[redacted], Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
London
WC1V 6NA

15th December 2011

Dear [redacted]

Re: Ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion – Appraisal Consultation Document

Thank you for your letter dated 17th November inviting comments on the Appraisal Consultation Document (ACD) and Evaluation Report for the above appraisal.

Novartis is very disappointed that the preliminary guidance from NICE does not recommend the use of ranibizumab for the treatment of visual impairment (VI) due to macular oedema (MO) secondary to retinal vein occlusion (referred to hereafter as RVO). We are concerned that the preliminary recommendation may be based on some assumptions and inputs to the cost effectiveness analysis that are not fully evidence-based. Should this recommendation become final guidance, people with visual impairment due to macular oedema secondary to retinal vein occlusion would be denied a sight-restoring treatment that is in fact a cost-effective use of NHS resources.

Based on our revised analyses, taking account of the comments of the Appraisal Committee, we believe that ranibizumab is cost-effective well below a £20,000 per Quality Adjusted Life Year (QALY) threshold when compared to dexamethasone implant for the treatment of both Branch and Central RVO (BRVO and CRVO) in the WSE (£6,600 and £11,656 per QALY, in BRVO and CRVO respectively). Ranibizumab is also cost-effective below a £20,000 threshold compared to observation for the treatment of CRVO in the WSE at £18,817 per QALY.

We are pleased that the Appraisal Committee has recognised that ranibizumab is a well-tolerated and effective treatment for VI due to MO secondary to both BRVO and CRVO. We are also reassured that the Committee has acknowledged the important impact of ranibizumab on patients' quality of life, when treatment is provided to the worse-seeing eye (WSE).

We believe, however, that there are a number of key issues that must be clarified with respect to the evidence submitted by Novartis, the rationale for our assumptions and the

implications inherent in alternative assumptions proposed by the Evidence Review Group (ERG). We consider that there are several important areas where elements of the base case we originally submitted were conservative and the ERG's approach results in a significant overestimation of the Incremental Cost Effectiveness Ratios (ICERs).

We would therefore be grateful for the Committee's further consideration of the key issues summarised below:

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

6. *The use of un-pooled transition probabilities based on the sham/0.5 mg ranibizumab-treated patients after 6 months should not be applied to the laser arm of the model, as this attributes the benefit of just starting ranibizumab to laser-treated patients*
7. *The inclusion of bevacizumab as a comparator in this STA is inappropriate*
8. *The limitations of the ERG's approach to the comparison versus bevacizumab have not been fully explored*
    a. *The studies of bevacizumab in RVO include less than 100 patients, and have important methodological shortcomings*
    b. *The method of the ERG's indirect comparison appears to be flawed*
    c. *The interpretation of the indirect comparison result as there being no clinically meaningful difference is not appropriate given the large variance around the point estimate*
    d. *The reason for assumed bias in the indirect comparison towards ranibizumab is unclear and appears not to be evidence-based*
    e. *There are important safety considerations that should not be ignored*
    f. *There is no basis for a cost-minimisation analysis, where equivalent efficacy and safety have not been demonstrated*
9. *Ischaemic disease has not been adequately defined*

These points are discussed in detail in section A of our response below. We urge NICE to reconsider its preliminary guidance in light of our comments.

Our response is structured as follows:

A. *Comments on the ACD*
B. *Summary of the cost-effectiveness of ranibizumab in the WSE*
C. *Inaccuracies in the ACD and evaluation report*
D. *References*

I hope that our comments are of value. If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]

A. Main Comments on the ACD

1. Utilities values

The Novartis cost-effectiveness analysis was originally based on treatment of the BSE, in line with cost effectiveness analyses used in previous NICE technology appraisals for ophthalmic conditions and in light of the paucity of published evidence for the utility gain associated with treatment of the WSE.[1] We were pleased to hear the Committee confirm, at its meeting to develop the ACD, that it would find it unethical to make recommendations that would prevent treatment for a reversible condition of the WSE and that the Committee considered there was an important utility benefit to patients receiving treatment in the WSE.

It may be helpful to reiterate here that, similarly to the Committee, Novartis considers that there is considerable benefit to patients derived from improving vision in the WSE. The original cost-effectiveness model set WSE utilities to a constant value for all BCVA health states, as described in paragraph 3.13 of the ACD and in the pre-briefing report, only to enable the WSE scenario analyses presented in our submission (Figures B59 to B62).

In light of the Committee's comments, we acknowledge the need to present a base case analysis for treatment of patients with predominantly WSEs affected with RVO. However, we are concerned that the ERG's approach has led to a significant underestimation of the benefit that patients derive from improved vision in the WSE. We present below our concerns; a summary of the results of alternative scenarios are presented in section B.

a) Fitting the 'Brazier utilities' to the model

Novartis believe that both the utilities estimated by Brown et al.[2] and Brazier et al.[3, 4] are acceptable for use in the cost effectiveness model. Brown was selected as it included 7% RVO patients. However, we understand that the methodology used in eliciting the Brazier utilities may be preferable for this NICE appraisal. Our concern, however, is the way in which the ERG has applied the utility estimates to the cost effectiveness analysis.

We consider the ERG's approach will significantly underestimate the utility gains associated with improving visual acuity. As the ERG has noted, '*some simplifying assumptions were made surrounding the application of a smaller set of utility values to a larger number of health states'* (page 108 of ERG report v1). In response to our concerns about this, the ERG confirmed that the limitations of its approach included '*a lack of calibration of the model to the smaller set of utility values*' (ERG response to the factual accuracy check of ERG report).

The ERG's choice of fewer utility values appears to be based on its concern that the cost-effectiveness model should be based on a ≥15 letter change in BCVA. However, the clinical specialists attending the Committee Meeting unanimously confirmed that a ≥10 letter

change in BCVA was clinically meaningful; the model structure based on 10 letter changes was therefore accepted by the Committee. Thus, it is important that the Brazier utilities are fitted to each of the health states of the model structure.

We would also highlight that in expressing its preference for the Brazier utilities, the TA155 Appraisal Committee had considered a cost-effectiveness model that applied a larger set of utility values than the ERG proposes. Furthermore, in making adjustments between the manufacturer and the Assessment Group model, the Assessment Group for TA155 adjusted the Brazier utilities through a simple linear regression.[5]

Since TA155, the Brazier utilities have been published by Czoski-Murray et al. alongside a linear (ordinary least squares) regression model that estimates the relationship between VA and health state utilities, with an adjustment for patient age.[4] The equation, using Table 6 of the publication, is the following:

Utility value = 0.860 – 0.368×(VA in logMAR) [-0.001×age]

Thus, it is possible to derive Brazier utilities for each of the 8 BCVA health states in the RVO cost effectiveness model in a similar way to that employed by the TA155 Assessment Group, and including an age adjustment. The alternative utility values applied to the health states of the model using each approach are presented in Table 1 below. For this calculation, the upper and lower ETDRS letter scores in each health state were averaged to estimate the utility level applicable to each health state, after transformation from the logMAR scale. This ensures that utilities based on the regression equation apply specifically to each health state (detailed calculations are presented in Appendix 1). The implications of the ERGs application of the Brazier utilities, compared to Brazier utilities fitted to the model structure, are illustrated in Figure 1.

Cost effectiveness analyses using the appropriately adjusted Brazier utilities are presented in Section B.

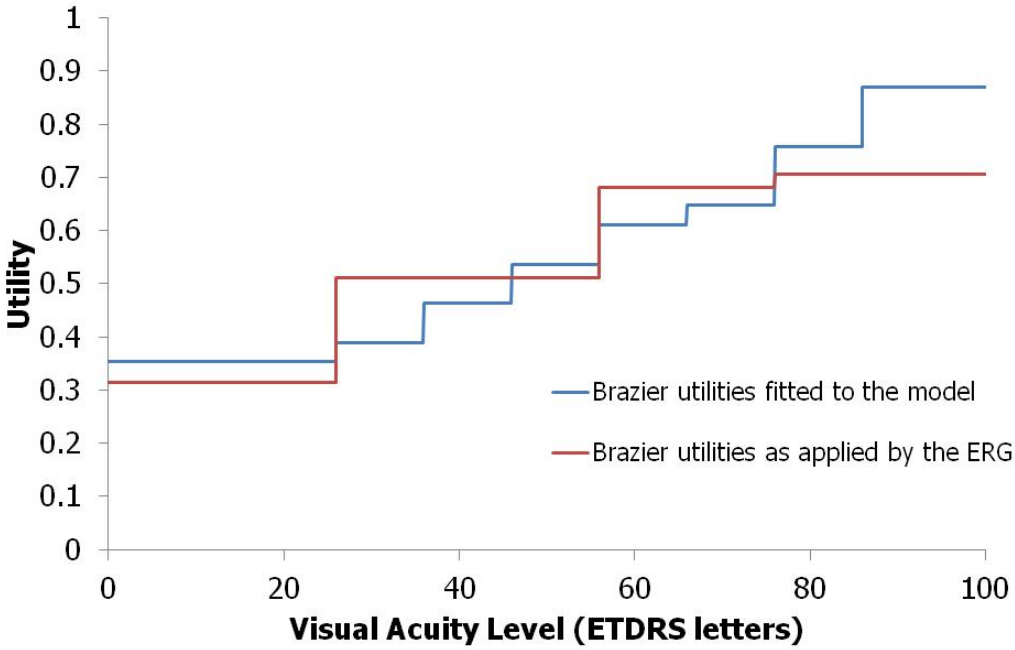
Table 1: Comparison of utilities derived from Brazier et al.[4]

Health states for model	Brazier utilities using the Czoski-Murray algorithm*
86-100 letters	0.869
76-85 letters	0.758
66-75 letters	0.648
56-65 letters	0.611
46-55 letters	0.537
36-45 letters	0.464
26-35 letters	0.390
≤25 letters	0.353

Health states implied by the ERG	ERG utilities
76-100 letters	0.706
56-75 letters	0.681
26-55 letters	0.511
≤25 letters	0.314

* Calculated using equation above, the average of the upper and lower ETDRS letters scores in each health state was used to estimate the utility level applicable to each health state, after transformation from the logMAR scale.

Figure 1: Comparison of the utilities applied in the ERG model to those of the original model structure



b) Assumptions about utility gain from treatment of the WSE

Novartis acknowledge the Committee's preference for WSE base case analysis. However, we are concerned that the approach proposed by the ERG will not capture adequately the full utility gain from treatment.

We understand from the ERG's report that an overall utility loss of 0.1 was applied to the WSE. This was achieved by adjusting the slope of the WSE utility curve to give a difference of 0.1 between the best and the worst BCVA health states. The ERG cites the HTA monograph for TA155 as the source of this approach, where a 0.1 decrement in utility was associated with the state of blindness in the WSE. We have been unable to identify this utility estimate within the monograph. However, we are aware that the TA155 Committee drew attention to a 0.1 estimate during its considerations of that technology appraisal and that this estimate is derived from a utility elicitation study by Brown and colleagues.[6] The study methodology is summarised in Table 2.

Table 2: Methodology of the Brown et al. 2001 study[6]

Objective	To ascertain whether patients with good visual acuity in one eye have the same quality of life as patients with good vision in both eyes
Design	Cross-sectional comparative study
Country	USA
Participants	Consecutive patients with good vision (20/20 or 20/25) in one or both eyes
Definition of unilaterally vision impaired group	Patients with visual impairment less than 20/40 (6/12 or 70 ETDRS letters) in one eye.
Number of patients	Good vision in both eyes: N=66 Good vision in only one eye: N=81
Number of patients with unilateral good vision, by visual acuity in poorer eye	20/40–20/50: N = 24 20/70–20/100: N = 12 20/200–20/400 N = 14 Counting fingers–light perception N = 25 No light perception N = 6
Method	Standardised patient interview
Main outcome measure	Time trade-off utility values

As can be seen from Table 2, the Brown study was designed to identify whether patients with good visual acuity in both eyes have *the same quality of life* as patients with good vision in only one eye. The authors acknowledge that their attempts to determine whether worse visual acuity in the WSE is associated with worse utility values generated uncertain results and that more data is needed.[6] We note the very small sample sizes when unilaterally affected patients are grouped by visual acuity (Table 2), and that inconsistent results make conclusions impossible.

