SECTION A – Clarifications of the clinical data:

A1. The submission lists two exploratory outcomes that are not listed in the Clinical Study Reports for BRAVO and CRUISE: (i) the proportion of patients who gained ≥ 10 letters at 6 months; and (ii) the proportion of patients who lost ≥ 10 letters at 6 months. Please confirm that these are post-hoc analyses?

That is correct. The outcome 'proportion of patients with 10 letter changes' was not predefined in the study protocols. These were included to support the economic model, which is built on health states representing 10-letters levels.

A2. The pre-specified primary outcome listed in BRAVO and CRUISE is mean change from baseline BCVA at month 6, with percentage of patients who gained 15 or more letters at month 6 listed as a secondary outcome. Please comment on why "the proportion of patients with an improvement in best corrected visual acuity, as measured by an improvement from baseline to six months of 10 or more letters read on an Early Treatment Diabetic Retinopathy Study Chart at four metres, equivalent to 0.2 logMAR" (page 48) has been chosen as the primary outcome for the systematic review of the literature.

A loss of 15 letters is the gold standard for a clinically significant loss of vision in the clinical trial setting. This is a standard trial endpoint, particularly in the US - where the pivotal ranibizumab RVO studies were developed - in order to meet the requirements of the US Food and Drug Administration. However, a loss of 10 letters can be associated with a substantial decline in health related quality of life – for example, inability to drive, increased dependency, role limitations and impaired mental health. A change in 10 letters on the ETDRS scale is generally accepted by UK clinicians to be clinically meaningful. Therefore, a 10 letter improvement was chosen as the primary outcome of the systematic review. 10 letter changes were also selected as the basis of the health states in the cost effectiveness model, for the same reason. The mean change in BCVA from baseline was also a primary outcome for the review, although this statement was omitted from the submission in error.

A3. For the BRAVO RCT, how many people in the sham group had oedema that spontaneously resolved at 3 months (based on a visual acuity of ≥20/40 and OCT <250 microns)?

Spontaneous resolution was not defined in the ranibizumab trials, and there is no widely accepted definition in clinical practice. The visual acuity and CFT criteria noted above indicate partial improvement in oedema, rather than resolution, and there could be further improvements possible (Note: OCT is the instrument used to measure central foveal thickness (CFT)). These values were used as laser treatment and ranibizumab retreatment criteria in BRAVO, after the treatment phase of monthly injections, but may not allow for optimal treatment. Rather, the ranibizumab SmPC advises rather to continue monthly injections until stable maximal visual acuity is attained (which may be greater than 20/40).

However, as requested, the number of patients in the sham group meeting a criteria of visual acuity ≥20/40 and CFT <250 microns at month 3 is provided [redacted]

A4. For the BRAVO RCT, please populate the grid below to indicate the mean change in best-corrected visual acuity (BCVA) in the sham group at the time points listed and the number of people who achieved the specified levels of improvement in visual acuity.

Table 1: Visual acuity outcomes in the sham group up to 3 months.

BRAVO	*Month 1*	*Month 2*	*Month 3*
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

A5. For the BRAVO RCT, please populate the grid below to indicate the mean change in BCVA at the time points listed and the number of people in the ranibizumab 0.5 mg group who achieved specified levels of improvement in visual acuity (percentages are given in the manufacturer's submission).

Table 2: Patient visual acuity outcomes for the ranibizumab 0.5 mg group up to 3 months.

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

A6. For all those patients in BRAVO who received laser treatment within the 6 month treatment period, please populate the table below.

In BRAVO, patients could receive laser at month 3, 4 or 5 during the treatment period if laser treatment criteria were met (please refer to original submission for full definition). Thus, the time of the last observation prior to laser treatment differs depending on when laser was applied (Table 3, Table 4 and Table 5). Outcomes at month 6 and 12 are also presented for all patients who received laser at by month 6 (Table 6).

Analysis of the proportion of patients receiving laser by month 6 and gaining at least 10 and at least 15 letters is underway, and will be available in July.

It is important to highlight the small sample size in each subgroup, as well as the imbalance in patient numbers between treatment and control arms. Furthermore, there is a significant selection bias in this analysis because patients were not randomised to laser. It is therefore recommended that these data are interpreted with caution.

Table 3: Patient visual acuity outcomes for patients who received laser treatment at month 3

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

Table 4: Patient visual acuity outcomes for patients who received laser treatment at month 4

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

Table 5: Patient visual acuity outcomes for patients who received laser treatment at month 5

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

Table 6: Patient visual acuity outcomes for patients who received laser treatment by month 6

[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]	[redacted]
[redacted]		
[redacted]		

A7. In accordance with the NICE final scope and the NICE Methods Guide, using available data and providing an account of any potential bias, please provide comparisons between:

i. ranibizumab versus dexamethasone for BRVO and CRVO;
ii. ranibizumab versus bevacizumab in BRVO and CRVO;
iii. ranibizumab versus grid pattern photocoagulation in BRVO (as opposed to sham followed by rescue laser).

As described in section 5.7 of the submission, a systematic review of the RCT evidence for bevacizumab, dexamethasone and laser photocoagulation was conducted. As further described in this section of the submission, the data identified was in adequate and/or insufficiently homogeneous to permit a valid indirect comparison to the ranibizumab RCT data.

A8. The exclusion criteria for BRAVO and CRUISE indicate that people with prior episodes of RVO were excluded from the trials, yet tables B7 and B8 indicate that [redacted] people in BRAVO and CRUISE, respectively, had prior therapy for RVO in the study eye. Please comment on the cause of this apparent discrepancy.

*These patients had received prior treatment for the **current** RVO, in accordance with the inclusion/exclusion criteria of the protocols and any subsequent amendments.*

A9. Please supply full details for the search terms and search strategies, and the databases and resources searched to identify non-RCT data for bevacizumab (discussed in Appendix 20 [page 380]).

A range of databases indexing published research were searched for non-randomised studies of bevacizumab macular oedema caused by RVO. The searches were limited to human studies in the large bibliographic databases (such as MEDLINE), and to the English language. No date limits were applied. The databases and resources searched are shown in Table 7. The search strategies are presented in Figure 1 and Figure 2 *and Figure 3.*

Table 7: Databases and resources searched

Resource	***Interface/URL***
MEDLINE and MEDLINE In-Process	*OvidSP*
EMBASE	*OvidSP*
Cochrane Database of Systematic Reviews (CDSR)	*Cochrane Library/Wiley Interscience*
Cochrane Central Register of Controlled Trials (CENTRAL)	*Cochrane Library/Wiley Interscience*
DARE Database of Abstracts of Reviews of Effects (DARE)	*Cochrane Library/Wiley Interscience*
Health Technology Assessment Database (HTA)	*Cochrane Library/Wiley Interscience*
NHS Economic Evaluation Database (NHS EED)	*Cochrane Library/Wiley Interscience*
Science Citation Index (SCI)	*Web of Science*

Figure 1: Search strategy used in MEDLINE and MEDLINE in-Process (OvidSP) [redacted]

[redacted]

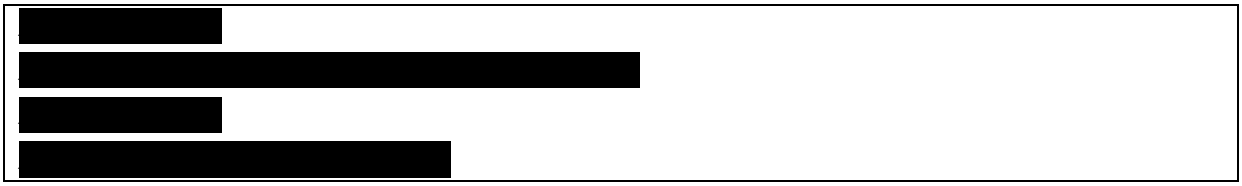


Figure 2*: Search strategy used in EMBASE (OvidSP)*

Figure 3: Search strategy used in CDSR, CENTRAL, DARE, HTA and NHS EED (Wiley interscience)

