, the difference between HS1-HS7 is presented.

Table 13: BSE QoL values across TA229, TA283 and the current assessment

STA			RANI	RANI	DEXA	AFLI	AFLI
Source			Brown	Czoski	..	Czoski	Brown
HS	ETDRS	Mid	QoL	QoL	QoL	QoL	QoL
HS1	86–100	93.0	0.920	0.706	[redacted]	0.854	0.842
HS2	76–85	80.5	0.880	0.706	[redacted]	0.762	0.769
HS3	66–75	70.5	0.770	0.681	[redacted]	0.688	0.710
HS4	56–65	60.5	0.755	0.681	[redacted]	0.615	0.652
HS5	46–55	50.5	0.670	0.511	[redacted]	0.541	0.594
HS6	36–45	40.5	0.665	0.511	[redacted]	0.467	0.535
HS7	26–35	30.5	0.645	0.511	[redacted]	0.394	0.477
HS8	<25	12.5	0.510	0.314	[redacted]	0.261	0.372
HS1-HS7			0.275	0.195	[redacted]	0.460	0.365

The above suggests the within the current assessment both BSE quality of life functions apply somewhat larger quality of life decrements than in the other assessments. This applies with greater force to the Czoski-Murray values than the Brown values.

For the Brown derived values the company values for ranibizumab are slightly compressed at the top end; i.e. there is a ceiling effect, while the aflibercept ERG linear function extrapolates beyond this. Similarly, the aflibercept ERG linear function is extrapolated using the downward tick for 20/400 with the Brown values tending to lie a little above the linear line for 30 letters.

For the Czoski-Murray values the ranibizumab ERG values are based upon the means for the four values within Czoski-Murray which again tends to limit the best and worst states compared to the extrapolation based upon the linear function of Czoski-Murray. The current ERG is not comfortable with an assumption that the BSE moving from HS5 to HS7 has no quality of life impact.

For the WSE the percentages applied within the current assessment of 30% and 15% can be presented.

Table 14: WSE QoL values across TA229, TA283 and the current assessment

STA			RANI	DEXA	AFLI	AFLI	AFLI	AFLI
Source			Brown	..	Czoski	Brown	Czoski	Brown
WSE %			..	..	30%	30%	15%	15%
HS	ETDRS	Mid	QoL	QoL	QoL	QoL	QoL	QoL
HS1	86–100	93.0	0.920	[redacted]	0.854	0.842	0.854	0.842
HS2	76–85	80.5	0.916	[redacted]	0.833	0.825	0.842	0.832
HS3	66–75	70.5	0.909	[redacted]	0.816	0.811	0.832	0.825
HS4	56–65	60.5	0.898	[redacted]	0.799	0.798	0.823	0.817
HS5	46–55	50.5	0.885	[redacted]	0.782	0.784	0.813	0.809
HS6	36–45	40.5	0.868	[redacted]	0.765	0.771	0.803	0.802
HS7	26–35	30.5	0.848	[redacted]	0.748	0.757	0.794	0.794
HS8	<25	12.5	0.822	[redacted]	0.717	0.733	0.777	0.780
HS1-HS7			0.072	[redacted]	0.106	0.084	0.060	0.048

For the WSE the values applied appear to be broadly in line between the ranibizumab and the dexamethasone assessments. If the Czoski-Murray values are to be used the 15% adjustment appears to be closer to the other assessments than the 30% adjustment. A factor of 18% brings them into line and revises the £21,492 per QALY ICER to £23,568 per QALY. If the Brown values are to be used the 30% adjustment appears to be closer to the other assessments than the 15% adjustment. A factor of 25% brings them into line and revises the £27,324 per QALY ICER of SA05 to £29,039 per QALY. The 30% and 15% adjustments appear to straddle the values of the other assessments.

Other differences between the assessments

The clinical effectiveness inputs for the main comparisons cannot readily be compared.

FEI at baseline is higher in the current assessment than in the dexamethasone assessment.

The BSE proportion at baseline is in line with or lower in the current assessment.

Anti-VEGF dosing is now somewhat higher for the current assessment.

Health states:

- DEXA: 6 health states: mid 20 letter bands, HS1 ≥ 69, HS5 ≤ 38
- RANI: 8 health states: mid 10 letter bands, HS1 ≥ 85, HS8 ≤ 25
- AFLI: 5 health states: mid 15 letter bands HS1 ≥ 80, HS5 ≤ 35

Clinical effectiveness: Impenetrable for main comparisons

- DEXA: TPMs from patient count data of trial
- RANI: TPMs from patient count data of trial it appears
- AFLI: TPMs from R MSM or patient count data of trial

Decline off treatment

- DEXA: ??
- RANI: 1% drop 1 or 2 HS annually
- AFLI: 2% drop health state annually

BSE at baseline:

- DEXA: 10% expert opinion, though ERG 3% from trial
- RANI: 100% BSE model, ERG ??
- AFLI: 2.2% trial

FEI:

- DEXA: 3.0% baseline, Weibull function thereafter
- RANI: n.a.
- AFLI: 6.5% baseline, 2.5% annual

Dosing anti-VEGF 1st line:

- DEXA: n.a.
- RANI: 8.0yr1, 2.5yr2
- AFLI: 9.0 yr1, 4.2 yr2, 3.2 yr3 – yr10

Dosing dexamethasone:

- DEXA: 1.79 yr1, 0.38 yr2, 0.08 yr3
- RANI: 2.0yr1, 2.0yr2
- AFLI: 1.00 6mth-1yr, 1.69 yr2, 0.93 yr3, 0.21 yr4, 0.10 yr5