Thus Novartis considers that, whilst this study demonstrates a clear difference in utility between patients with good bilateral vision and those with good unilateral vision, it is not appropriate to assume that the 0.1 difference between these two groups captures the difference in utility for patients with *blindness* in the WSE. Indeed, we note the range of utilities elicited from unilaterally affected patients was 0.33 to 1.0, suggesting that as much as 0.64 difference in utility in some patients with unilateral vision loss.[6] Furthermore, we note that the Brown study includes patients with good bilateral vision as the reference group. In the ranibizumab pivotal studies for RVO, [redacted] had BCVA in the fellow eye of <73 letters (20/40), in BRAVO and CRUISE respectively.[7] Therefore, one would expect the impact of poor vision in the WSE to be greater than that observed in Brown's sample, particularly if treating the WSE results in this eye becoming the BSE, something very unlikely to have happened in the Brown sample.

We suggest that the 0.1 difference in utility might be more appropriately interpreted as the difference between patients with good bilateral vision and patients with WSE BCVA lower than 20/40 (approximately equivalent to 70 letters) in one eye and 20/20 or 20/25 vision in the other. Thus, over the entire range of BCVA health states from good vision to blindness

in the WSE the overall utility benefit would be greater than 0.1. Utility gains from treating the WSE would also be influenced by the BCVA level in the BSE, and whether the WSEs become BSEs as a result of treatment.

The benefit to patients of treating the WSE is confirmed by the BRAVO and CRUISE results in the VFQ-25, which suggest a statistically significant improvement with ranibizumab in patient-reported visual function versus the control groups by month 1.[8, 9]

In section B, we present ICERs for WSE analyses altering the assumptions for the overall utility loss associated with blindness proposed by the ERG for utility gain. We consider that the most appropriate overall utility benefit from treating the WSE is 0.3. This is based on an increased slope of the WSE utility curve to 0.043, which approximates a 0.1 difference between no visual impairment in the WSE (health state 86-100 letters) and BCVA of 73 letters (health state 66-75 letters) and a similar difference applied to health states representing similar reductions in BCVA (Table 3). A 0.3 overall benefit of treating the WSE represents more than 40% less overall benefit than treating the BSE.

Table 3: Utilities assumed for the WSE in the revised model

Health states of model	Utilities assumed for the WSE
86-100 letters	0.869[1]
76-85 letters	0.826
66-75 letters	0.783
56-65 letters	0.740
46-55 letters	0.687
36-45 letters	0.654
26-35 letters	0.611
<25 letters	0.568

1. Assumed to be equivalent to BSE utility in this health state, in line with the ERG's approach

The proportion of the population assumed to be treated in the WSE in the analyses presented in section B is based on the percent of the BRAVO and CRUISE populations, as presented in Table 4 and Table 5 below, and reflects the base case assumptions for BSE/WSE proportions accepted in the appraisal of dexamethasone implant.[10] This assumption is unchanged from and therefore consistent with the ERG's additional analyses and therefore should be acceptable to the committee.

Table 4: Proportions of BSE and WSE (study eye) at baseline in BRAVO[9]

	Sham (N=132)	0.3 mg ranibizumab (N=134)	0.5 mg ranibizumab (N=131)
WSE	121 (91.7%)	118 (88.1%)	125 (95.4%)
BSE	8 (6.1%)	9 (6.7%)	4 (3.1%)
Same*	3 (2.3%)	7 (5.2%)	2 (1.5%)

Table 5: Proportions of BSE and WSE (study eye) at baseline in CRUISE[8]

	Sham (N=130)	0.3 mg ranibizumab (N=132)	0.5 mg ranibizumab (N=130)
WSE	117 (90.0%)	123 (93.2%)	120 (92.3)
BSE	8 (6.2%)	3 (2.3%)	7 (5.4%)
Same*	5 (3.8)	6 (4.5%)	3 (2.3%)

*[redacted]

2. Inconsistencies in the Committee's appraisal of dexamethasone implant for the treatment of RVO and its appraisal of ranibizumab for the treatment of RVO

a) Excess mortality associated with RVO

The suggestion that an excess mortality risk specifically associated with RVO should be introduced into the model is inconsistent with the NICE technology appraisal of dexamethasone implant for RVO (TA229), where such an adjustment was not required. Given the same condition and patient population were considered in TA229 and the present appraisal; it is unclear why the same Committee has drawn different conclusions on this point.

Novartis maintains that there is little evidence that RVO is associated with an overall increase in mortality rate (above that caused by visual impairment) (Table 6). The risk ratio (RR) of 1.6 used by the ERG relates to deaths caused by myocardial infarction (MI) only, and thus is not an appropriate multiplier for an overall risk of death. In fact, the source of this RR, Tsaloumas et al. 2000, found that there was no difference in mortality rate caused by ischaemic heart disease or cerebrovascular accident between RVO patients and the general population and actually that RVO patients had a significantly lower mortality rate from malignancies than the general population ($p<0.05$).[11] Therefore the RR implemented by the ERG as an adjuster for overall mortality increase associated with RVO is incorrect and would result in an overestimation of mortality risk in patients with RVO.

The ERG and the Committee's preferred ICERs reported in the ACD are therefore underestimating the cost effectiveness of ranibizumab.

Table 6 below presents the 7 studies that have been cited in relation to mortality risk associated in RVO in the evaluations reports for the ranibizumab and dexamethasone RVO Single Technology Appraisals (STAs), and further studies identified through a recent NHS Evidence Review.[12] The authors of this review did not conclude an increased risk of death was associated with RVO, but rather that 'the body of evidence from observational studies on this subject are conflicting'. As can be seen from the table, 8 of the 13 studies do not assess overall mortality,[11, 13-19] 3 studies found no increased risk of mortality,[20-22] and 2 studies only found an increased mortality rate for RVO in patients under 70 years old.[23, 24]

The starting age of patients in the ranibizumab cost effectiveness model was 66.4 for BRVO and 67.6 for CRVO; therefore based on the studies by Cugati et al.[23] and Xu et al.[24], patients entering the ranibizumab cost effectiveness model would be at excess risk of mortality for a short period of time only and it is arguable that any increased risk should not be applied for the whole time horizon.

Furthermore, since the Tsaloumas study was published, RVO management guidance by the Royal College has altered to improve control of systemic risk factors associated with RVO. With the improvements in management, and medications to manage these risk factors such as antihypertensives, lipid-lowering medications and anti-platelet medications, it is highly likely that any mortality risk identified by Tsaloumas and colleagues would have been reduced over the last decade since its publication.

In addition, when compared to those patients who have the same cardiovascular risk factors, but who are not identified due to not having presented to the hospital, it is likely that patients presenting with RVO will actually have an improved life expectancy compared to those not suffering from RVO, due to the additional systemic management of their risk factors.

In conclusion, an excess mortality risk associated with RVO in patients aged over 65 is uncertain and, if present, is unlikely to be as great as the risk for MI observed by Tsaloumas and colleagues and applied to the model by the ERG. Whilst this evidence clearly stands on its own merit, it is also consistent with the assumptions applied by the committee in TA229.

Table 6: Studies on Mortality Rates Associated with RVO (Christoffersen 2007 to Xu 2007 have been cited by previous STAs, Elman 1990 to Rubinstein 1976 are additional from the NHS Evidence Review[12])

Study ID	Increased mortality associated with RVO?
Christoffersen 2007[20]	No increased mortality with BRVO
Cugati 2007[23]	RVO in people ages 43 to 69 was associated with a 2.5-fold risk of cardiovascular mortality
Ho 2009[13]	Increased risk of stroke
Martin 2002[14]	Higher cardiovascular risk
Tsaloumas 2000[11]	Higher rate of death from MI in RVO patients than in general population, but lower rate of death from malignancies. No overall mortality rates given.
Werther 2011[15]	Increased risk of stroke, but no increased risk of MI
Xu 2007[24]	RVO is associated with higher mortality than the general population in people under 70 (Chinese population)
Elman 1990[21]	Mortality was not increased in CRVO cases as compared with United States mortality rates
Hu 2009[16]	RVO does not predict acute myocardial infarction
Klein 2000[17]	BRVO at baseline did not have an increased 8-year risk of mortality due to ischemic heart disease in the Beaver Dam study
Mansour 1992[22]	Patients with CRVO do not carry a higher risk of mortality and morbidity than matched controls derived from national surveys
Priluck 1980[18]	CRVO associated with cardiovascular mortality
Rubinstein 1976[19]	RVO associated with cardiovascular mortality

b) Time horizon

In order to present a conservative economic case, Novartis selected to use a 15 year time horizon in the base case. In contrast, the ERG and Committee considered a lifetime time horizon was appropriate for the dexamethasone implant cost effectiveness analysis (TA229).

We would like to draw the Committee's attention to this important difference between the two analyses; the implication of which is to favour ICERs presented for dexamethasone implant during that appraisal. Combined with the absence of an excess risk of mortality applied to the dexamethasone implant model, the longer time horizon used in TA229 would generate lower ICERs because patients entering the model have longer to benefit from improved vision as a result of treatment.

If we apply a consistent time horizon as per TA229, we note that a lifetime time horizon in the ranibizumab analysis improves the ICER by up to 18%. Scenarios of treatment of the WSE including a lifetime time horizon are presented in section C.

3. Relevant comparators for CRVO

We consider that best supportive care remains an important comparator for patients with CRVO:

- Dexamethasone implant has not been subject to mandatory NHS funding for a significant period of time and we also note the Pre-briefing Report refers to statements from the clinical specialists that '*uptake throughout the NHS has been slow*'.
- There are some patients in whom dexamethasone is contraindicated.
- We note statements in the ACD that bevacizumab is not universally available, and is used only in some NHS Centres. There are some hospitals in the NHS where the use of intravitreal bevacizumab is not permitted.
- We note that the NICE Business Planning Tool for implementing guidance for dexamethasone implant assumes a 2% estimated uptake of bevacizumab after implementation of NICE guidance.[25] If expert opinion to NICE suggests that only 2% of patients with RVO are expected to be treated with bevacizumab, then we suggest that much less emphasis need be placed on this unlicensed medication as a comparator, compared to licensed interventions and standard of care treatments. The inclusion of bevacizumab as a comparator is discussed further in section 7.

Therefore best supportive care, as outlined in the NICE Scope for this appraisal, remains a relevant comparator for the treatment of CRVO.

4. The extent of bias in comparisons to dexamethasone implant

Our decision not to undertake adjusted indirect comparisons of ranibizumab to dexamethasone implant were based on the differences between the enrolled populations as well as difficulties in identifying BRVO and CRVO specific data from the published evidence reporting the pooled GENEVA studies. We accept that this is a cautious approach, but highlight the Committee's agreement that our modelled estimates of comparative effectiveness give similar results to the ERG's formal indirect comparisons when the errors in the ERG's approach are corrected (Appendix 2 and Table 23).

We would like to draw attention to a section in the pre-briefing report (Section 3.2) that suggests the ERG and the Committee's concerns about bias in the analysis was based upon a further misunderstanding of assumptions in the cost effectiveness analysis (noted below in section C, section 2). Rather than assuming equivalent effectiveness of dexamethasone

implant and laser/best supportive care from month 7, the analysis actually assumes equivalent effectiveness of dexamethasone implant and ranibizumab from month 7 onwards. Thus, concerns in favour of ranibizumab in this regard would appear to be unfounded. We also highlight that to assume equivalent efficacy between ranibizumab and dexamethasone implant may be further biased against ranibizumab, given this approach does not reflect the decrease in BCVA observed in the GENEVA studies around 60 days after implantation.[26]

The Committee's concerns outlined in the ACD are that bias in the comparisons generated by the differences in the duration of MO between the GENEVA and BRAVO/CRUISE patient populations would favour ranibizumab. We emphasise that the extent of this bias is not known and therefore the implications for the ICER may in fact be minimal. However, in light of the Committee's concern, we have re-examined the reported durations of MO in the GENEVA studies and note that it was calculated at the baseline visit. Conversely, in the BRAVO and CRUISE studies, duration of MO was calculated at the screening visit which was at least 30 days prior to the baseline visit. Thus, the mean duration of MO in the ranibizumab studies was assessed at least 1 month prior to assessment in the dexamethasone implant studies, and comparisons of the two should take this into account.

[redacted].With regards to GENEVA, the study investigators stated that '*In eyes with CRVO … improvements in the sham group were greater with shorter duration of ME, but the response to treatment was not*.' [26] There may be differences between the two drugs in the relationship between duration of MO and response to disease.