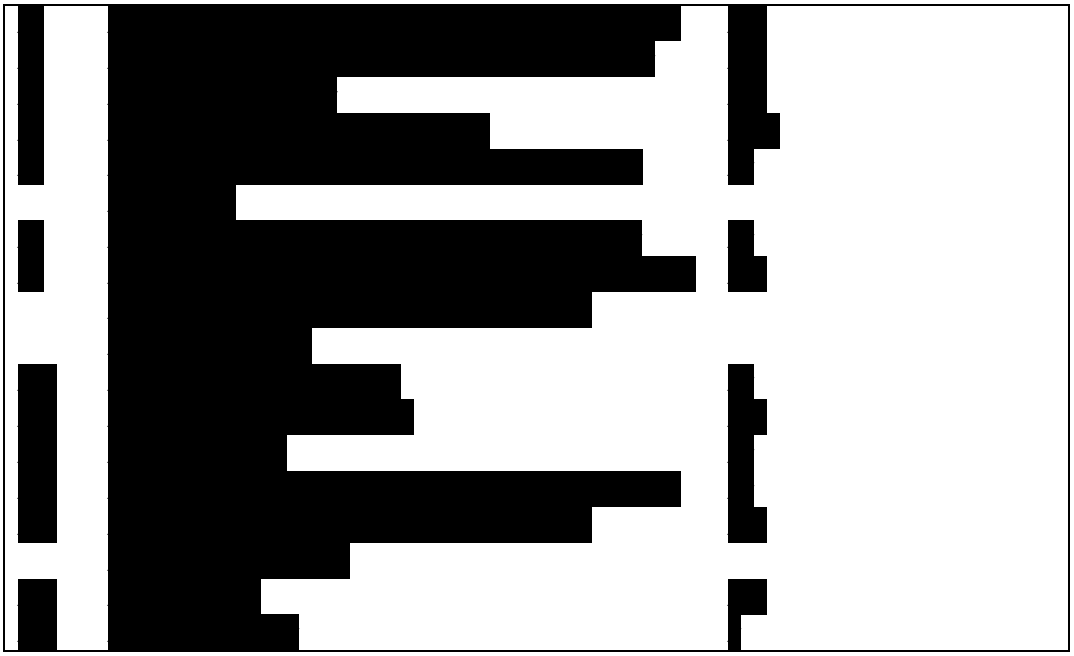
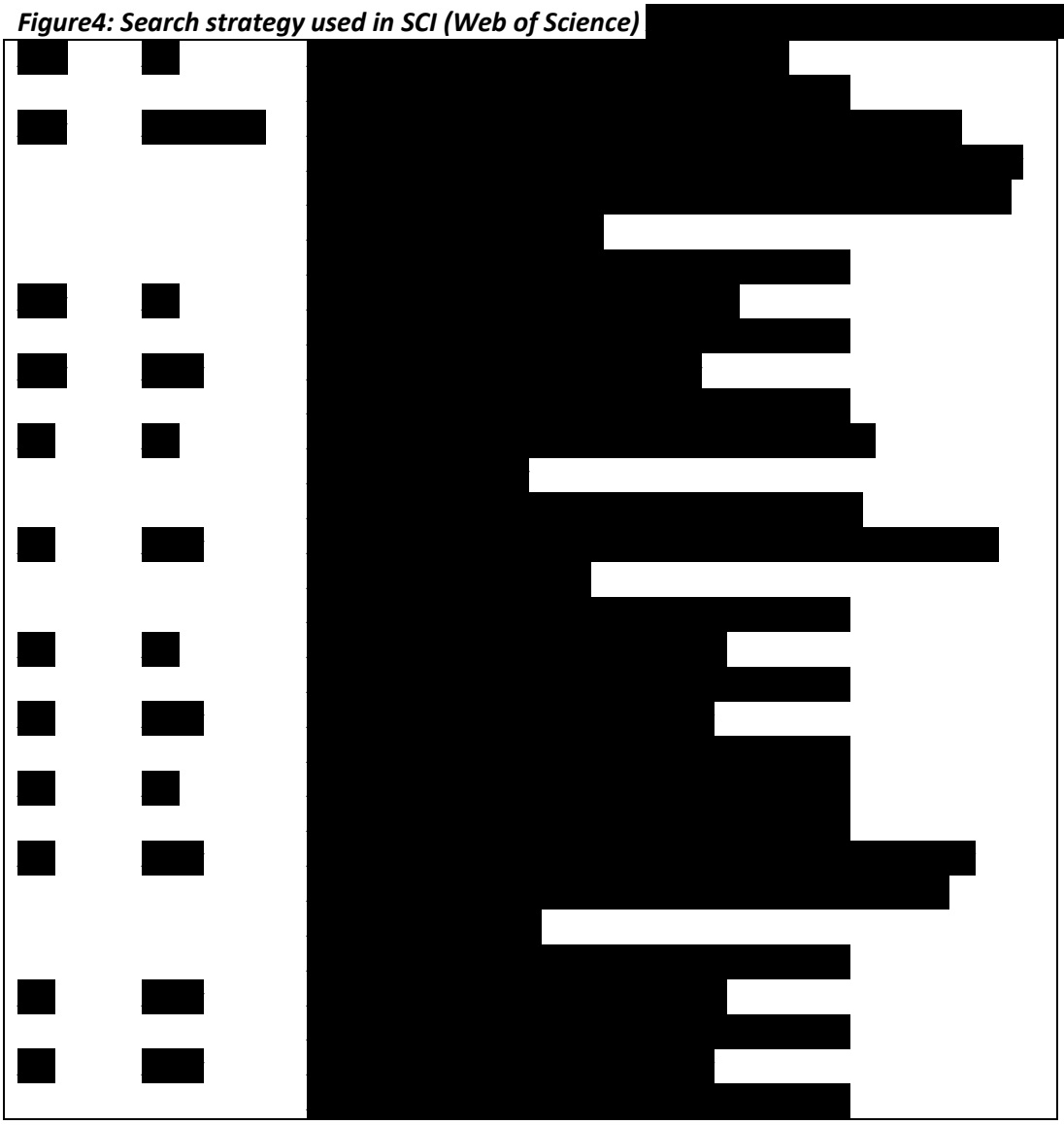


Figure4: Search strategy used in SCI (Web of Science)



[redacted]

A10. Please clarify whether the criteria applied for treatment for those continuing from BRAVO into HORIZON (given in table B5, page 64) were also applied to those enrolling in HORIZON from the CRUISE RCT (not listed in table B5, page 64).

Yes, the criteria applied for treatment for those continuing from BRAVO into HORIZON were also applied to those enrolling in HORIZON from the CRUISE RCT.

A11. Please clarify whether presence of macular ischaemia was assessed in people entering BRAVO and CRUISE?

Yes, the presence of macular ischaemia was assessed at screening and at baseline. Patients with a brisk afferent pupillary defect – a well recognised clinical sign of significant retinal ischaemia were excluded from the studies (Table B6 of the submission: Eligibility criteria in the RCTs). Percentage of greater than 10 disc area (DA) of capillary non-perfusion was assessed at baseline (Tables B7 and B8: Baseline characteristic of participants). This represents a common definition of ischaemia.

SECTION B – Clarifications of the economic data

B1 Priority question. Please provide individual patient level data so that the ERG can validate the transition probabilities presented in the model.

The patient level data is provided in confidence, under separate cover.

B2 Priority question. Within the model on the sheet entitled "Nice Outputs", there is a table (D188:O222) describing the data availability of each subgroup per treatment. This table states that data are available for Bevacizumab in all BRVO patients. The ERG group requests details of these data and the results of any analyses performed on these data.

The RCTs and non-RCTs identified for bevacizumab are described in the submission at sections 5.7 and appendix 10.8. Further detail is available in the report of the non-RCT systematic review which is provided with this response (academic in confidence).

Given that bevacizumab is not considered an appropriate comparator in this appraisal, for the reasons described in the submission, no cost effectiveness analysis of ranibizumab vs bevacizumab is provided.

It may be helpful to explain that the model structure was developed before a complete exploration of the evidence through the systematic reviews described in the submission. Thus, the development of the model did not presuppose the outcome of the review of evidence for the clinical effectiveness or the potential to conduct indirect comparison of bevacizumab and ranibizumab. Nor did the model development presuppose the conclusion of Novartis that the use of bevacizumab in the NHS was not routine or best practice.

B3 Priority question. Please provide a scenario analysis in which the model uses the pre-specified trial outcome of a gain/loss of ≥ 15 letters rather than the analysis of 10 or more letters.

It has not been possible to provide such a scenario analysis in the time requested, as this would require extensive reanalysis of the patient level data and reconfiguration of the model structure.

B4. Please provide the unpooled 7 to 12 month transition probability matrices of the ranibizumab and sham arms in BRAVO.

The non-pooled transition probabilities for months 7 to 12 are shown in Table 8. However, it should be noted that patients in the standard care (laser) arm received ranibizumab during this period. Since they had experienced less effectiveness during the first six months, it may be argued that they had a greater capacity to benefit from ranibizumab during this time.

Table 8*: Non-pooled collapsed transition probabilities for BRVO for months 7-12*

	Ranibizumab	***Standard care (laser)***
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%*

B5. Please provide full calculation details of the incorporation of dexamethasone into the model, indicating which values were taken from the Haller 2010 paper, how they were manipulated and applied to the model.

The GENEVA clinical studies (Haller J.A., et al. Ophthalmology. 2010; 117:1134-46) provided evidence of the benefits of a dexamethasone IVT implant over sham in treating macular oedema due to RVO. The publications on the GENEVA studies as well as the manufacturer's submission to NICE for dexamethasone (Allergan 2010) provided evidence on the risk ratios of experiencing a gain of 15 and 10 letters, but no evidence was available to build full transition probability matrices representing the outcomes required for the model at each timepoint:

- *gain ≥20 letters*
- *gain ≥10 and <20 letters*
- *lose <10 and gain <10 letters*
- *lose ≥10 and < 20 letters*
- *lose ≥ 20 lines.*

Additionally, the available risk ratios were for specific study time points only and for the change from baseline rather than for that specific period (i.e. between 2 and 6 months). No transition probability details were available from the Ozurdex model.

Table 9, based on the data from manufacturer submission (manufacturer submission table 31 [BRVO] and 32 [CRVO], page 63), provides the relative risks that can be calculated for dexamethasone over sham injections for the % of patients experiencing a gain of ≥10 letters over different periods of time. It can be seen that the relative risk of achieving an outcome reduces over time, although it is always greater than 1 suggesting a benefit of dexamethasone over sham.

Table 9: Patients with an improvements in BCVA of ≥10 letters (pooled GENEVA studies)

	Dexamethasone	*Sham*	*Relative risk*
BRVO			
Month 1	*42.6*	*20.1*	*2.119*
Month 2	*51.9*	*29.4*	*1.765*
Month 3	*47.1*	*31.2*	*1.510*
Month 6	*41.2*	*33.0*	*1.248*
CRVO			
Month 1	*45.6*	*12.2*	*3.738*
Month 2	*49.3*	*19.7*	*2.503*
Month 3	*36.0*	*23.1*	*1.558*
Month 6	*26.5*	*23.8*	*1.113*

Since no similar data was available for the categories of BCVA loss and improvement considered in the economic model, a simple assumption was to assume the same relative risk at Month 1 and invert it to represent the relative risk of losing 10 letters (for example, 1/2.119 = 0.47). However this is likely to underestimate the benefits of dexamethasone. To avoid such a simplifying assumption, we assumed that the mean change from baseline at Month 1 for both dexamethasone and sham follow a normal distribution in GENEVA study in order to be able to compare the sham results from GENEVA and the control results from BRAVO & CRUISE at Month 1 and to develop a transition probability matrix that could be used in the economic model as a crude indirect comparison. This approximation is described below.

Additionally, it is not appropriate to assign two risk ratios to different model periods (for instance, if a treatment's risk ratio for improvement of 2 lines was 2.0 at one month, and 2.0 at six months, this would imply that all of the 'benefit' was observed in the first month, and the benefit had simply been retained for the remainder). Applying the ratio of 2.0 to subsequent months in the model would lead to double-counting of those benefits. Therefore, a single assignment of a risk ratio at Month 1 was considered to be sufficient to represent indirectly the benefits of dexamethasone versus ranibizumab. Beyond Month 1, the same transition probabilities of ranibizumab were assumed for dexamethasone, which given the dexamethasone results presented in Haller paper provides a conservative assumption for comparison.