We would like to draw the committee's attention to evidence which strongly suggests our cost effectiveness analysis against dexamethasone implant is already conservative:

a) Impact of a comparison at 3 months

By undertaking the indirect comparison for BRVO for months 1 to 3 only, the analysis does not take account of the decline in efficacy of dexamethasone implant beyond 3 months after implantation (Haller et al. 2010[26][figure 6] and Haller et al. 2011[27]), which is not seen for ranibizumab. It should be noted that this decline in efficacy over time for dexamethasone implant was the reason that the first GENEVA study did not meet its regulatory primary endpoint.[27] A higher frequency of

dexamethasone implantation than investigated in the GENEVA clinical trial is obviously required to reach stable efficacy, which could be predicted to increase the safety signal dramatically.

b) Dexamethasone implant retreatment frequency is conservative in the base case

In the modelled comparison, the retreatment frequency for dexamethasone was based on the GENEVA studies (injection every 6 months). However, given the observed decline in efficacy beyond 3 months and the observations of clinical specialists who use dexamethasone implant in UK practice, it is likely that retreatment would be needed more frequently. Clinical experts suggest retreatment may be given every 4 months, which was accepted by the TA229 Committee (Paragraph 4.11 of the TA229 Final Appraisal Determination [FAD][10]).

Therefore the base case costs of acquisition and administration are biased towards dexamethasone implant, as these may not reflect the true costs that would be seen in clinical practice. This suggests that the base case analysis underestimates the cost effectiveness of ranibizumab. A scenario analysis including retreatment frequency in year 1 as expected in routine practice (3 injections) is presented in section C and demonstrates a significant reduction.

c) Adverse event rates are conservative in the base case

The Committee noted, when appraising dexamethasone implant, that the safety of this new technology in the long term is uncertain concluding that '... *there were some concerns about the long term safety of dexamethasone treatment because the marketing authorisation is based on a evidence base trial with two re-treatments over 360 days and the manufacturer assumed that up to six treatments would be given and there are limited data on long-term treatment and multiple re-treatment*.' Therefore, as well as offering a conservative estimate of dexamethasone acquisition and administration costs, the ranibizumab cost-effectiveness analysis may underestimate the costs of treating additional adverse events observed with more frequent dexamethasone implant treatment, including raised intraocular pressure, glaucoma and cataract.

Subsequent to our original submission, we have adjusted the model to include adverse event rates in year 2 (see Section B for results).[27, 28] Adverse events for dexamethasone implant have also been updated for year 1, based on the 12 month outcomes of the GENEVA studies (published since our submission). The adjustments for dexamethasone implant in year 1 are also based on rates reported at 12 months of GENEVA; we acknowledge the limitations of a simplification by reapplying these

rates at year 2. For example, this would not account for the cumulative effect of multiple implants or the onset of cataracts. However, it is noteworthy that this adjustment decreases the ICER vs dexamethasone implant by 11% and 14% compared to the base case analysis suggesting an important impact of adverse events (CRVO and BRVO respectively).

Thus, we draw the Committee's attention to its previous, stated concerns about the uncertainty of dexamethasone retreatment frequency and the safety associated with an increased retreatment frequency than was observed in the GENEVA studies. Our revised analyses show a large reduction in the ICER for ranibizumab when these issues are approached in a way that is less conservative for ranibizumab. We therefore conclude that the cost effectiveness analysis may be biased towards dexamethasone implant because it may further underestimate the costs and disutility associated with steroid-related ocular adverse events.

d) Mean number of ranibizumab injections is conservative in the base case

The ranibizumab cost-effectiveness model applies the mean number of injections administered to the HORIZON cohort, without adjusting for those patients treated during BRAVO/CRUISE that did not enter HORIZON. The impact of making this adjustment is presented in Table 7 below, suggesting again that the base case analysis is conservative and may underestimate the cost effectiveness of ranibizumab. Scenario analysis included this less conservative injection frequency is presented in section B.

Table 7: Mean number of injections in the base case and after adjustment for those patients that did not enter HORIZON

	Mean injections in year 2 (base case)	[redacted]	**Reduction in the ICER compared to base case(%)**
BRVO	2.5		27% vs dexamethasone
CRVO	3.8		6% vs dexamethasone 15% vs best supportive care

NOTE: 19 patients who completed BRAVO[29, 30] and 15 patients who completed CRUISE[30, 31] did not enter HORIZON from the 0.5 mg ranibizumab arms. These patients were assumed not to receive any further injections after year 1 in the adjusted scenario presented above

e) Presence of ischaemic disease and neovascularisation

The ERG states that the presence of neovascularisation in the GENEVA sham population suggests that some patients in the trial had ischaemic disease and therefore the dexamethasone treatment effect may be underestimated in the GENEVA population (page 63 of the ERG report v1). We note that the GENEVA investigators also speculate as to this limitation of the study, and go on to note that

'*no conclusions should be drawn from the present study regarding the effectiveness of DEX implant in ischemic patients*.' We also note in the manufacturer's submission for dexamethasone that, with respect to patients with ischaemic RVO, '*These patients could not be adequately identified from the GENEVA clinical trial data and are therefore not included* [in a subgroup analyses]'.

Nonetheless, exploring the ERG's suggestion that this might be a source of bias between the trials, the proportion of patients across the studies with retinal and iris neovascularisation is presented in Table 8. The occurrence of neovascularisation is higher in the sham groups of the BRAVO and CRUISE studies, than the GENEVA studies. Thus, this suggests that, contrary to the ERG's suggestion, the indirect comparison of ranibizumab with dexamethasone implant would in fact be biased in favour of dexamethasone.

Table 8: Neovascularisation at 6 months in the BRAVO, CRUISE and GENEVA trials

	BRAVO[7, 9]		**CRUISE[7, 8]**		**GENEVA[32]**	
	sham	**0.5 mg ranibizumab**	**sham**	**0.5 mg ranibizumab**	**sham**	**0.7 mg dex**
Iris neovascularisation	**2.3%**	0%	**7.0%**	0.8%	**1.4%**	0.9%
Retinal neovascularisation	[redacted]	[redacted]	[redacted]	[redacted]	**1.9%**	1.7%

5. Comparisons to dexamethasone implant in BRVO patients with macular haemorrhage

Since making our submission for the present appraisal, the Committee has made its recommendation that dexamethasone implant should be considered a treatment option for patients with BRVO for whom treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage (MH) or for those patients in whom laser has not been effective. Therefore, comparisons of ranibizumab to dexamethasone implant should be limited to these subgroups of patients to reflect UK clinical practice. We present in Section B the results of an analysis comparing ranibizumab to dexamethasone using the WSE assumptions detailed above, and suggest that this is the focus of the Committee's decision-making for patients with BRVO. We present analyses of ranibizumab to laser in appendix 4 for completeness.

Table 9 below demonstrates that there is little difference in efficacy of dexamethasone implant between the subgroups of patients with MH and the whole BRVO population of the GENEVA studies. The between treatment group differences for the proportion of eyes

achieving at least a 15-letter improvement from baseline to day 180 were 4% and 2.4% for the full population and MH subgroup, respectively. A test of interaction on the original regulatory primary endpoint (proportion of eyes achieving at least 15-letter improvement from baseline to day 180) demonstrated no significant difference between the MH and no MH subgroups (p=0.295).

Table 9: Efficacy of macular haemorrhage BRVO subgroups in the GENEVA clinical trial

	GENEVA whole BRVO population[26] (pooled from 2 trials)		**GENEVA subgroup with macular hemorrhage[32] (pooled from 2 trials)**	
	Dex 0.7 mg	**Sham**	**Dex 0.7 mg**	**Sham**
Number of patients in subgroup	427	426	255	260
% with an improvement in BCVA of ≥15 letters from baseline at day 90	22%	13%	25.9%	14.6%
% with an improvement in BCVA of ≥15 letters from baseline at day 180	22%	18%	23.9%	21.5%

Similarly, there is little difference between the MH subgroup (defined as definite MH) and the whole population of the BRAVO trial, either at baseline (Table 10), 6 months (Table 11) or 12 months (Table 12). A test of interaction on the primary endpoint of BRAVO (mean change from baseline in BCVA score at 6 months), found no significant interaction between the MH subgroup and the non-MH subgroup (p=0.725); Results with ranibizumab were consistently and statistically significantly better than the control in both subgroups. The mean number of injections with 0.5 mg ranibizumab during BRAVO was 8.2, comparable to 8.4 in the full population (table B16 of original submission). Therefore, we consider that a comparison of the whole population of BRAVO to the whole BRVO population of GENEVA can reliably represent the comparison of the MH subgroup of each trial. The use of the full study population from BRAVO allows for improved reliability of the transition probabilities in the model, than if generated from subgroup data.

Table 10: Population characteristics of the whole population and the MH subgroup from BRAVO[7, 9]

	BRAVO population		**Macular Haemorrhage BRAVO subgroup**	
	Sham N=132	**0.5 mg ranibizumab N=131**	**Sham** [redacted]	**0.5 mg ranibizumab** [redacted]
Baseline Age (yrs), mean (SD)	65.2 (12.7)	67.5 (11.8)	[redacted]	[redacted]
Baseline BCVA (letters), mean (SD)	54.7 (12.2)	53.0 (12.5)	[redacted]	[redacted]
Baseline CFT (µm), mean (SD)	488.0 (192.2)	551.7 (223.5)	[redacted]	[redacted]
Mean duration of BRVO at baseline (months), mean (SD)	3.7 (3.7)	3.3 (3.1)	[redacted]	[redacted]

Table 11: Outcomes of the whole population and the MH subgroup from BRAVO at 6 months[7, 9]

	Whole BRAVO population			Macular Haemorrhage BRAVO subgroup		
	Sham N=132	**0.5 mg ranibizumab N=131**	**P value for ranibizumab vs sham**	**Sham**	**0.5 mg ranibizumab**	**P value**
Mean (SD) change from baseline in BCVA score at month 6, ETDRS letters	7.3 (13.0)	18.3 (13.2)	P<0.0001			
(95% CI for mean)*	(5.1 – 9.5)	(16.0 – 20.6)				
Difference in means (95% CI for difference)*	-	11.0 (7.8 – 14.2)				
Test of interaction for MH vs no MH	-	-	-			
Proportion of patients who gained ≥ 15 ETDRS letters at Month 6, n (%)	(28.8%)	(61.1%)	P<0.0001			
(95% CI for percentage)**						
Difference in percentage (vs. sham)† (95% CI for difference)†						
Proportion of patients who lost < 15 ETDRS letters at Month 6, n (%)	126 (95.5%)	129 (98.5%)				
(95% CI for percentage)††						
Difference in percentage (vs. sham)‡ (95% CI for difference)‡						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Derived from the t-distributions, ** By normal approximation [redacted]

NR, not reported. The last-observation-carried-forward method was used to impute missing data.

Table 12: Outcomes of the whole population and the MH subgroup from BRAVO at 12 months[7, 29]

	Whole BRAVO population			**Macular Haemorrhage BRAVO subgroup**		
	Sham / 0.5 mg N=132	**0.5 mg ranibizumab N=131**	**P value for ranibizumab vs sham**	**Sham / 0.5 mg** [redacted]	**0.5 mg ranibizumab** [redacted]	**P value** [redacted]
Mean (SD) change from baseline in BCVA score at month 12, ETDRS letters (95% CI for mean)*	12.1 (14.4) (9.6 - 14.6)	18.3 (14.6) (15.8 – 20.9)	P=0.0007	[redacted]	[redacted]	[redacted]
Proportion of patients who gained ≥ 15 ETDRS letters at Month 12, n (%)	58 (43.9%)	79 (60.3%)	P<0.05	[redacted]	[redacted]	[redacted]
Proportion of patients who lost < 15 ETDRS letters at Month 12, n (%)	124 (93.9%)	128 (97.7%)	NR	[redacted]	[redacted]	[redacted]
Proportion of patients who gained ≥ 10 ETDRS letters at Month 12, n (%)	80 (60.6%)	96 (73.3%)	NR	[redacted]	[redacted]	[redacted]
Proportion of patients who lost ≥ 10 ETDRS letters at Month 12, n (%)	9 (6.8%)	3 (2.3%)	NR	[redacted]	[redacted]	[redacted]

* Derived from the t-distributions. NR, not reported. The last-observation-carried-forward method was used to impute missing data.

6. Pooled vs. un-pooled transition probabilities for months 7-24 for BRVO

The Committee raised concerns that the use of pooled transition probabilities during months 7-24 in the model may not be an appropriate method to estimate effectiveness of the grid laser photocoagulation (laser) arm beyond 6 months. We accept that pooling the data for ranibizumab 0.5 mg and sham/0.5 mg arms beyond 6 months may not be ideal. However, we would like to highlight that there is no data from the BRAVO trial that allows estimation of laser efficacy after 6 months, because ranibizumab is added to the control arm at this time point. Therefore the pooling approach originally used applies the same effectiveness estimates to the laser and the ranibizumab arms of the model from month 6 and beyond. Inherent in this approach is the important assumption that patients with laser and ranibizumab experience the same probability of improving and worsening BCVA beyond month 6 of treatment. Pooling the data from both treatment arms also allowed us to use all patient observations to calculate the transition probabilities.

Inappropriateness of the un-pooled transition probabilities to represent the sham/0.5 mg ranibizumab arm after 6 months

We accept that using pooled data from the 0.5 mg and the 0.5 mg/sham arms of BRAVO is open to criticism. However, to apply un-pooled transition probabilities from the respective arms is to assume that laser treated patients would respond as patients treated with delayed ranibizumab (see slope after 6 months in Figure 2 and the un-pooled transition probabilities for the sham/0.5 mg arm in Table 13). That is to say, use of the un-pooled transition probabilities means that the benefits of starting ranibizumab after 6 months are attributed to standard of care in the model. This is not intuitive, nor in line with clinical expectation.

Novartis accepts that there may be a small rise in visual acuity between month 6 and month 12 in patients with BRVO who are treated with laser. However, the current published evidence does not support the conclusion that this is either a clinically meaningful gain in vision, or that it is as large as that seen in the sham/0.5 mg ranibizumab arm within the second six months of the BRAVO trial.

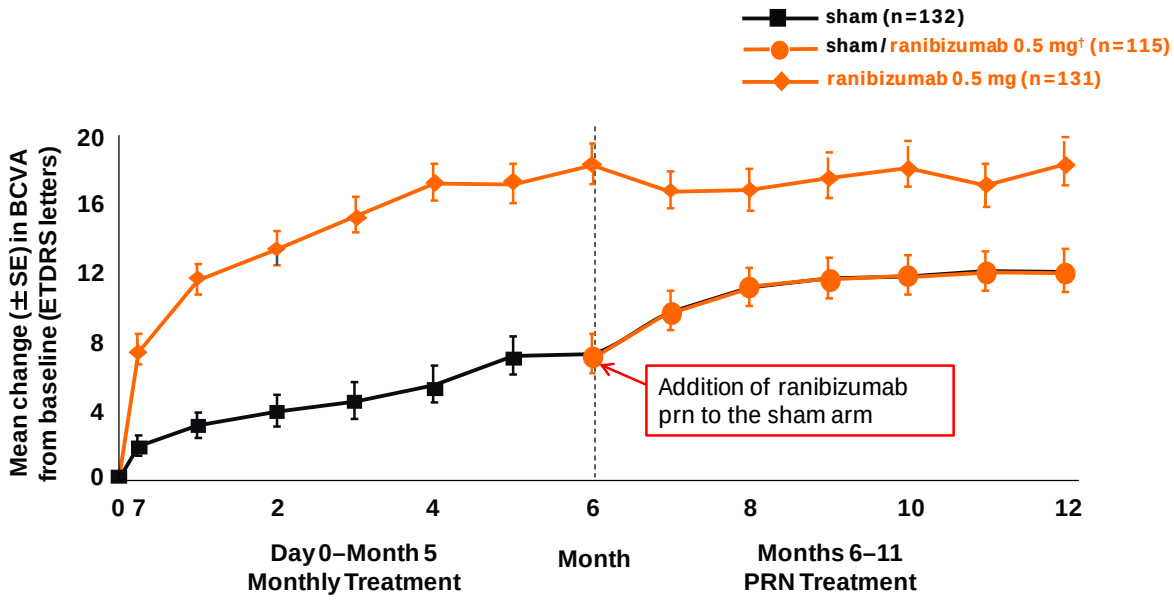
- The SCORE BRVO study (Scott et al 2009[33]) found that there was an increase in vision from month 8 to 12 of 2.6 letters, which is neither a clinically meaningful increase, nor as large as the sham/0.5 mg ranibizumab 6 to 12 month rise of 4.8 letters (a rise from 7.3 letters at six months to 12.1 letters at 12 months).[29] Due to the large drop-off in enrolled patients after month 12 in the SCORE study (52% to 62% completed 24 months and 28% to 34% completed 36 months), meaningful conclusions cannot be drawn about longer term efficacy of laser beyond 1 year.[33]

- These findings validate those in the pivotal BVOS study, which found that in the patients who completed 3 years of follow-up, an average gain of 1.3 lines (approximately 7 ETDRS letters) over baseline was seen;[34] while this indicates that there is a lack of significant vision gain in the long term over and above that seen in the first six months of BRAVO with laser treatment (7.3 letters), the characteristics of those patients who dropped out of this study may confound the analysis.

In summary, it is clear that the additional efficacy gained in the second six months of the BRAVO study by the patients starting ranibizumab in the sham/0.5 mg ranibizumab arm is over and above that seen in the pivotal studies of patients on sham/laser alone to date as exemplified by the BVOS and SCORE BRVO studies.[33, 34] This is most likely due to the use of ranibizumab in these patients in BRAVO, and provides a strong justification as to why this data is not appropriate for use in the 6 to 12 month transition probabilities for the sham arm. We therefore urge the Appraisal Committee to disregard the ERG's analysis applying the transition probabilities derived from sham/0.5 mg ranibizumab treated patients to the laser arm of the model.

We present in section B, the results of an analysis where the conservative assumption of equivalent transition probabilities in the treatment and comparator arms of the model is retained in months 7 to 24, but data from only the 0.5 mg ranibizumab arm is used for both arms (see Table 13 below).

Figure 2: Mean change in BCVA over time in BRAVO, demonstrating the effect of delayed ranibizumab treatment in the sham arm after 6 months[29]



†Sham patients received 0.5 mg ranibizumab PRN treatment from Month 6 to 11

*P<0.0001 vs. sham (pair-wise ANOVA), **P<0.05 vs. sham (post hoc analyses, pairwise ANOVA)

BCVA: best-corrected visual acuity, ETDRS: Early Treatment Diabetic Retinopathy Study, PRN: pro re nata, SE: standard error

Randomized patients, LOCF: last observation carried forward

Campochiaro et al. Ophthalmology 2010
Ho et al. ARVO 2010

Note: Graph is for illustrative purposes; the cost effectiveness model is parameterised by proportion of patients gaining and losing lines of BCVA (Table 13).

Table 13: 7 to 12 month transition probabilities from BRAVO patient level data

Transition	0.5 mg Ranibizumab transition probabilities	Sham / 0.5 mg ranibizumab transition probabilities
Gain >4 lines	1.5%	1.5%
Gain 2 to 4 lines	17.1%	17.3%
No change	64.6%	69.6%
Lose 2 to 4 lines	14.2%	10.7%
Lose >4 lines	2.6%	0.9%

Use of HORZON data to estimate to the transition probabilities for months 13-24

Since the original Novartis RVO model was developed, individual patient level data have become available from the HORIZON extension study. These data have now been analysed and entered into the model as a scenario analysis (see Section C for results). The model structure was adapted slightly to accommodate the new data: the cycle length in year 2 was changed to 3 months to match the HORIZON follow-up periods and patients with different visual acuity levels were modelled separately to avoid a ceiling effect occurring in the model, which led to a lack of replication of the study results. For further details on the model adaptations, please see Section E, Appendix 3.

7. Inclusion of bevacizumab as a comparator in this STA

Novartis strongly believes and has consistently maintained throughout this appraisal that bevacizumab is not a valid comparator for ranibizumab in the treatment of RVO. Our reasons for this conclusion may be summarised as follows:

a) Bevacizumab does not satisfy the definition of a comparator as set out in NICE's procedure guides

The approach to selection of comparators is set out in NICE's Guide to the Methods of Technology Appraisal, paragraph 2.2.4:

"*Relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment. ...Relevant comparator technologies may also include those that do not have a marketing authorisation ... for the indication defined in the scope but that are used routinely for the indication in the NHS*".

While NICE's procedures envisage that comparators may be products which do not have a marketing authorisation for the indication defined in the Scope, we do not understand this to include products which are unlicensed, as opposed to being used for an 'off-label' indication (see (b) below). In this context, formulations of bevacizumab used for

administration in the eye do not have any marketing authorisation for the form in which it is supplied for intravitreal administration (i.e. altered dose, altered packaging, altered method of delivery all result in a substantially manipulated product that thus becomes unlicensed as confirmed by MHRA) irrespective of the indication; they are therefore unlicensed and fall outside the definition of comparators under NICE's procedures.

Furthermore, the use of unlicensed bevacizumab does not represent routine and best practice for the treatment of RVO within the NHS and, in view of the availability of alternative licensed therapies, Novartis submits that any other conclusion would be very surprising. The intravitreal administration of a formulation which has undergone no regulatory scrutiny, in circumstances where the data supporting such use are very limited, cannot be viewed as "best practice", particularly in circumstances where alternative treatments, tested and authorised for such use, are available.

b) ***Endorsement of bevacizumab as a valid comparator for ranibizumab in the treatment of RVO clearly supports use of bevacizumab in this indication, even though such use is unlicensed, and therefore undermines the medicines regulatory regime.***

NICE has sought to create a distinction between an appraisal of a technology for an indication for which it is not authorised (which will not be undertaken by NICE unless the Secretary of State specifically directs) and use of comparators which are not authorised for the particular indication under consideration. Even if NICE will not recommend use of a product for an indication which is not covered by its marketing authorisation, the fact that guidance may be based on a comparison with such a product, clearly demonstrates endorsement by NICE for use of the product as a valid alternative treatment for the relevant indication and therefore undermines the regulatory regime.

While, in the case of a product, which has a marketing authorisation, but is being used for an unlicensed indication, there is likely to be a lack of evidence for its efficacy in that indication and the risk of adverse effects in the particular patient population, in the case of an unlicensed product, the position is far more uncertain. In addition to the lack of regulatory review of data relating to efficacy and safety, there has been no consideration by the regulatory authorities of the quality of the product, its purity, the standard of manufacturing and its appropriateness for administration by the chosen route. The consideration by NICE of technologies which are unlicensed wholly bypasses the proper regulatory process and presents even higher risks for patients than those associated with use of medicinal products "off-label". NICE's acceptance of unlicensed medicines as comparator products would require the Institute to act outside its remit, assuming at least some of the functions which should properly be undertaken by the regulatory authority and exposing the Institute to potential liability should patients suffer injury as a result of treatment using such products.

Bevacizumab is authorised for intravenous administration for the treatment of various cancers; the formulations prepared for administration via the intravitreal route have no authorisation for any indication. The fact that bevacizumab is not authorised for

intravitreal administration means that the product has not been manufactured to the standards required for ophthalmological therapies and there has been no regulatory review of the pharmaceutical and quality data or inspection of the manufacturing site in the context of potential use in the eye. As confirmed by the MHRA, the administration of bevacizumab via the intravitreal route therefore constitutes unlicensed, rather than "off-label" use.

It should also be recognised that there is considerable uncertainty in relation to the supply chain for bevacizumab for use in ophthalmic indications. Any person who manufactures bevacizumab for administration in the eye (i.e. from intravenous preparations of bevacizumab) requires a "specials" licence from the MHRA to permit such activity. The reliability and extent of supplies from such sources seems doubtful, particularly if ophthalmic treatment with bevacizumab increases beyond the limited amounts currently used.

Use of bevacizumab as a comparator for ranibizumab endorses its use in the treatment of RVO, undermines the regulatory process and, by accepting such a comparison as valid, NICE potentially exposes itself to liability in relation to its use.

c) ***The evidence on the efficacy and safety of bevacizumab in the treatment of RVO is minimal and insufficient to form the basis for appraisal***

The safety and efficacy of bevacizumab in the treatment of RVO is very limited and is insufficient to form any basis for appraisal. This is an import point for the Committee to consider and our position is expanded in section 8.

Finally the safety data for use of bevacizumab in ophthalmological indications, including RVO, is too limited to allow it to be regarded as a standard therapy (section 8).

In summary, bevacizumab is unlicensed for intravitreal administration and the data supporting its efficacy and safety in RVO are very limited. We firmly believe it does not therefore provide a valid or proper comparator for ranibizumab and should not be considered in the guidance.