Data identified from published sources:

- *Haller et al. 2010 reported the probability of (gain ≥3 lines [15 letters]) at Day 30 (publication Figure 7) for both dexamethasone IVT implant and sham.*
- *The manufacturer submission to NICE reported probabilities of categorical changes from baseline BCVA (≥ 15 letters improvement, ≥ 15 letters worsening) for dexamethasone and sham at Day 30 (manufacturer submission, Table 28 page 61 [BRVO] and Table 29 page 62 [CRVO]).*
- *The manufacturer submission also presented the probability of (gain ≥2 lines (10 letters) at Day 30 (manufacturer submission, Table 31 [BRVO] and Table 32 [CRVO], page 63).*

None of these data had the desired form and could not be used directly as inputs to the model (as noted previously).

Thus, the following method was used to estimate relative risks for dexamethasone IVT implant that could be used in the economic model. This methodology was used separately for BRVO and CRVO.

The manufacturer submission to NICE reported the mean change from baseline for both dexamethasone (x1) and sham (x2) as well as the lower (ll) and upper (ul) limit of the 95% normal approximation confidence interval for the difference between mean changes from baseline of dexamethasone versus sham (x1-x2) at Day 30 (page 59 Table 25 [BRVO] and Table 26 [CRVO]). Assuming that the standard deviation for dexamethasone is equal to standard deviation for sham (s1=s2=s), the common standard deviation s can be derived as

$$s=(ul-x1+x2)/1.96*sqrt(1/n1+1/n2)$$

where n1 and n2 are number of patients in the dexamethasone and sham groups, respectively. If it is assumed that the change from baseline X1 (X2) comes from the normal distribution model with mean = x1 (x2) and standard deviation s for dexamethasone (sham): X1 (X2) ∼N(x1(x2), s), probabilities to

gain ≥4 lines (gain ≥20 letters)
gain ≥2 and <4 lines (gain ≥10 and <20 letters)
no change (lose <2 and gain <2 lines) (lose <10 and gain <10 letters)
lose ≥2 lines and < 4 (lose ≥10 and < 20 letters)
lose ≥4 lines (lose ≥ 20 lines)

can be estimated for dexamethasone as the following areas under curve

Prob (X1 (X2) ≥20)		*p11*
Prob (10 ≥X1 (X2) <20)		*p12*
1-sum of other probabilities in the vector	=	*100-p11-p12-p13-p14*
Prob (-20 <X1 (X2) ≤-10)		*p13*
Prob (X1(X2) ≤-20)		*p14*

and foror sham as the following areas under curve

Prob (X1 (X2) ≥ 20)		*p21*
Prob (10 ≥ X1 (X2) <20)		*p22*
1-sum of other probabilities in the vector	=	*100-p21-p22-p23-p24*
Prob (-20 <X1 (X2) ≤-10)		*p23*
Prob (X1(X2) ≤-20)		*p24*

Risk ratios r1=p11/p21, ... up to, r4=p14/p24 can then be calculated and multiplied by p1l, ... p4l, where

p1l is the probability of (gain ≥4 lines [20 letters]) for control group)

...

p4l is the probability of (lose ≥4 lines (20 letters) for control group)

in order to obtain an 'indirect estimate' of dexamethasone IVT implant effect over the control group from BRAVO or CRUISE.

The dexamethasone 'indirect' estimates imputed into the model are then:

	BRVO	*CRVO*
*r1*p1l*	*1.49*	*1.52*
*r2*p2l*	*1.19*	*1.27*
*100- r1*p1l- r2*p2l- r3*p3l- r4*p4l*	*0.91*	*1.01*
*r3*p3l*	*0.67*	*0.81*
*r4*p4l*	*0.5*	*0.67*

These relative risks are applied to the month 1 progression rates of the standard care (control) arm in the model, to estimate crude progression rates for dexamethasone compared to ranibizumab.

In month 2, a relative risk of 1 was applied to derive dexamethasone progression rates to avoid double counting as described previously.

As no published data for dexamethasone was identified for months 7 or beyond, the 7-12 month data for ranibizumab was applied to approximate dexamethasone progression. Thus, the model assumes identical effectiveness for ranibizumab and dexamethasone from month 7.

In order to validate the proposed models N(X1, s), N(X2,s) for dexamethasone IVT implant and sham, different probabilities reported by Haller et al 2010 and the manufacturer submission for dexamethasone can be estimated from the model described above and compared (table 10). Results of that comparison suggest that the model proposed is appropriate.

The above calculations demonstrate the uncertainty surrounding any comparisons between ranibizumab and dexamethasone IVT implant. The populations in BRAVO, CRUISE and GENEVA were very different (Lowenstein A., et al. 2nd World Congress on Controversies in Ophthalmology 2011). Furthermore, the definition of the control groups was different. These issues violate the similarity assumption which is a prerequisite for a valid indirect comparison. Thus, any comparisons between ranibizumab and dexamethasone IVT implant should be considered as exploratory and interpreted with caution.

Table 10: Calculated and observed probabilities of improvement and worsening of BCVA in month 1

	Dexamethasone (pooled GENEVA)		*Sham (pooled GENEVA)*	
	Calculated	*Manufacturer submission*[1]	*Calculated*	*Manufacturer submission*[1]
BRAVO, Month 1				
gain ≥15 letters (gain ≥3 lines)	*20.6%*	*21.3%*	*7.9%*	*7.9%*
gain >5 and <15 letters (gain >1 and <3 lines)	*46.5%*	*47.7%*	*36.1%*	*36.9%*
lose <5 and gain ≤5 letters (lose <1 and gain ≤1 line)	*28.5%*	*25.8%*	*42.7%*	*44.1%*
lose ≥5 and <15 letters (lose ≥1 and <3 lines)	*4.3%*	*5.5%*	*12.4%*	*9.7%*
lose ≥15 letters (lose ≥3 lines)	*0.1%*	*0%*	*0.9%*	*1.4%*
gain ≥10 letters (gain ≥2 lines)	*42.5%*	*42.6%*	*21.7%*	*20.1%*
CRUISE, Month 1				
gain ≥15 letters (gain ≥3 lines)	*23.3%*	*21.3%*	*8.7%*	*6.8%*
gain >5 and <15 letters (gain >1 and <3 lines)	*34.8%*	*41.2%*	*24.7%*	*24.5%*
lose <5 and gain ≤5 letters (lose <1 and gain ≤1 line)	*29.1%*	*30.1%*	*35.9%*	*48.3%*
lose ≥5 and <15 letters (lose ≥1 and <3 lines)	*10.8%*	*3.7%*	*23.2%*	*13.6%*
lose ≥15 letters (lose ≥3 lines)	*1.9%*	*3.7%*	*7.5%*	*6.8%*
gain ≥10 letters (gain ≥2 lines)	*39.7%*	*45.6%*	*18.5%*	*12.2%*
1. Pooled results from the GENEVA studies				

B6. Please provide the following summaries:

i. Tabular comparisons of the following trial results:

a. Proportion of patients gaining 15 letters

b. Proportion of patients losing 15 letters

c. Proportion of patients gaining 10 letters

d. Proportion of patients losing 10 letters

versus those obtained from the model for all BRVO and all CRVO patients at 3, 6 and 12 months

The model is based on a Markov approach. Whilst it records the number of patients in each state at any one time, it does not follow patients individually throughout the model, instead using a cohort approach to model the proportion of patients. It is not, therefore, possible to determine the proportion of patients who have gained or lost lines at different timepoints. The model will report how many patients move between each state in each cycle. However, it cannot record whether the same patients are moving during the next cycle, or whether those movements are by different patients. As such, Markov models are unable to generate the outputs that are being requested.

ii. Tornado plots of all deterministic sensitivity analysis;

The submission document contains detailed univariate sensitivity analyses over wide ranges for each parameter. This allows the user to assess various factors for each parameter:

- *How the ICER is affected by all plausible ranges for the parameter;*
- *How sensitivity the model is to that parameter (i.e. the slope of the curve);*
- *Threshold analysis (i.e. at what value does the ICER fall above/below a given value).*

Tornado plots, whilst providing a useful at-a-glance summary, do not fulfil all of the uses described above. As requested, tornado plots are presented below for the univariate sensitivity analyses, using the values presented in Table 11, Table 12, Table 13 and Table 14.

Table 11: Univariate sensitivity analysis for BRVO (ranibizumab versus grid laser)

Base case	***£24,610***	***Low Value***		***High Value***	
Parameter	***Basecase Value***	***Value***	***ICER***	***Value***	***ICER***
Cost of ranibizumab	*£742.17*	*£371.09*	*£10,889*	*£1,113*	*£38,332*
Duration of treatment	*2.00*	*1*	*£14,899*	*3*	*£32,135*
Frequency of treatment (year 1)	*8.00*	*4*	*£11,299*	*12*	*£37,922*
Frequency of treatment (year 2)	*2.5*	*0*	*£16,691*	*6*	*£35,698*
Frequency of treatment (year 3)	*0*	*n/a*	*n/a*	*1*	*£27,778*
Frequency of visits (year 2)	*6*	*4*	*£23,586*	*8*	*£25,634*
Frequency of visits (year 3+)	*2*	*0*	*£15,667*	*4*	*£33,553*
Time horizon	*15*	*2*	*£145,141*	*25*	*£17,978*
% BSE at 12 months	*100%*	*3.55%*	*£37,133*	*10.65%*	*£36,074*
Tx effectiveness probs - month 1	*1*	*0.75*	*£82,416*	*1.25*	*£14,428*
Tx effectiveness probs - month 2 to 6	*1*	*0.75*	*£82,416*	*1.25*	*£14,428*
Tx effectiveness probs - month 7 to 12	*1*	*0.75*	*£90,837*	*1.25*	*£14,028*
Comp effectiveness probs - month 1	*1*	*0.75*	*£18,054*	*1.25*	*£31,646*
Comp effectiveness probs - month 2 to 6	*1*	*0.75*	*£9,837*	*1.25*	*£62,339*
Comp effectiveness probs - month 7 to 12	*1*	*0.75*	*£9,819*	*1.25*	*£62,421*
Natural deterioration	*0.03%*	*0.00%*	*£23,695*	*0.40%*	*£42,261*
Mortality rates	*1*	*0.5*	*£23,370*	*2*	*£27,134*
Administration costs	*1*	*0.50*	*£21,543*	*1.50*	*£27,677*
Follow up cost multiplier	*1*	*0.50*	*£24,053*	*1.50*	*£25,167*
Cost of blindness	*£6,068*	*£3,034*	*£28,029*	*£9,102*	*£21,192*
% stopping after 3 months	*10.0%*	*3.0%*	*£23,948*	*9.0%*	*£22,625*
Discount rates	*3.5%*	*0.0%*	*£18,409*	*6.0%*	*£29,235*

Figure 4: Tornado diagram BRVO (ranibizumab versus grid laser)

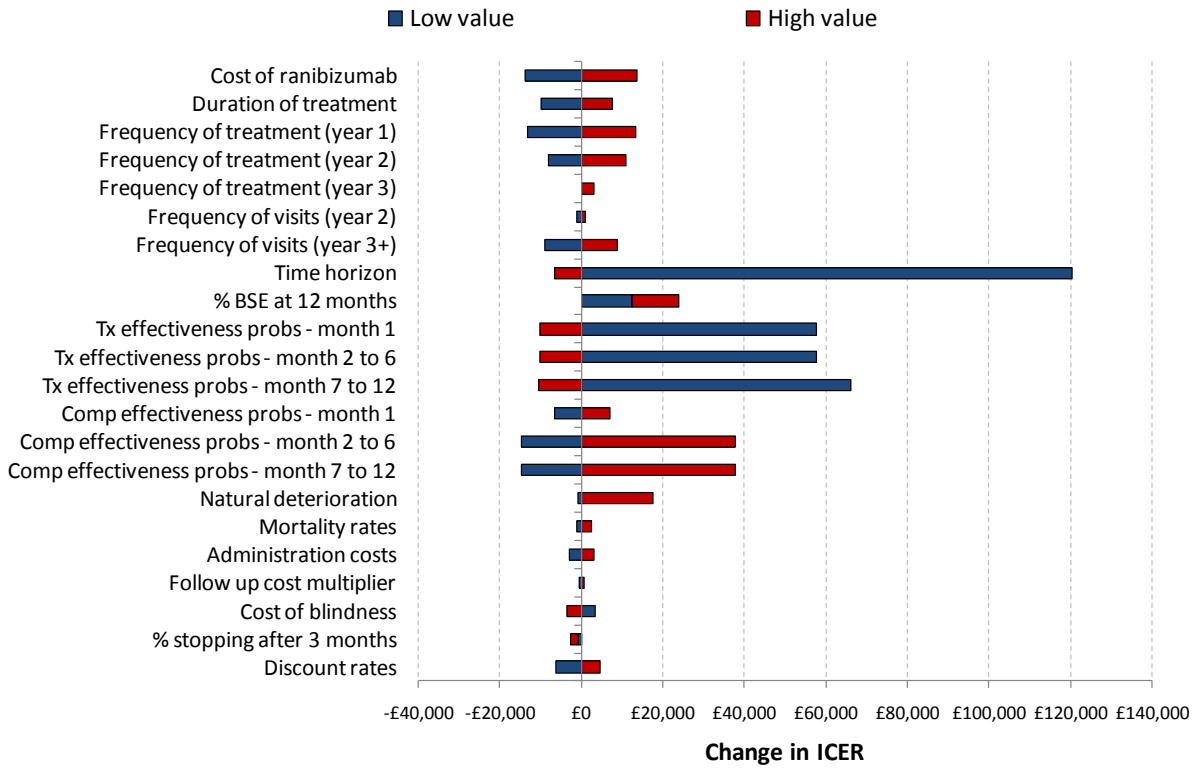


Table 12: Univariate sensitivity analysis for BRVO (ranibizumab versus dexamethasone)

Base case	***£10,883***	***Low Value***		***High Value***	
Parameter	***Basecase Value***	***Value***	***ICER***	***Value***	***ICER***
Cost of ranibizumab	*£742.17*	*£371.09*	*Dominant*	*£1,113*	*£28,873*
Duration of treatment	*2.00*	*1*	*Dominant*	*3*	*£20,749*
Frequency of treatment (year 1)	*8.00*	*4*	*Dominant*	*12*	*£28,336*
Frequency of treatment (year 2)	*2.5*	*0*	*£501*	*6*	*£25,419*
Frequency of visits (year 2)	*6*	*4*	*£9,541*	*8*	*£12,226*
Frequency of dexamethasone tx (year 1)	*2*	*1*	*£16,324*	*n/a*	*n/a*
Frequency of dexamethasone tx (year 2)	*2*	*0*	*£21,237*	*n/a*	*n/a*
Frequency of dexamethasone visits (year 2)	*8*	*4*	*£13,567*	*10*	*£9,542*
Time horizon	*15*	*2*	*£70,911*	*25*	*£7,451*
% BSE at 12 months	*100%*	*3.55%*	*£21,387*	*10.65%*	*£20,502*
Tx effectiveness probs - month 1	*1*	*0.75*	*£106,448*	*1.25*	*£3,669*
Tx effectiveness probs - month 2 to 6	*1*	*0.75*	*£106,448*	*1.25*	*£3,669*
Tx effectiveness probs - month 7 to 12	*1*	*0.75*	*£141,677*	*1.25*	*£3,440*
Comp effectiveness probs - month 1	*1*	*0.75*	*£6,237*	*1.25*	*£15,938*
Comp effectiveness probs - month 2 to 6	*1*	*0.75*	*£604*	*1.25*	*£51,185*
Comp effectiveness probs - month 7 to 12	*1*	*0.75*	*£560*	*1.25*	*£52,037*
Natural deterioration	*0.03%*	*0.00%*	*£10,205*	*0.40%*	*£26,920*
RR for dexamethasone	*1*	*0.75*	*£5,788*	*1.25*	*£19,408*
Mortality rates	*1*	*0.5*	*£9,792*	*2*	*£12,903*
Administration costs (all other treatments)	*1*	*0.50*	*£6,229*	*1.50*	*£15,537*
Administration costs (dexamethasone)	*1*	*0.5*	*£13,574*	*1.5*	*£8,193*
Follow up cost multiplier (all treatments)	*1.00*	*0.50*	*£12,403*	*1.50*	*£9,364*

Cost of blindness	*£6,068*	*£3,034*	*£14,124*	*£9,102*	*£7,643*
% stopping after 3 months	*0.1*	*0.03*	*£10,016*	*0.09*	*£8,281*

Figure 5: Tornado plot for BRVO (ranibizumab versus dexamethasone)

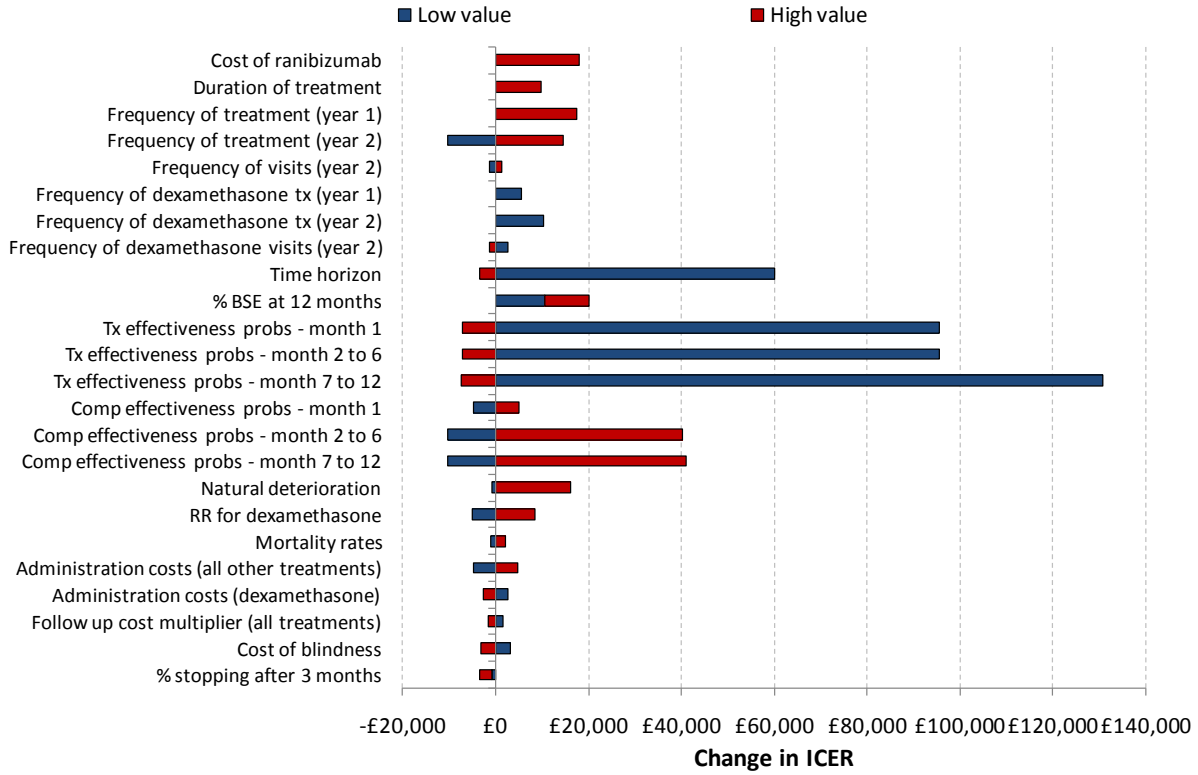


Table 13: Univariate sensitivity analysis for CRVO (ranibizumab versus grid laser)