8. Conclusions of the ERG with respect to the adjusted indirect comparison versus bevacizumab

a) Quality of the included studies

Whilst the ERG discusses the heterogeneity of the patients included in the indirect comparison, there is no discussion of the poor quality of the bevacizumab studies. A crucial limitation of the ERG's analysis arises from the methodological shortcomings of the included studies (Table 14). It is especially important to emphasise that the number of eyes treated with bevacizumab across the two studies included in the ERG's indirect comparison is less than 75.

Only the smaller study by Russo and colleagues presents visual acuity outcomes by proportion of patients experiencing categorised changes in BCVA. It is the proportion of patients experiencing categorised changes in vision that is used to parameterise the Novartis cost-effectiveness model, and is traditionally used in Markov models to analyse cost-effectiveness of interventions in ophthalmology conditions.[1, 32, 35] Thus, the published data for bevacizumab in RVO is further limited to only 15 bevacizumab-treated eyes when considering the proportions of patients experiencing categorised changes in vision. This means that the effectiveness of bevacizumab in RVO in any cost effectiveness analysis would be based entirely on 15 eyes studied in a quasi-randomised, open label study. Such an approach is unreliable, at best. We note that the Committee recognised the difficulties of the evidence base for bevacizumab during its appraisal of dexamethasone implant.[10]

Furthermore, we highlight to the Committee that Russo and colleagues reported only the proportion of patients experiencing an improvement of at least 15 letters. The proportion of patients experiencing deterioration in BCVA, by any categorisation, was not reported. Thus, the published data is not adequate to determine movement of patients between health states in a Markov structure and may overestimate the effect of bevacizumab on BCVA.

Table 14: Methodological shortcomings and risk of bias in the bevacizumab studies

Study ID	Shortcomings
Moradian et al. 2011[36]	• Small sample size (81 eyes with acute BRVO) • Very short follow-up (12 weeks, only 2 injections of bevacizumab administered) • Not stated whether an intention to treat analysis was performed • Number of withdrawals was not stated
Russo et al. 2009[37]	• Very small sample size (30 eyes with BRVO) • Quasi-randomised • Unmasked

b) Methodology of the indirect comparison

The use of the Russo et al. study for the indirect comparison of ranibizumab versus bevacizumab is inappropriate due to the fact that standard deviations are not reported by Russo for the values of change from baseline. The ERG appears to have used the standard deviations for the point estimate of BCVA at follow-up for the change from baseline, which is not good statistical practice, appropriate or reliable.

Therefore, we suggest that the ERG's indirect comparison of ranibizumab and bevacizumab appears to be flawed.

Table 15: Details of the standard deviations used by the ERG

1. As reported by Russo el at, likely a typographical error
2. Applied by the ERG, but not reported in the publication

	Values reported in the Russo et al. publication[37] (Table 2)		**Values used by the ERG (Tables 20 and 24)**	
	Bev	**GLP**	**Bev**	**GLP**
Baseline BCVA, mean logMAR (SD)	0.87 (0.16)	0.89 (0.13)	0.87 (0.16)	0.89 (0.13)
BCVA at 3 months follow up, mean logMAR (SD)	0.55 **(18)**[1]	0.67 **(12)**[1]	0.55 (0.18)	0.67 (0.12)
BCVA change from baseline, mean logMAR (SD)	0.32	0.22	-0.32 **(0.18)**[2]	-0.22 **(0.12)**[2]
BCVA change from baseline, mean ETDRS letters (SD)	NR	NR	**16 (9)**[3]	**11 (6)**[3]

Abbreviations: Bev, bevacizumab; GLP, grid laser photocoagulation; NR, not reported

c) Interpretation of the indirect comparison result

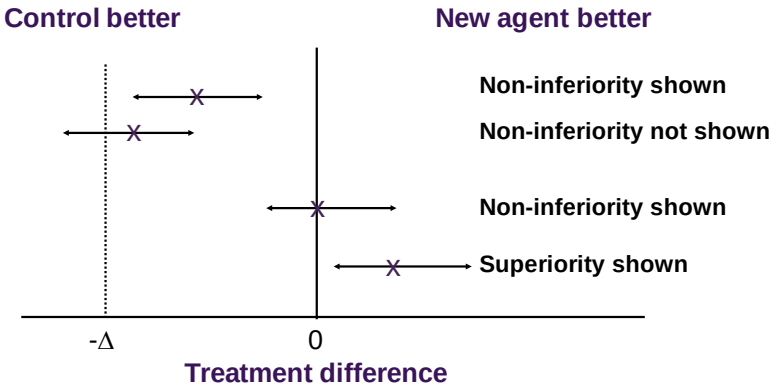
The ERG concludes that the difference of 3 letters between ranibizumab and bevacizumab at 3 months is not clinically meaningful. On page 73 of its report, the ERG draws on the non-inferiority margin of the CATT study as supporting evidence for its conclusion.

Firstly, we highlight that the CATT study primary endpoint was non-inferiority at 12 months. The ERG's exploratory indirect comparison compares outcomes after only 3 months. Secondly, whilst the US CATT study uses a 5 letter non-inferiority margin,[38] the UK IVAN study has been designed with a 3-4 letter margin.[39]

Furthermore, the credible interval of the difference [-10.07 to 4.35] from the indirect comparison is beyond the non-inferiority margin and the equivalence limits of both CATT and IVAN (see Figure 3 and Figure 4 for explanation of non-inferiority and

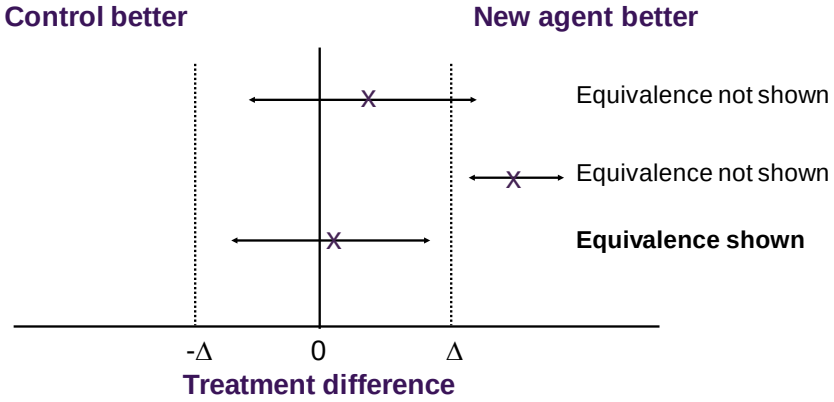
equivalence, respectively).[38, 39] Thus, neither non-inferiority nor equivalence of bevacizumab to ranibizumab at month 3 can be concluded on the basis of the indirect comparison.

Figure 3: Interpretation of confidence intervals for non-inferiority



-Δ = non-inferiority margin

Figure 4: Interpretation of confidence intervals for equivalence



(-Δ, Δ = Equivalence limits)

d) Direction of bias in the indirect comparison

The ERG's view, as presented in the ACD, is that its exploratory indirect comparisons of ranibizumab and bevacizumab are likely to provide overly optimistic estimates of the efficacy of ranibizumab.

Within its report, the ERG notes that the differences in the trial populations of the respective studies suggest bias in favour of bevacizumab with respect to duration of MO, but in favour of ranibizumab with respect to proportion of patients with

ischaemia. However, the ERG and Committee's rationale for concluding an overall bias in favour of ranibizumab is unexplained. In particular, we note that the 20% of patients in the Moradian 2011 study have foveal ischaemia. As noted in section 9 below, ischaemia is a continuum and as the authors of this study did not define 'foveal ischaemia', it is not possible to make comparisons to the level or location of ischaemia that may be observed in BRAVO patients.

Thus, we suggest that the ERG's conclusion about the direction of bias in the indirect analysis in favour of ranibizumab is overly speculative and is not evidence-based. We are concerned that the Committee has relied upon this view in reaching conclusions about relative clinical effectiveness of bevacizumab and ranibizumab.

e) Safety considerations

We are concerned that the inclusion of an unlicensed medicine, as opposed to a medicine prescribed outside of its marketing authorisation, as a comparator in a NICE appraisal may compromise patient safety.

The Committee is aware of the retrospective data drawn from 136,008 treated patients, which suggests emerging safety signals for bevacizumab.[40-42] At the Committee meeting, the Committee heard the clinical and patient experts concerns that bevacizumab's "*safety in the eye is not assured*" and that there should not be widespread use of a product unlicensed for use in the eye where a licensed alternative exists. It is therefore extremely disappointing that the Committee concluded that ranibizumab and bevacizumab "*could be similar in terms of safety*" and has seemingly disregarded the views of its stakeholders that uncertain safety of an unlicensed product is not satisfactory basis on which to conclude equivalent safety.

Similarly, it is concerning that the ERG considered that the absence of any evidence – in its view - to suggest a difference in the safety profile of the two products was an appropriate basis to conclude equivalent safety (discussed further in section f below). We emphasise that, in the absence of regulatory review or adequate trials to fully assess safety, it is inappropriate to draw conclusions about safety based on a lack of data. This suggests that the ERG and the Committee have a working assumption that the two products have an equivalent safety profile, when there is no evidence base to support such an important assumption.

Thus, we would highlight to the Committee that there are emerging safety signals for the use of unlicensed intravitreal bevacizumab. It is inappropriate to try to establish cost effectiveness prior to a full safety assessment by the regulatory authorities. In the NICE report on the feasibility of an appraisal of bevacizumab in wet AMD and other eye conditions, it was stated that, "*there are concerns that recommendations on the clinical and cost effectiveness of intravitreal bevacizumab may be interpreted as a guarantee of safety, and without a specific regulatory review of quality and safety of the product this may be misleading*." [43]

We note that the Committee has interpreted statements from the clinical specialists that '*because a license has not been sought for the use of bevacizumab in the eye, its safety is not assured*'. We are concerned that this interpretation in the ACD suggests that the Committee considers, should an application be made, then a license for bevacizumab use in the eye would be granted. Given that the currently available data for efficacy, safety and quality of the use of bevacizumab in RVO (the focus of this appraisal) is limited to one published study with treatment of bevacizumab in 15 eyes, there is no basis for the Committee to accept such an assumption. This assumption also undermines the role of the regulatory authority in making its own assessment.

Regulators in the UK and elsewhere have expressed significant concerns over the use of unlicensed bevacizumab for eye conditions. The MHRA issued a Drug Safety Alert making specific reference to concerns over such use, stating:

> "Off-label intravitreal use of bevacizumab (Avastin, licensed for treatment of various solid cancers) has been associated with reports of severe eye inflammation and sterile endophthalmitis. The production methods, formulation, and doses for bevacizumab were developed for use in oncology. Its use in the ophthalmology setting has not been authorised." [44]

The FDA in the US has recently published a warning for doctors on intravitreal use of bevacizumab:

> "The U.S. Food and Drug Administration (FDA) is alerting health care professionals that repackaged intravitreal injections of Avastin (bevacizumab) have caused a cluster of serious eye infections in the Miami, Florida area."
>
> "Health care professionals should be aware that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections. Health care professionals should ensure that drug products are obtained from appropriate, reliable sources and properly administered."[45]

Health Canada raised the safety issues of using bevacizumab for intraocular use back in 2008,[46] and have recently published another warning for physicians:[47]

> "Three clusters of serious ocular complications, including acute ocular inflammation, endophthalmitis, and infectious endophthalmitis resulting in blindness, have been recently reported in Florida, Tennessee, and California, all associated with intravitreal injection of AVASTIN. Although these clusters continue to be investigated, it is possible that the events of blindness from streptococcal endophthalmitis in Florida were due to repackaging of AVASTIN without proper aseptic technique." [47]
> "The production methods, formulation and dosages for AVASTIN were specifically developed for intravenous use in the oncology setting. Use of AVASTIN in the ophthalmology setting is not authorized in Canada." [47]

The Australian label for the use of bevacizumab states the following warning on the intraocular use of this medication:

> **"**Severe Eye Infections Following Compounding for Unapproved Intravitreal Use
> Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of AVASTIN compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness"[48]

It is also important to highlight that the presence of marketing approval in itself does not guarantee safety. Despite intensive testing, there are examples of serious safety implications of products only identified through post-marketing surveillance, particularly for rare events. A well-known example is Vioxx, where an increased risk of serious thrombotic events, including stroke and myocardial infarction, was identified through post-marketing surveillance. A more recent example is that of bevacizumab in its licensed use oncology. Bevacizumab was approved for the treatment of metastatic breast cancer in the USA and Canada in 2008. However, this license has recently been revoked (November 2011) as it was decided by the FDA and Health Canada that the risk of potentially life-threatening adverse events with bevacizumab was not outweighed in this indication by the clinical benefit.[49, 50] The adverse events were *'severe high blood pressure; bleeding and hemorrhaging; heart attack or heart failure; and the development of perforations in different parts of the body such as the nose, stomach, and intestines*.' [49]

Therefore, in the absence of a sponsor for unlicensed bevacizumab and no formal post-marketing surveillance, no pharmacovigilance programme and probable under-reporting of adverse events, the emerging safety signals suggested through retrospective studies are of greater significance.