Base case	***£11,428***	***Low Value***		***High Value***	
Parameter	***Basecase Value***	***Value***	***ICER***	***Value***	***ICER***
Cost of ranibizumab	*£742.17*	*£371.09*	*£2,145*	*£1,113*	*£20,712*
Duration of treatment	*2.00*	*1*	*£2,977*	*3*	*£17,766*
Frequency of treatment (year 1)	*9.00*	*4*	*£2,160*	*12*	*£16,990*
Frequency of treatment (year 2)	*3.8*	*0*	*£4,741*	*6*	*£15,300*
Frequency of treatment (year 3)	*0*	*n/a*	*n/a*	*1*	*£13,188*
Frequency of visits (year 2)	*9*	*6*	*£10,291*	*12*	*£11,997*
Frequency of visits (year 3+)	*4*	*2*	*£6,585*	*6*	*£16,272*
Time horizon	*15*	*2*	*£110,558*	*25*	*£7,764*
% BSE at 12 months	*100%*	*3.55%*	*£24,630*	*10.65%*	*£23,487*
Tx effectiveness probs - month 1	*1*	*0.75*	*£20,502*	*1.25*	*£7,590*
Tx effectiveness probs - month 2 to 6	*1*	*0.75*	*£20,502*	*1.25*	*£7,590*
Tx effectiveness probs - month 7 to 12	*1*	*0.75*	*£27,649*	*1.25*	*£6,335*
Comp effectiveness probs - month 1	*1*	*0.75*	*£9,384*	*1.25*	*£13,277*
Comp effectiveness probs - month 2 to 6	*1*	*0.75*	*£5,128*	*1.25*	*£20,298*
Comp effectiveness probs - month 7 to 12	*1*	*0.75*	*£3,939*	*1.25*	*£23,609*
Natural deterioration	*0.03%*	*0.00%*	*£11,110*	*0.40%*	*£16,211*
Mortality rates	*1*	*0.5*	*£9,959*	*2*	*£14,105*
Administration costs (all other treatments)	*1*	*0.50*	*£9,027*	*1.50*	*£13,830*

Follow up cost multiplier (all treatments)	*1*	*0.50*	*£11,506*	*1.50*	*£11,351*
Cost of blindness	*£6,068*	*£3,034*	*£16,018*	*£9,102*	*£6,839*
% stopping after 3 months	*6.0%*	*3.0%*	*£10,973*	*9.0%*	*£10,061*
Discount rates	*3.5%*	*0.0%*	*£7,393*	*6.0%*	*£14,484*

Figure 6: Tornado plot for CRVO (ranibizumab versus grid laser)

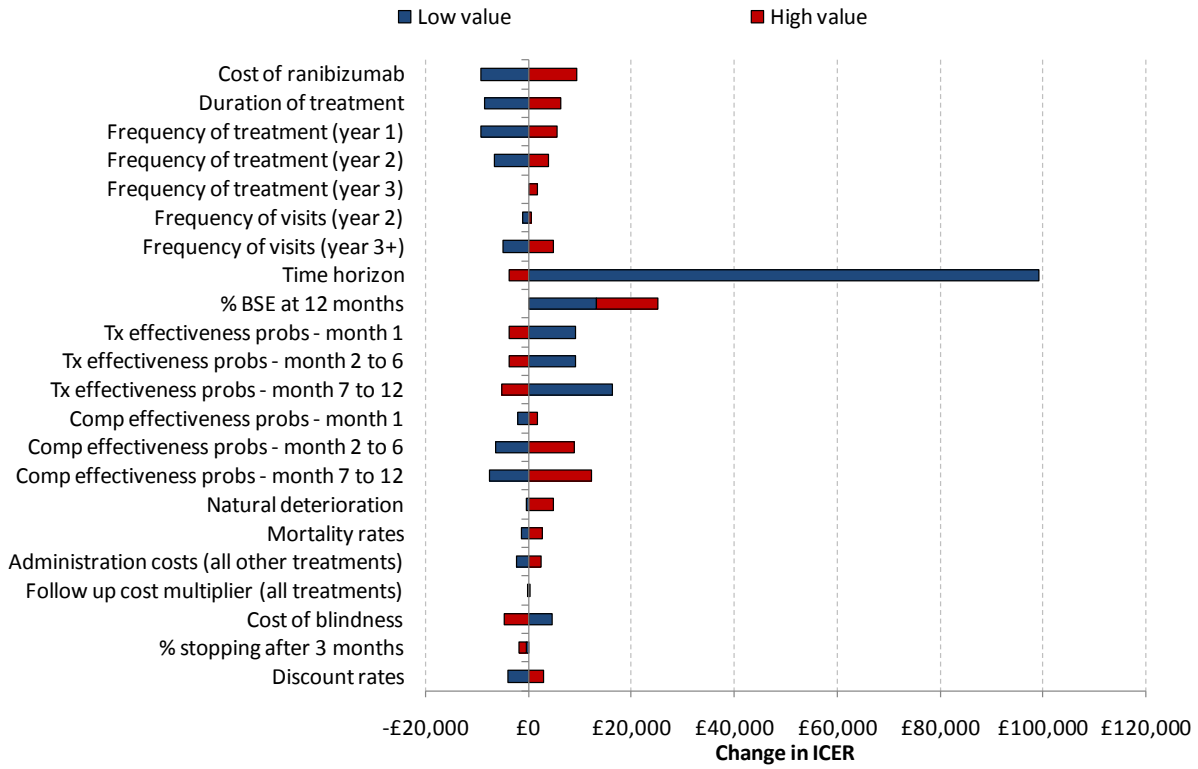
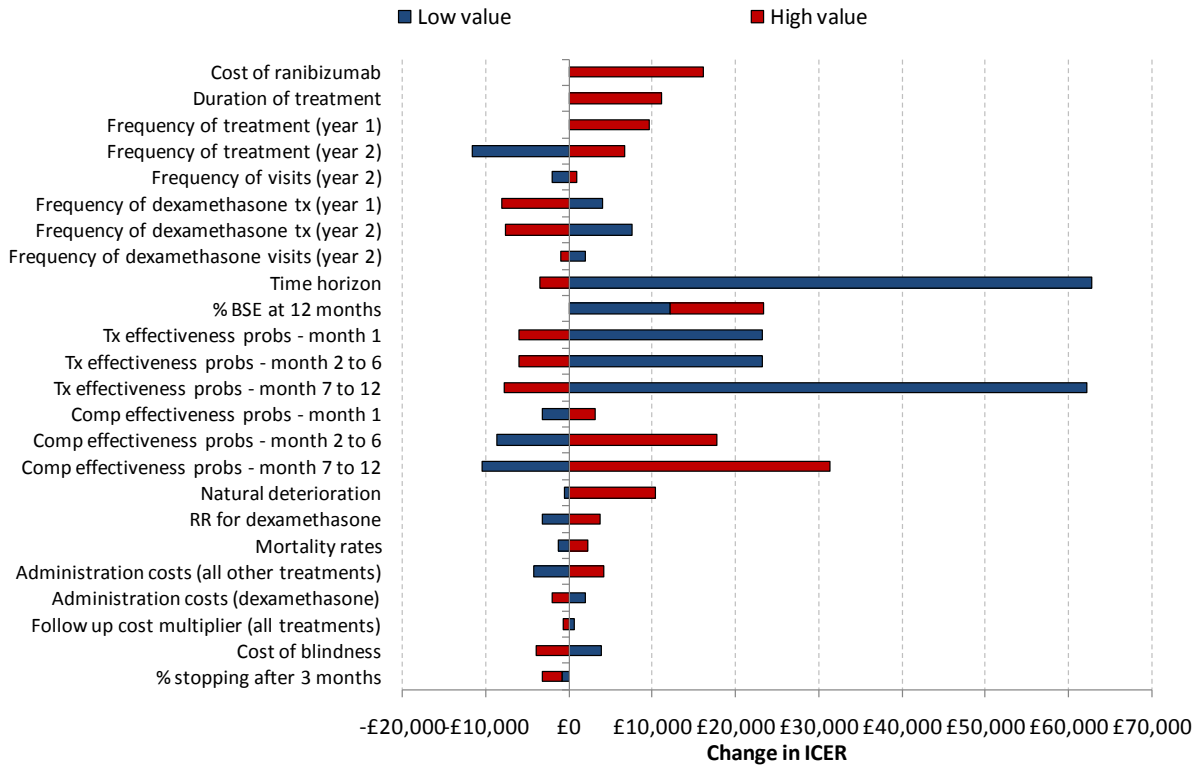


Table 14: Univariate sensitivity analysis for CRVO (ranibizumab versus dexamethasone)

Base case	***£12,027***	***Low Value***		***High Value***	
Parameter	***Basecase Value***	***Value***	***ICER***	***Value***	***ICER***
Cost of ranibizumab	*£742.17*	*£371.09*	*Dominant*	*£1,113*	*£28,203*
Duration of treatment	*2.00*	*1*	*Dominant*	*3*	*£23,070*
Frequency of treatment (year 1)	*9.00*	*4*	*Dominant*	*12*	*£21,716*
Frequency of treatment (year 2)	*3.8*	*0*	*£375*	*6*	*£18,773*
Frequency of visits (year 2)	*9*	*6*	*£10,044*	*12*	*£13,018*
Frequency of dexamethasone tx (year 1)	*2*	*1*	*£16,054*	*4*	*£3,973*
Frequency of dexamethasone tx (year 2)	*2*	*0*	*£19,666*	*4*	*£4,388*
Frequency of dexamethasone visits (year 2)	*8*	*4*	*£14,007*	*10*	*£11,037*
Time horizon	*15*	*2*	*£74,895*	*25*	*£8,576*
% BSE at 12 months	*100%*	*4%*	*2420860%*	*11%*	*2316266%*
Tx effectiveness probs - month 1	*1*	*0.75*	*£35,194*	*1.25*	*£5,944*
Tx effectiveness probs - month 2 to 6	*1*	*0.75*	*£35,194*	*1.25*	*£5,944*
Tx effectiveness probs - month 7 to 12	*1*	*0.75*	*£74,247*	*1.25*	*£4,251*
Comp effectiveness probs - month 1	*1*	*0.75*	*£8,813*	*1.25*	*£15,150*
Comp effectiveness probs - month 2 to 6	*1*	*0.75*	*£3,409*	*1.25*	*£29,801*
Comp effectiveness probs - month 7 to 12	*1*	*0.75*	*£1,637*	*1.25*	*£43,317*
Natural deterioration	*0.03%*	*0.00%*	*£11,463*	*0.40%*	*£22,338*
RR for dexamethasone	*1*	*0.75*	*£8,778*	*1.25*	*£15,721*

Mortality rates	*1*	*0.5*	*£10,760*	*2*	*£14,317*
Administration costs (all other treatments)	*1*	*0.50*	*£7,842*	*1.50*	*£16,212*
Administration costs (dexamethasone)	*1*	*0.5*	*£14,015*	*1.5*	*£10,039*
Follow up cost multiplier (all treatments)	*1.00*	*0.50*	*£12,703*	*1.50*	*£11,351*
Cost of blindness	*£6,068*	*£3,034*	*£15,946*	*£9,102*	*£8,108*
% stopping after 3 months	*0.06*	*0.03*	*£11,233*	*0.09*	*£9,645*

Figure 7: Tornado plot for CRVO (ranibizumab versus dexamethasone)



iii. A complete summary table of all model parameters;

A summary of the location of the model parameters in the original submission is presented in Table 15. Table 16 is a table presenting each of the model parameters.

Table 15: Source of model parameters in submission

Input parameter	Table in submission
Treatment-dependent parameters	
Effectiveness of treatment (broken down by months 1, months 2 to 6, months 7 to 12 and months 13 to 24).	See Tables B44 to B46 and appendices.
Adverse events	See Table B48
Treatment-independent parameters	
Starting characteristics (age, VA)	See Tables B49 and B50
Mortality (by age)	Various
Mortality related to VA	See Table B47
Quality of life scores	See Tables B53 to B56
Cost parameters	
Unit cost of interventions	Table B59
Frequency of visits	Tables B61 and B62
Follow up visit costs	Table B60
Cost of blindness	Table B63
Cost of adverse events	Tables B64 to B66

Table 16: All model parameters

Input Parameter	Base-case value	Range/Variation	Source
Values specific to BRVO			
Population Parameters			
Baseline Age	66.43	5 (normal distribution)	BRAVO
Baseline health state distribution (BCVA letter score)			
86-100	0.0%	n/a	BRAVO
76-85	0.4%	n/a	BRAVO
66-75	17.2%	n/a	BRAVO
56-65	33.6%	n/a	BRAVO
46-55	26.0%	n/a	BRAVO
36-45	13.7%	n/a	BRAVO
26-35	7.3%	n/a	BRAVO
<25	1.9%	n/a	BRAVO
Transition Probabilities			
Month 1			
Ranibizumab Gain at least 4 lines	30.8%	Multiplier 0.1(lognormal)	BRAVO (data on file)
Ranibizumab Gain between 2 and 4 lines	42.3%	Multiplier 0.1(lognormal)	BRAVO (data on file)
Ranibizumab No change	24.6%	Multiplier 0.1(lognormal)	BRAVO (data on file)
Ranibizumab Lose between 2 and 4 lines	2.3%	Multiplier 0.1(lognormal)	BRAVO (data on file)
Ranibizumab Lose at least 4 lines	0.0%	Multiplier 0.1(lognormal)	BRAVO (data on file)
Standard care Gain at least 4 lines	11.4%	Multiplier 0.1(lognormal)	BRAVO (data on file)
Standard care Gain between 2 and 4 lines	28.8%	Multiplier 0.1(lognormal)	BRAVO (data on file)

Standard care No change	*40.2%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Lose between 2 and 4 lines	*17.4%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Lose at least 4 lines	*2.3%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Months 2 to 6			
Ranibizumab Gain at least 4 lines	*2.9%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab Gain between 2 and 4 lines	*22.6%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab No change	*60.5%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab Lose between 2 and 4 lines	*12.3%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab Lose at least 4 lines	*1.7%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Gain at least 4 lines	*2.9%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Gain between 2 and 4 lines	*20.8%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care No change	*59.8%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Lose between 2 and 4 lines	*15.0%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Lose at least 4 lines	*1.5%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Months 7 to 12			
Ranibizumab Gain at least 4 lines	*1.5%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file) Assumption: the data was pooled across both treatment arms for months 7 to 12 to generate month 7 to 12 transition probabilities.*
Ranibizumab Gain between 2 and 4 lines	*17.2%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab No change	*67.1%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab Lose between 2 and 4 lines	*12.5%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Ranibizumab Lose at least 4 lines	*1.7%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Gain at least 4 lines	*1.5%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Gain between 2 and 4 lines	*17.2%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care No change	*67.1%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Standard care Lose	*12.5%*	*Multiplier*	*BRAVO (data on file)*

between 2 and 4 lines		*0.1(lognormal)*	
Standard care Lose at least 4 lines	*1.7%*	*Multiplier 0.1(lognormal)*	*BRAVO (data on file)*
Resource Use			
Ranibizumab injection frequency year 1	*8.0*	*0.8 (gamma: α, 100; β, 0.08)*	*BRAVO*
Ranibizumab follow up visit frequency year 1	*4.0*	*Varies with injection frequency*	*Assumption; SPC (based on a total of 12 visits of any type per year)*
Ranibizumab injection frequency year 2	*2.5*	*0.25 (gamma: α, 100; β, 0.0025)*	*HORIZON (data on file)*
Ranibizumab follow up visit frequency year 2	*3.5*	*Varies with injection frequency*	*Assumption; HORIZON, expert opinion (based on a total of 6 visits of any type per year)*
Ranibizumab injection frequency year 3	*0.0*	*0-1*	*Assumption; expert opinion*
Ranibizumab follow up visit frequency year 3	*2.0*	*0-4*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Grid laser administration frequency year 1	*1.5*	*n/a*	*SCORE study*
Grid laser follow up visit frequency year 1	*2.5*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Grid laser administration frequency year 2	*1.0*	*n/a*	*SCORE study*[2]
Grid laser follow up visit frequency year 2	*3.0*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Grid laser administration frequency year 3	*0.0*	*n/a*	*Assumption; expert opinion*
Grid laser follow up visit frequency year 3	*2.0*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Dexamethasone injection frequency year 1	*2.0*	*1-4*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*
Dexamethasone follow up visit frequency year 1	*6.0*	*Varies with injection frequency*	*Assumption (based on a total of 8 visits of any type per year)*
Dexamethasone injection frequency year 2	*2.0*	*0-4*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*
Dexamethasone follow up visit frequency year 2	*6.0*	*Varies with injection frequency*	*Assumption (based on a total of 8 visits of any type per year)*
Dexamethasone injection	*0.0*	*n/a*	*Assumption; expert opinion*

frequency year 3			
Dexamethasone follow up visit frequency year 3	*2.0*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Values specific to CRVO			
Population Parameters			
Baseline Age	*67.61*	*n/a*	*CRUISE*
Baseline health state distribution (BCVA letter score)			
86-100	*0.0%*	*n/a*	*CRUISE*
76-85	*0.0%*	*n/a*	*CRUISE*
66-75	*13.5%*	*n/a*	*CRUISE*
56-65	*26.9%*	*n/a*	*CRUISE*
46-55	*21.2%*	*n/a*	*CRUISE*
36-45	*16.2%*	*n/a*	*CRUISE*
26-35	*15.0%*	*n/a*	*CRUISE*
<25	*7.3%*	*n/a*	*CRUISE*
Transition Probabilities			
Month 1			
Ranibizumab Gain at least 4 lines	*23.08%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Gain between 2 and 4 lines	*45.38%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab No change	*26.15%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Lose between 2 and 4 lines	*4.62%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Lose at least 4 lines	*0.77%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Gain at least 4 lines	*4.62%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Gain between 2 and 4 lines	*22.31%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care No change	*51.54%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Lose between 2 and 4 lines	*18.46%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Lose at least 4 lines	*3.08%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Months 2 to 6			
Ranibizumab Gain at least 4 lines	*2.46%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Gain between 2 and 4 lines	*20.62%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab No change	*63.38%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Lose between 2 and 4 lines	*12.15%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Lose at	*1.38%*	*Multiplier*	*CRUISE (data on file)*

least 4 lines		*0.1(lognormal)*	
Standard care Gain at least 4 lines	*1.54%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Gain between 2 and 4 lines	*19.08%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care No change	*61.38%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Lose between 2 and 4 lines	*15.23%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Lose at least 4 lines	*2.77%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Months 7 to 12 and Year 2			
Ranibizumab Gain at least 4 lines	*3.40%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file) Assumption: the month 2-6 transition probabilities were reapplied for months 7-12.*
Ranibizumab Gain between 2 and 4 lines	*18.53%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab No change	*60.71%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Lose between 2 and 4 lines	*13.97%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Ranibizumab Lose at least 4 lines	*3.40%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Gain at least 4 lines	*1.54%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Gain between 2 and 4 lines	*19.08%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care No change	*61.38%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Lose between 2 and 4 lines	*15.23%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Standard care Lose at least 4 lines	*2.77%*	*Multiplier 0.1(lognormal)*	*CRUISE (data on file)*
Year 3 and beyond			
Monthly rate of VA deterioration	*0.031%*	*0-0.4%*	*Beaver Dam Eye study*
Resource Use			
Ranibizumab injection frequency year 1	*9.0*	*0.9 (gamma: α, 100; β, 0.09)*	*CRUISE*
Ranibizumab follow up visit frequency year 1	*3.0*	*Varies with injection frequency*	*Assumption; SPC (based on a total of 12 visits of any type per year)*
Ranibizumab injection frequency year 2	*3.8*	*0.38 (gamma: α, 100; β, 0.038)*	*HORIZON (data on file)*
Ranibizumab follow up visit frequency year 2	*6.2*	*Varies with injection frequency*	*Assumption; HORIZON, expert opinion (based on a total of 10 visits of any type per year)*