The absence of a full pharmacovigilance programme, instigated post-license at the requirement of the regulator and funded by the drug sponsor, means that the NHS would be obliged to deliver such a programme. The need for '*adequate ongoing safety surveillance*' should bevacizumab be recommended for use in the eye was highlighted by NICE in July 2010. Moreover, the ACD states that Committee '*noted that it would be desirable to collect data relating to the safety of bevacizumab for the treatment of macular oedema secondary to RVO*' (paragraph 4.25). The cost of a safety surveillance programme would be a significant burden to the NHS. [redacted]

[redacted]

These costs should be incorporated into any comparison of ranibizumab and bevacizumab, as well as the uncertain costs arising from the treatment of adverse events associated with the use of bevacizumab in the eye (section f). Their absence from the ERG's exploratory analysis and the Committee's discussion is of concern.

f) Rationale for a cost-minimisation analysis

The ERG's use of a cost-minimisation analysis is fundamentally flawed when the efficacy and safety of bevacizumab and ranibizumab in RVO has not been established as equivalent.[52, 53] It is well accepted that cost-minimisation analysis can only be employed when there is reliable evidence of equivalence (see Figure 4) from an equivalence trial.[53] Furthermore, it is important to have equivalence established for the entire treatment duration. There is no such evidence for the comparison of bevacizumab and ranibizumab for the treatment of visual impairment due to MO secondary to RVO. A reliable indirect comparison of these therapies is prevented by the poor quality trial evidence for bevacizumab and the approach taken (see Section 7).

Furthermore, equivalence should take into account all meaningful benefits to patients and thus should include safety differences. The safety differences between bevacizumab and ranibizumab are discussed above (Section 8).

In light of this, it is not appropriate to assume equivalent safety and efficacy of ranibizumab and bevacizumab in the treatment of visual impairment caused by macular oedema secondary to RVO. In the absence of established equivalence, it has previously been concluded that "*it would be potentially misleading to use such flawed analyses [cost-minimisation analysis] as the basis for healthcare decision-making*."[52]

Furthermore, several important costs have been omitted from the analysis of costs performed by the ERG:

- Despite the Committee's acknowledgement that the safety of unlicensed bevacizumab use should be monitored by the NHS in the absence of a sponsor, this cost was not factored in to the ERG's analysis. Although it is unclear how to accurately capture the cost of this programme to the NHS,[43] it should not be ignored.
- The cost and disutility of arterial thromboembolic events (ATEs) and other AEs experienced by patients treated with unlicensed bevacizumab would significantly impact the overall cost, even if included based only on 1 year of bevacizumab treatment. The longer term effects of repeated bevacizumab use are even more uncertain.
- The additional cost of ensuring patients are fully informed and consented prior to treatment with an unlicensed product, given a licensed alternative exists, has not been included.

- The recently issued NICE Business Planning tool assumes a 25:75 split of outpatient to day case visits to administer intravitreal bevacizumab. This has not been accounted for in the ERG's exploratory analysis.
- Given that the large scale provision of split vials of bevacizumab by manufacturers under a 'Specials' license is not legal, the local cost of aliquoting should be included. Vials must be split locally to ensure adherence to MHRA requirements to deliver unlicensed medication only in response to a clear clinical need for an individual patient.
- Alternative scenarios have not been considered where the per vial cost of bevacizumab (£246.66) is used per injection, in centres where local compounding is not feasible or where the practice of vial-sharing is prohibited (which has become policy in some countries,[54] and so should be considered as a scenario).
- The additional costs associated with liability for prescribing unlicensed medication when a licensed alternative exists were not considered.

9. Definitions of ischaemia

It is not accurate to state that all patients with ischaemia were excluded from BRAVO and CRUISE. Relative Afferent Pupillary Defect (RAPD) is the severe end of the ischaemic spectrum and therefore the sentence in the ACD should refer to 'clinical signs of severe irreversible ischaemic visual loss' rather than 'ischaemic'. This more severe population is already excluded from the label describing ranibizumab. Patients with milder ischemia were therefore included in both BRAVO and CRUISE.

B. Summary of cost-effectiveness of ranibizumab under alternative scenarios

This section presents new cost-effectiveness analyses based on the comments provided in section A.

A revised base-case includes the following changes to reflect the Committee's concerns:

- Modelling of treatment of the WSE in 90% of the population
- Brazier utilities fitted to 10 letter change in BCVA
- Utility difference between best and worst BCVA health states in WSE utility of 0.3
- Unpooled transition probabilities for 7-24 months for BRVO: 0.5 mg arm data only for ranibizumab arm, with the standard of care arm set equal to that of the ranibizumab arm
- WSE mortality due to visual impairment (as implemented by the ERG)

Revised base case ICERs, and additional scenario analyses, are presented in Table 14 to Table 18. The inputs to the revised model are summarised in appendix 5.

Table 16: Scenario analysis for ranibizumab vs. dexamethasone implant in BRVO (each variable added incrementally to give cumulative ICERs)[with PAS ICERs]

Scenario	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Modelling of WSE: ERG scenario L (reduced Brazier utilities and 0.1 overall utility benefit of treating WSE)	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	34,598
Brazier utilities fitted to model	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	27,199
0.2 overall utility benefit of treating WSE	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	19,563
0.3 overall utility benefit of treating WSE	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	15,039
WSE VI mortality	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	14,967
0.5 mg ranibizumab (unpooled) transition probabilities applied to months 7-24 in treatment and comparator arms	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	14,922
Adverse events in year 2	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	13,300
Dexamethasone injection frequency, based on TA229	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	8,014
Lifetime time horizon	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	6,600
Proposed revised WSE base case	**Dexamethasone**	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	**6,600**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	4,818
HORIZON data for year 2 TPMs and updated model structure	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	**2,942**

Table 17: Scenario analysis for ranibizumab vs. best supportive care (BSC) in CRVO (each variable added incrementally to give cumulative ICERs)[with PAS ICERs]

Scenario	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Modelling of WSE: ERG scenario L (reduced Brazier utilities and 0.1 overall utility benefit of treating WSE)	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	49,323
Brazier utilities fitted to model	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	42,167
0.2 overall utility benefit of treating WSE	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	29,174
0.3 overall utility benefit of treating WSE	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	21,933
WSE VI mortality	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	21,776
Adverse events in year 2	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	22,269
Lifetime time horizon	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	22,105
Proposed revised WSE base case	**BSC**	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	**18,817**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	17,732
HORIZON data for year 2 TPMs and updated model structure	BSC	[redacted]	[redacted]			
	Ranibizumab			[redacted]	[redacted]	**13,364**

Table 18: Scenario analysis for ranibizumab vs. dexamethasone in CRVO (each variable added incrementally to give cumulative ICERs)[with PAS ICERs]

Scenario	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Modelling of WSE: ERG scenario L (reduced Brazier utilities and 0.1 overall utility benefit of treating WSE)	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	42, 147
Brazier utilities fitted to model	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	34,984
0.2 overall utility benefit of treating WSE	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	24,899
0.3 overall utility benefit of treating WSE	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	19,023
WSE VI mortality	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	18,900
Adverse events in year 2	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	17,503
Dexamethasone injection frequency, based on TA229	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	13,521
Lifetime time horizon	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	11,656
Proposed revised WSE base case	**Dexamethasone**	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	**11,656**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	9,860
HORIZON data for year 2 TPMs and updated model structure	Dexamethasone	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	**5,762**

C. Inaccuracies in the ACD and evaluation report

1. Inaccuracies in the ACD

Paragraph 3.1: In this paragraph and throughout the ACD refers to the manufacturer's submitted evidence as relating to the target population of people with macular oedema secondary to retinal vein occlusion. This may be more accurately described, at least in the first instance as, people with visual impairment due to macular oedema secondary to retinal vein occlusion. This is the licensed indication and the population defined in the STA Scope.

Paragraph 3.1: the ACD states that no formal indirect comparisons were undertaken because there was no direct evidence for ranibizumab versus comparators in the Scope. This is not correct. The reasons for not presenting indirect comparisons are described in our submission in section 5.7. The suggestion that we considered an indirect comparison was not possible is repeated at paragraphs 3.20 and 4.6.

Paragraphs 3.2 and 4.5: It may be helpful to clarify that in the BRAVO study, patients meeting the criteria for rescue laser treatment were able to receive *one* laser administration at month 3, 4 or 5 and *one* laser at month 9, 10 or 11.

Paragraph 3.8: We would like to inform the Appraisal Committee that the intraocular pressure safety data for BRAVO and CRUISE are no longer academic in confidence and they are now available online for the 0.5 mg ranibizumab and sham groups.

i. The BRAVO safety data are available here: http://www.lucentis.com/hcp/rvo/bravo-safety-rvo.html
ii. The CRUISE safety data available here: http://www.lucentis.com/hcp/rvo/cruise-safety-rvo.html

Paragraph 3.9: The ACD notes only some of the reasons proposed in our original submission why the published data for bevacizumab was inadequate to conduct a reliable indirect comparison. This paragraph of the ACD currently reads that the reasons listed were the only reasons presented, which is not accurate. Also in this paragraph, the ACD suggests that our conclusion was that indirect comparisons could not be undertaken, when in fact we concluded that they *should not* undertaken and could not be undertaken *without bias*.

Paragraph 3.14: misspelling of intravitreal

Paragraphs 3.17 and 4.5: It is incorrect to state that all patients with ischaemia were excluded from BRAVO and CRUISE. RAPD is the severe end of the ischaemic spectrum and therefore the sentence in the ACD should state 'clinical signs of severe irreversible ischaemic visual loss' rather than 'ischaemic'. This more severe population is already excluded from the label.

Paragraph 3.18: We request that the sentence on the long term effect of laser is removed as there is a lack of data to support this assertion. In fact there is evidence from the SCORE study that the effects of laser peak at 12 months and then start to decline.[33]

Paragraph 3.26: The end of this paragraph is misleading in that it suggests a mortality risk associated for visual impairment was not applied to the cost effectiveness analysis at all. Rather, the ERG concluded that an additional mortality risk for VI in the WSE should be applied to the WSE analysis.

Paragraph 3.31: the first sentence of this paragraph states 'dexamethasone intravitreal implant', but we believe this should read 'bevacizumab'.

Paragraph 4.5: The following sentence is incorrect: 'It was also noted that ranibizumab provided sustained gains in BCVA at 12 months in both BRAVO and CRUISE, but that these were not statistically significant'. The p values were not available at the time of submission; they have now been published and demonstrate that the differences in both BRAVO and CRUISE between the 0.5 mg ranibizumab randomised group and the sham/0.5 mg ranibizumab were statistically significant ($p<0.01$).[29, 31]

Paragraph 4.9: The first sentence is missing the term BRVO, to acknowledge the ERG's view that an indirect comparison could have been performed for BRVO only.

Paragraph 4.9: This paragraph refers to section 3.22 for the ERG's view of its exploratory comparison of ranibizumab and bevacizumab. There is no statement at paragraph 3.22 that their estimates are considered optimistic with respect to ranibizumab efficacy, and no explanation for this statement in the ACD.

2. Inaccuracies in the Premeeting Briefing

Section 3.11 (page 28): the briefing incorrectly states that the transition probabilities for dexamethasone implant are assumed not to vary from laser or BSC after month 1 in the exploratory cost effectiveness analysis. This is incorrect. In months 6 to 24, the transition probabilities are assumed not to vary for ranibizumab.