Ranibizumab injection frequency year 3	*0.0*	*0-1*	*Assumption; expert opinion*
Ranibizumab follow up visit frequency year 3	*4.0*	*2-6*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Standard care administration frequency year 1	*0.0*	*n/a*	*Assumption*
Standard care follow up visit frequency year 1	*6.0*	*n/a*	*Assumption; expert opinion (based on a total of 6 visits of any type per year)*
Standard care administration frequency year 2	*0.0*	*n/a*	*Assumption*
Standard care follow up visit frequency year 2	*4.0*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Standard care administration frequency year 3	*0.0*	*n/a*	*Assumption*
Standard care follow up visit frequency year 3	*4.0*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Dexamethasone injection frequency year 1	*2.0*	*1-4*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*
Dexamethasone follow up visit frequency year 1	*6.0*	*Varies with injection frequency*	*Assumption (based on a total of 8 visits of any type per year)*
Dexamethasone injection frequency year 2	*2.0*	*0-4*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*
Dexamethasone follow up visit frequency year 2	*6.0*	*Varies with injection frequency*	*Assumption (based on a total of 8 visits of any type per year)*
Dexamethasone injection frequency year 3	*0.0*	*n/a*	*Assumption; expert opinion*
Dexamethasone follow up visit frequency year 3	*4.0*	*n/a*	*Assumption; expert opinion (based on a total of 4 visits of any type per year)*
Values Independent of Indication			
Model Structure			
Time horizon	*15 years*	*1-25*	*Assumption; NICE Reference case*
Discount rate costs	*3.5%*	*0% costs and QALYs, 6% costs and QALYs*	*NICE Reference case*
Discount rate benefits	*3.5%*	*0% costs and 3.5% QALYs*	*NICE Reference case*
% BSE at baseline	*100%*	*Beta distribution (α, 522; β, 0)*	*Assumption*
% BSE at 12 months	*100%*	*Beta distribution (α, 522; β, 0)*	*Assumption*
Treatment-dependent parameters			

Duration of treatment	*2 years*	*1-5*	*Expert opinion*
Adverse events (events per patient, %)			
Ranibizumab - Cataracts	*6.60%*	*Beta distribution (α, 34; β, 488)*	*BRAVO/CRUISE Data on file.*
Ranibizumab - IOP increased (treated with drug)	*10.0%*	*Beta distribution (α, 52; β, 470)*	*BRAVO/CRUISE Data on file.*
Ranibizumab - IOP increased (treated with surgery)	*0.0%*	*n/a*	*BRAVO/CRUISE Data on file.*
Ranibizumab - Stroke	*0.05%*	*n/a*	*Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate*
Standard care BRVO (laser) - Cataracts	*0.00%*	*n/a*	*Assumption*
Standard care BRVO (laser) - IOP increased (treated with drug)	*0.00%*	*n/a*	*Assumption*
Standard care BRVO (laser) - IOP increased (treated with surgery)	*0.00%*	*n/a*	*Assumption*
Standard care BRVO (laser) - Stroke	*0.05%*	*n/a*	*Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate*
Standard care CRVO (observation) - Cataracts	*0.00%*	*n/a*	*Assumption*
Standard care CRVO (observation) - IOP increased (treated with drug)	*0.00%*	*n/a*	*Assumption*
Standard care CRVO (observation) - IOP increased (treated with surgery)	*0.00%*	*n/a*	*Assumption*
Standard care CRVO (observation) - Stroke	*0.05%*	*n/a*	*Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate*
Dexamethasone - Cataracts	*14.80%*	*n/a*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*
Dexamethasone - IOP increased (treated with drug)	*50.40%*	*n/a*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular*

			oedema caused by retinal vein occlusion STA. September 2010.
Dexamethasone - IOP increased (treated with surgery)	*1.40%*	*n/a*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*
Dexamethasone - Stroke	*0.05%*	*n/a*	*Assumption; RR of stroke in RVO applied to annual haemorrhagic stroke rate*
Treatment-independent parameters			
Risk ratio for mortality, by VA status			
86-100	*1.00*	*1.0-3.0*	*Assumption, Christ 2008*
76-85	*1.00*	*1.0-3.0*	*Assumption, Christ 2008*
66-75	*1.00*	*1.0-3.0*	*Assumption, Christ 2008*
56-65	*1.00*	*1.0-3.0*	*Assumption, Christ 2008*
46-55	*1.23*	*0.1 (lognormal)*	*Christ 2008*
36-45	*1.23*	*0.1 (lognormal)*	*Christ 2008*
26-35	*1.54*	*0.1 (lognormal)*	*Christ 2008*
<25	*1.54*	*0.1 (lognormal)*	*Christ 2008*
Utility scores			
VA 86-100 letters	*0.920*	*n/a*	*Brown 1999*
VA 76-85 letters	*0.880*	*n/a*	*Brown 1999*
VA 66-75 letters	*0.770*	*n/a*	*Brown 1999*
VA 56-65 letters	*0.755*	*n/a*	*Brown 1999*
VA 46-55 letters	*0.670*	*n/a*	*Brown 1999*
VA 36-45 letters	*0.665*	*n/a*	*Brown 1999*
VA 26-35 letters	*0.645*	*n/a*	*Brown 1999*
VA<25 letters	*0.510*	*n/a*	*Brown 1999*
Death	*0.000*	*n/a*	*Assumption*
Cataracts	*-0.14*	*0.0284 (normal)*	*Brown et al. 2007*
IOP increased (treated with drug)	*-0.01*	*0.0026 (normal)*	*Vaahtoranta-Lehtonen et al. (2007)*
IOP increased (treated with surgery)	*-0.01*	*0.0002 (normal)*	*Vaahtoranta-Lehtonen et al. (2007)*
Cost parameters			
Technology costs			
Ranibizumab - Technology cost	*£742.17*	*n/a*	*Novartis Pharmaceuticals UK Ltd*
Ranibizumab - Administration cost	*£192.00*	*£96-£288*	*NHS Reference Costs 2009/10 [Outpatient procedure (£137) + OCT (£55)]*
Ranibizumab - Follow up visit cost	*£151.00*	*£76-£277*	*Staffing (£96) + OCT (£55)*

Laser (BRVO) - Technology cost	*£0.00*	*n/a*	*Assumption; capital expenditure and maintenance costs are excluded*
Laser (BRVO) - Administration cost	*£110.59*	*£55.30-£165.89*	*NHS Reference Costs 2009/10 Outpatient procedure (£137) + OCT (£55). 57% of patients incur laser costs as per control arm of BRAVO*
Laser (BRVO) -Follow up visit cost	*£151.00*	*£76-£277*	*NHS Reference Costs 2009/10 Outpatient visit (£96) + OCT (£55)*
Observation (CRVO) - Technology cost	*£0.00*	*n/a*	*n/a*
Observation (CRVO) - Administration cost	*£0.00*	*n/a*	*n/a*
Observation (CRVO) - Follow up visit cost	*£151.00*	*£76-£277*	*NHS Reference Costs 2009/10 Outpatient visit (£96) + OCT (£55)*
Dexamethasone - Technology cost	*£870.00*	*n/a*	*BNF*
Dexamethasone - Administration cost	*£295.25*	*n/a*	*NHS Reference Costs 2009/10 Outpatient/daycase procedure (£240) {Weighted average of day case [25%] and outpatient [75%]} + OCT (£55)*
Dexamethasone -Follow up visit cost	*£151.00*	*£76-£277*	*NHS Reference Costs 2009/10 [Outpatient visit (£96) + OCT (£55)]*
Costs of blindness			
First year cost	*£6,286.10*	*Multiplier 0.2 (gamma: α, 25; β, 0.04)*	*Shyangdan D 2010, based on Meads and Hyde 2000*
Subsequent annual costs	*£6,067.93*	*Multiplier 0.2 (gamma: α, 25; β, 0.04)*	*Shyangdan D 2010, based on Meads and Hyde 2000*
Technology costs treating of adverse events			
Cataract	*£800*	*160 (gamma: α, 25; β, 32)*	*NHS reference cost 2009/10 BZ02Z: NHS Trusts Day Cases HRG Data= £800 (Phacoemulsification Cataract Extraction & Lens Implant).*
IOP increased (treated with drug)	*£31.67*	*4 (gamma: α, 25; β, 1.267)*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the*

			treatment of macular oedema caused by retinal vein occlusion STA. September 2010.
IOP increased (treated with surgery)	*£872.63*	*174.525 (gamma: α, 25; β, 5)*	*NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.*

iv. Plots of all Markov traces.