Section 3.2 (page 41): the inaccuracy above is repeated where the ERG's critique of the ranibizumab and dexamethasone comparison are noted to be 'strongly biased towards ranibizumab' because no additional benefit for dexamethasone was assumed beyond month 1. In fact, the benefit of ranibizumab and dexamethasone were assumed to be equivalent from months 7-12, and all the observed benefit of dexamethasone from months 1-6 is applied to month 1 in the modelled comparison. Based on the ERG's indirect comparisons demonstrating better efficacy for ranibizumab vs dexamethasone up to month 3/6 may be considered biased *against* ranibizumab.

Section 3.2 (page 39/40): the document suggests that Novartis could not provide the primary endpoint data for the BRAVO and CRUISE trials on request from the ERG. It would be more accurately recorded that we could not provide a new model using transition

probabilities based on 15 letter changes in BCVA within the 10 day deadline for response to the ERG's request. Preparation of such a model would take significantly longer to prepare.

3. The ERG's report

The Committee has concluded that ranibizumab was an extremely well-tolerated therapy in clinical trials. However, Novartis would like to clarify a point in response to a statement made by the ERG in its report.

The ERG stated (Section 5.4.4, paragraph 12):

> "The ERG is concerned that the manufacturer did not use safety data from the HORIZON extension study in the model, citing low incidence of events. HORIZON reports a slightly higher incidence of AEs than BRAVO and CRUISE, particularly transient ischaemic attack and myocardial infarction, suggesting that RVO patients may indeed be at a higher risk of cardiovascular death than the general population."

Novartis is unsure about what data this statement is based on. The safety data presented in the manufacturer's submission does not indicate an increase in adverse events in HORIZON compared to BRAVO and CRUISE and we can confirm that this is not the case when looking at the overall rates of ocular and non-ocular adverse events (see Table 19, confidential data not originally reported in Manufacturer's Submission). We have provided an analysis incorporating the safety data from HORIZON in Section B.

Table 19: Overall adverse events in BRAVO compared with HORIZON for patients with BRVO

	Frequency of adverse events at 12 months, n (%)		
	Sham/0.5mg	**0.3mg ranibizumab**	**0.5mg ranibizumab**
[redacted]			
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Overall adverse events in CRUISE compared with HORIZON for patients with CRVO

	Frequency of adverse events at 12 months, n (%)		
	Sham/0.5mg (n=93)	**0.3mg ranibizumab (n=103)**	**0.5mg ranibizumab (n=104)**
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

The rate of occurrence of transient ischaemic attacks and myocardial infarctions was reported in the Manufacturer's Submission and is presented again in Table 21 and Table 22. The following can be concluded:

- There is no evidence for an increased rate of myocardial infarction in HORIZON for either BRVO or CRVO patients (Table 21 and Table 22).
- For transient ischaemic attack, there were no instances in 12 months of BRAVO, but 3 in the BRAVO patients treated with 0.3 mg ranibizumab originally who entered HORIZON (Table 21). The small number of cases makes it hard to draw any conclusions.
- There is no evidence that the rate of transient ischaemic attack increased in CRVO patients from CRUISE to HORIZON (Table 22).

Table 21: Cardiovascular adverse events in BRAVO compared with HORIZON for patients with BRVO

	Frequency of adverse events at 12 months, n (%)		
	Sham/0.5mg (n=93)	**0.3mg ranibizumab (n=103)**	**0.5mg ranibizumab (n=104)**
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HORIZON – Patients from BRAVO[28]			
Transient ischaemic attack	0	3 (2.9%)	0
Acute myocardial infarction	0	0	0
Myocardial infarction	0	1 (1.0%)	1 (1.0%)

Table 22: Cardiovascular adverse events in CRUISE compared with HORIZON for patients with CRVO

	Frequency of adverse events at 12 months, n (%)		
	Sham/0.5mg (n=93)	**0.3mg ranibizumab (n=103)**	**0.5mg ranibizumab (n=104)**
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HORIZON – Patients from CRUISE[28]			
Transient ischaemic attack	0	1 (0.9%)	0
Acute myocardial infarction	0	1 (0.9%)	0
Myocardial infarction	0	0	0

The ERG's conclusions were drawn from very small N numbers in clinical trials. The larger observational studies of ranibizumab used in clinical practice in wet-AMD show a low rate of cardiovascular adverse events that does not increase over time.[40-42]

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E. Appendix

1. Calculation for conversion of Brazier utilities to appropriate health states

Bivariate equation (R^2=0.172)
U=(-0.368)(logMAR)+(- 0.001)(age)+0.860

Inputs that informs the utility table below

Input no 1 from the regression equation	-0.368
Input no 2 from the regression equation	-0.001
Input no 3 from the regression equation	0.86
Age*	65
Input utility when the equation gives a utility value that is >1	1

Health states in the model using the bivariate equation (assuming duration of visual loss is 1 year for the patient group)

EDTRS (SNELLEN)	SNELLEN lower end (e.g. =20/16)	logMAR equiv lower	SNELLEN higher end (e.g. =20/10)	logMAR equiv higher	Utilities lower VA level (Univariate)	Utilities higher VA level (Univariate)	Mean utility
86-100 (20/16-20/10)	1.25	-0.1	2	-0.3	0.8318	0.905	**0.869**
76-85 (20/32-20/20)	0.625	0.2	1	0	0.7214	0.795	**0.758**
66-75 (20/64-20/40)	0.3125	0.5	0.5	0.3	0.611	0.6846	**0.648**
56-65 (20/80-20/50)	0.25	0.6	0.4	0.4	0.5742	0.6478	**0.611**
46-55 (20/125-20/80)	0.16	0.8	0.25	0.6	0.5006	0.5742	**0.537**
36-45 (20/200-20/125)	0.1	1	0.16	0.8	0.427	0.5006	**0.464**
26-35 (20/320-20/200)	0.0625	1.2	0.1	1	0.3534	0.427	**0.390**
<25 (<20/320)	0.0625	1.2			0.3534		**0.353**

Please note that for BRAVO trial "Subjects were screened at the time of diagnosis of BRVO but no longer than 12 months after diagnosis." Approximately 10%−16% of subjects had a Snellen equivalent of 20/200 or worse at baseline, and the mean time since diagnosis was 3.3−3.7 months across the three treatment groups.

2. Correction of ERG's comparison of their RRs to the Manufacturer's RRs for the comparison of ranibizumab to dexamethasone implant.

The ERG claimed that the manufacturer's RRs applied for dexamethasone for BRVO of 0.55 and for CRVO of 0.30 should actually have been 0.79 and 0.40, respectively. Novartis pointed out that the MS RRs were for an improvement of 4 lines, whereas the figures of 0.79 and 0.40 were for an improvement of 2 lines. Therefore the equivalent RRs used in the MS were 0.70 and 0.51, respectively.

Table 23: Corrected version of Table 63 from ERG report, Relative risk (RR) of ranibizumab compared with dexamethasone intravitreal implant in patients (RR <1 favours ranibizumab, RR >1 favours dexamethasone intravitreal implant)

		Probability of gaining 10 letters (2 lines) or more		RR
		Ranibizumab	Dexamethasone	
BRVO	Manufacturer's model	0.731	0.512	0.70
	ERG indirect comparison	–	–	0.79
CRVO	Manufacturer's model	0.6848	0.3535	0.52
	ERG indirect comparison	–	–	0.40
Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ERG, evidence review group; RR, relative risk.				

3. Details of the changes to and the validation of the model with regards to entering year 2 data from HORIZON

As discussed in Section A6, new, longer-term data have become available from the HORIZON study since the original Novartis RVO model was developed. These data have now been analysed and entered into the model in order to ensure that the model represents the true treatment response as closely as possible.

The three-monthly follow up in HORIZON meant that it was impossible to generate monthly transition probabilities for the model. In order to allow the inclusion of these data in the model, the model structure was adjusted to allow each of the cycles in year 2 to be three months in duration. This ensured that the data inputs matched the structure of the model.

In order to validate the model, a simple comparison was undertaken, comparing the *modelled* average VA scores over time against the *actual* average VA scores from the trial.

The average *observed* VA scores over time, as observed in BRAVO and CRUISE are shown below, in Figure 5 and Figure 6, respectively. It should be noted that patients in the control group switched to active therapy after six months and, as such, the average VA scores for the control group should not be interpreted as reflecting the actual impact of placebo throughout the entire period. Further, the data after 24 months was based on only a small number of observations and should not be regarded as robust.

Figure 5: Average VA over time (BRAVO)

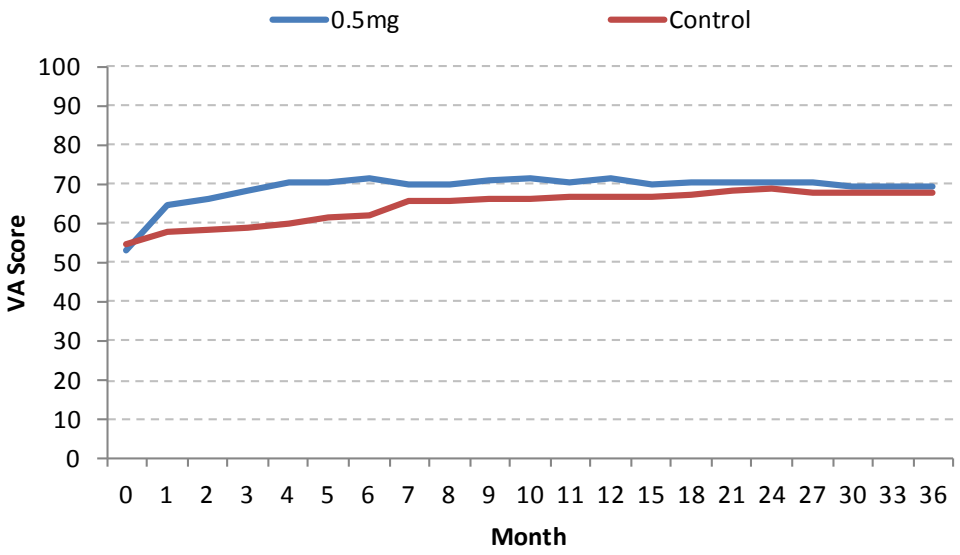


Figure 6: Average VA over time (CRUISE)

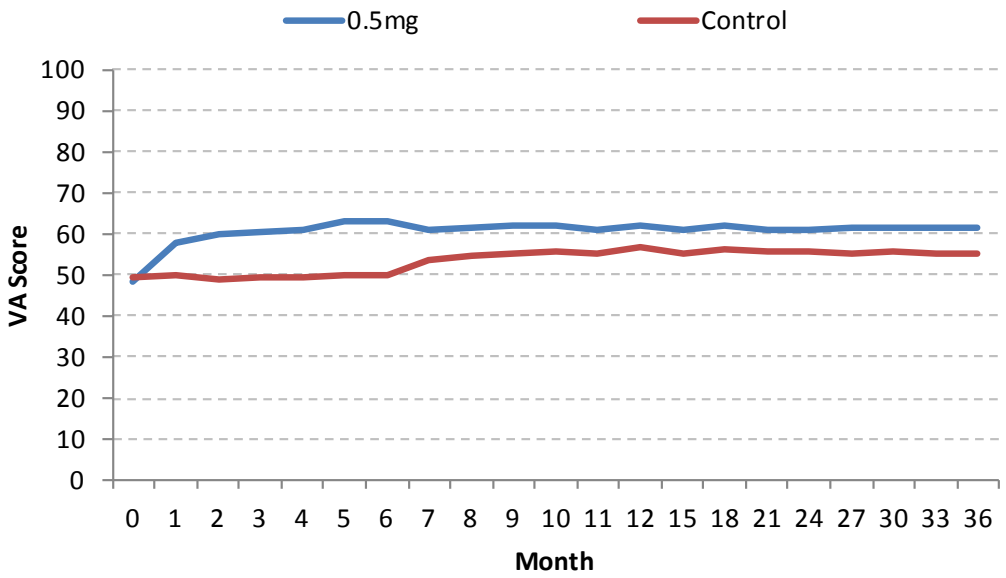


Figure 7 and Figure 8, below, show the modelled VA score (dashed lines), along with the observed data (solid lines).

Figure 7: Observed vs modelled average VA over time (BRVO)

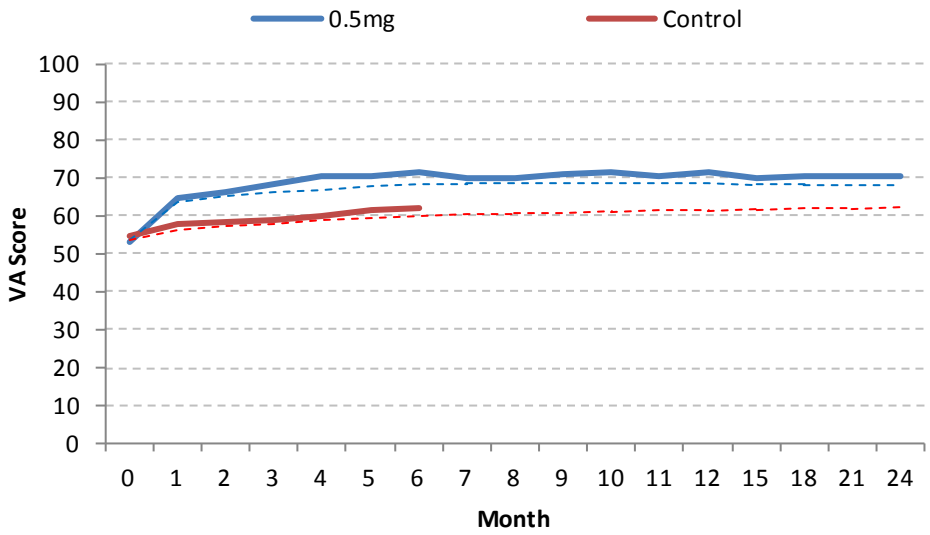
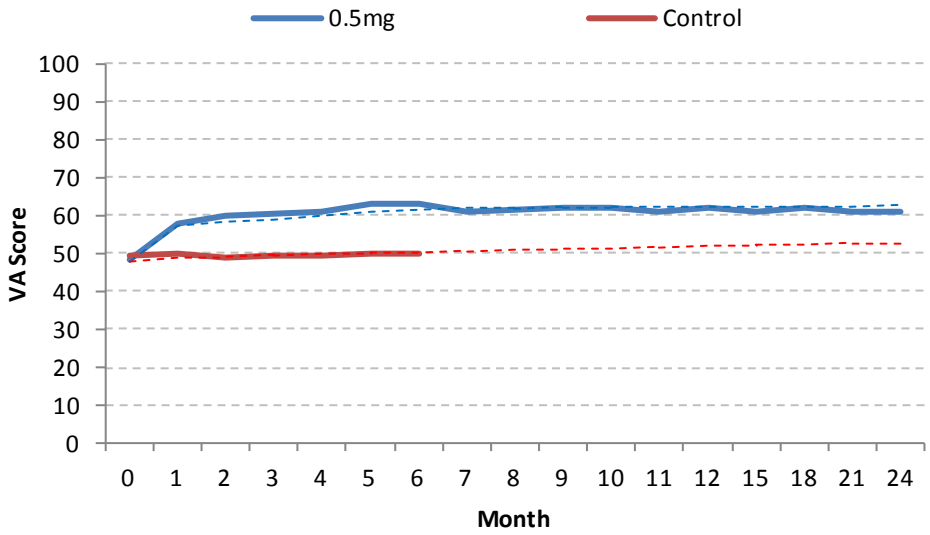


Figure 8: Observed vs modelled average VA over time (CRVO)



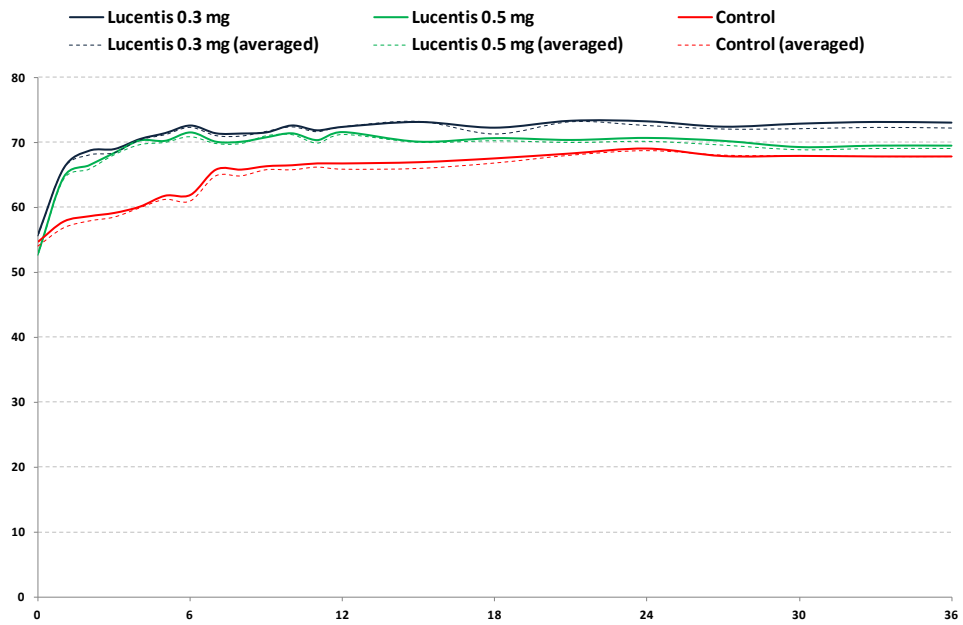
It might be noted that, particularly for BRVO, the modelled VA score is shown to be slightly lower than that of the observed BA score. This is also apparent in the CRVO data, though to a lesser extent.

It was suspected that the differences in modelled and observed VA could be down to one or more of the following effects:

1. The model uses VA *bands* rather than individual VA scores. Therefore, average VA in the model is calculated by taking the mid-point of each VA band. It might be, if more patients in each band in the trial were higher or lower than the mid-point, the modelled VA might not reflect the true value.
2. The model is experiencing a 'ceiling' effect. If all patients in the model (regardless of their current VA status) face a consistent probability of gaining and/or losing lines, then patients in the highest VA group would be 'unable' to improve, even though the data suggest that a given % will improve. Since those patients (in the model) *cannot* improve, some patients will fail to experience in improvement in VA and, as such, the 'ceiling effect' will mean that the average VA score over time will gradually fall below the observed value.

In order to test each of the above explanations, two tests were carried out. The first assessed the actual trial data, and compared the *exact* average VA score against the *implied* average VA score, if patients were grouped into bands and a midpoint was applied to each band. The impact of this test (for BRAVO patients) is shown below in Figure 9.

Figure 9: Actual average VA score versus implied VA score by group midpoints



As can be seen, the differences between the two approaches are minimal, and do not explain the differences seen between the observed and modelled outputs. This potential problem can, therefore, be eliminated.

In order to remove a potential ceiling effect, alternative transition probabilities were used in the model. These used different transition probabilities for patients in the following VA states:

- Patients with VA score >85;
- Patients with VA score between 76 and 85;
- All other patients.

This approach was taken since it is the top two VA groups that may be affected by the ceiling effect. The impact of this analysis was that the top groups had zero probability of 'gaining' lines that were not possible (i.e. the top group could not gain any lines, whilst the second-top group could not improve by two groups), but the probability of gaining for the 'other' patients was increased (the same number of patients in the trial improved, but this was as a greater proportion of those patients who had capacity for improvement).

The results of this analysis are shown in Figure 10 and Figure 11, below.

Figure 10: Observed vs modelled average VA over time (without ceiling effect) (BRVO)

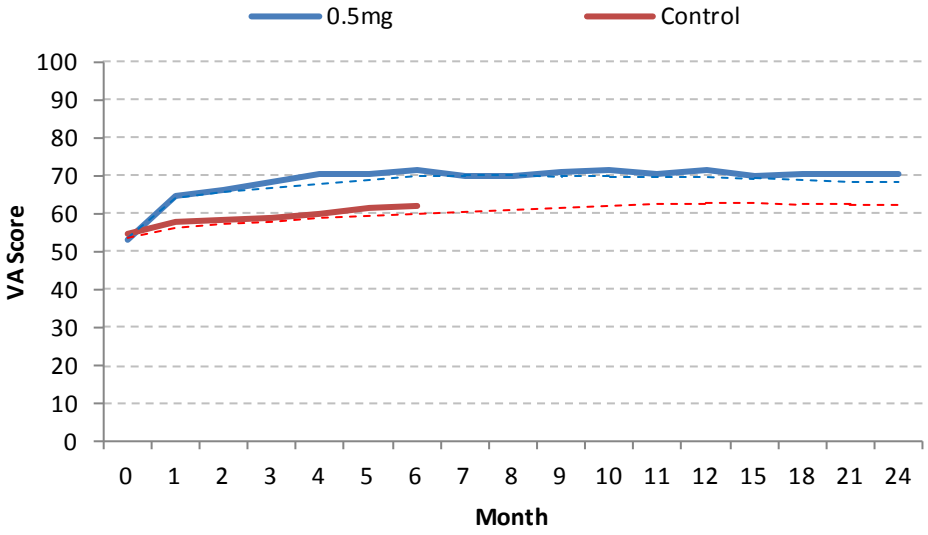
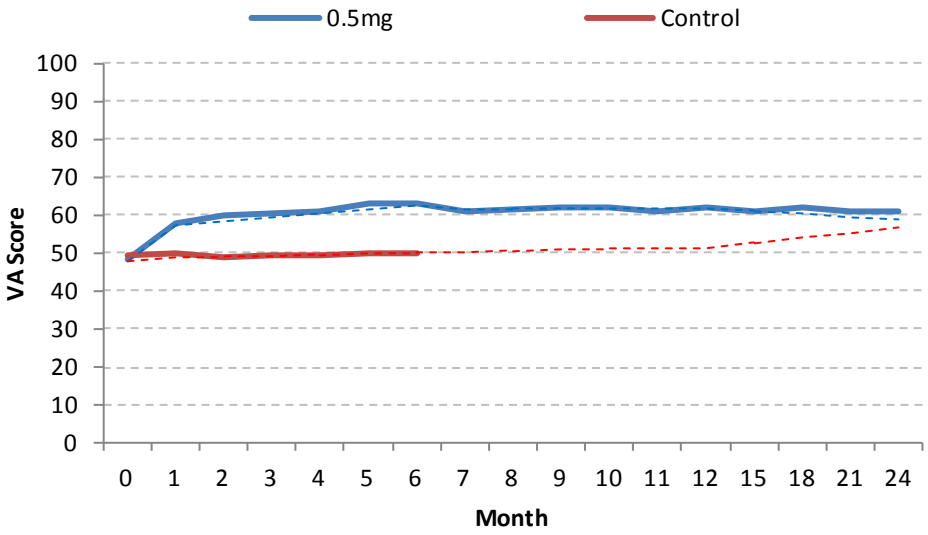


Figure 11: Observed vs modelled average VA over time (without ceiling effect) (CRVO)



These analyses demonstrate that the steps taken to avoid the ceiling effect have been successful. The modelled VA scores closely match the observed VA scores from the trial.

One significant note of caution should be taken, however. In order to calculate the transition probabilities for year 2 in the control group, data from the observed control arm's first six months were used. Specifically, the model uses the change between month 3 and month 6 (recall that the model cycles for year two are three months in duration). However, when probabilities were calculated for the three separate VA groups (see above), some of those groups had very few patients and, as such, the transition probabilities were based on very few observations. This was particularly true in the CRVO cohort, whose average VA score tended to be lower, leaving fewer patients in the top two groups. Therefore, the modelled probabilities for year two in the control group of the CRVO cohort are to be interpreted cautiously.

4. Scenario analyses for ranibizumab vs. laser in BRVO (each variable added incrementally)[with PAS ICERs]

Scenario	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Modelling of WSE: ERG scenario L (reduced Brazier utilities and 0.1 overall utility benefit of treating WSE)	Laser	**Not presented by the ERG**				
	Ranibizumab					
Brazier utilities fitted to model	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	68,319
0.2 overall utility benefit of treating WSE	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	46,831
0.3 overall utility benefit of treating WSE	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	35,027
WSE VI mortality	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	34,795
0.5 mg ranibizumab (unpooled) transition probabilities applied to months 7-24 in treatment and comparator arms	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	34,863
Adverse events in year 2	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	36, 138
Lifetime time horizon	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	30,918
Proposed revised WSE base case	**Laser**	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	**30,918**
Ranibizumab treatment frequency in year 2, adjusted for discontinuations	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	29,410
Proportion of patients receiving laser, based on SCORE study	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	28,922
HORIZON data for year 2 TPMs and updated model structure	Laser	[redacted]	[redacted]			
	Ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	**18,461**