Figure 8: Markov cohort trace – ranibizumab in BRVO

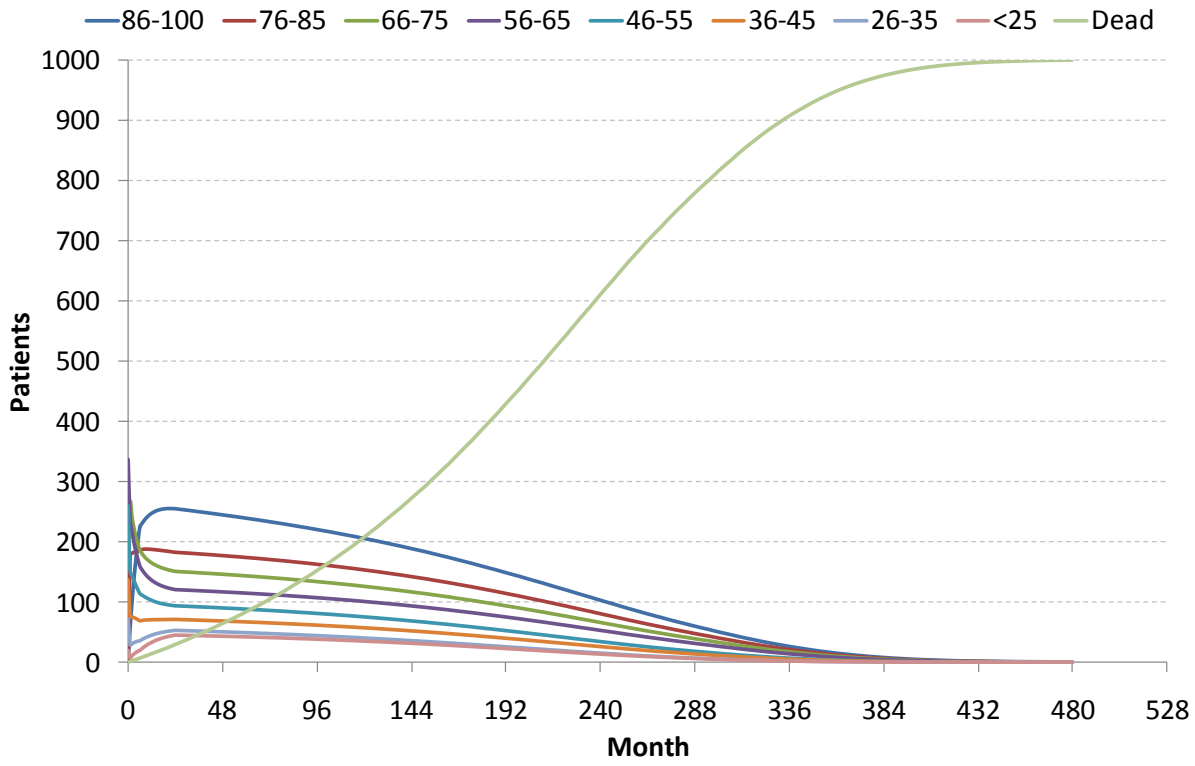


Figure 9: Markov cohort trace – standard care in BRVO

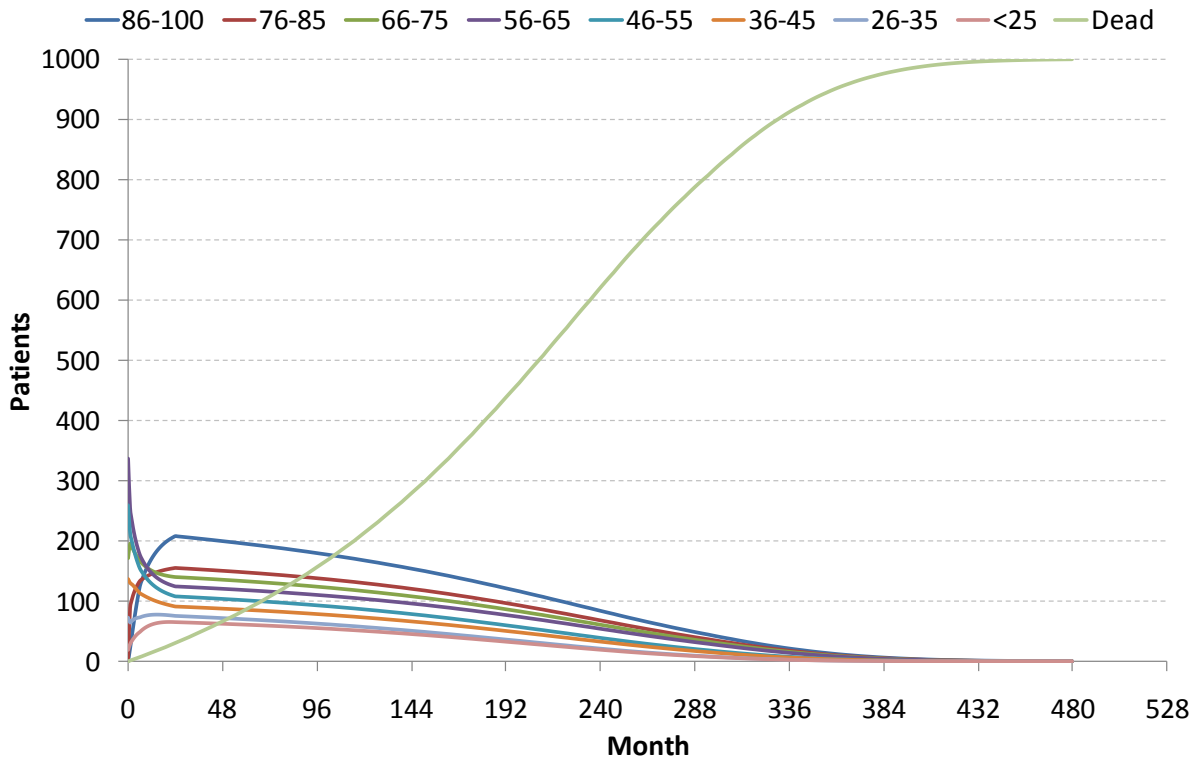


Figure 10: Markov cohort trace – ranbizumab in CRVO

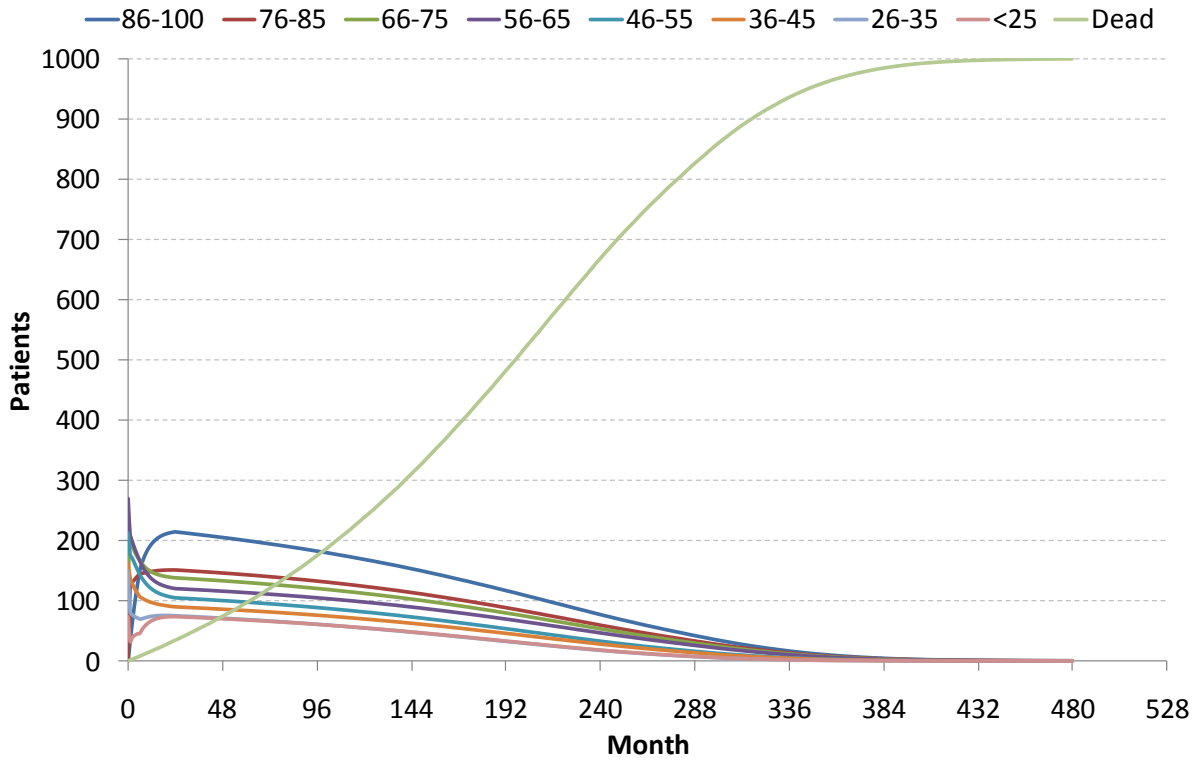
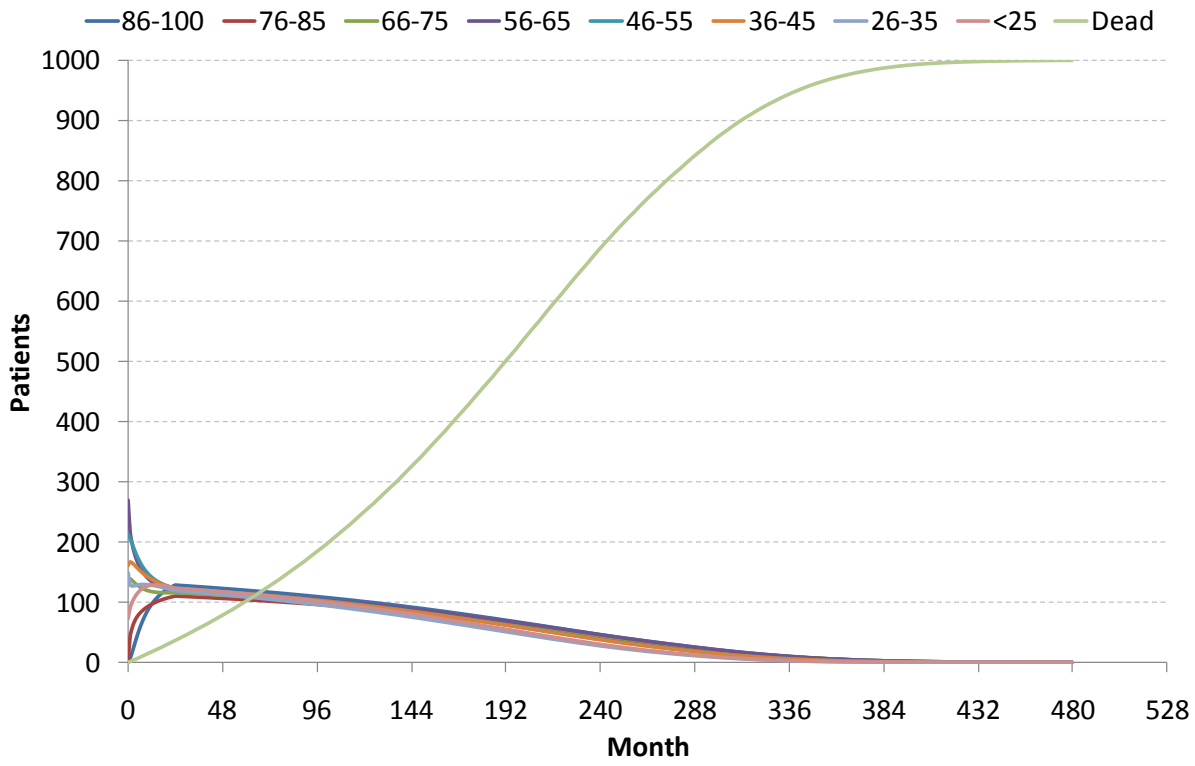


Figure 11: Markov cohort trace –standard care in CRVO



B7. The ERG requests an updated model that includes age adjusted utilities.

The UK population norms, published by Paul Kind in 1999 suggest the utilities by age presented in Table 17.

Table 17: UK population norm utilities (Kind 1999)

Age	*Utility*
<25	*0.94*
25 to 34	*0.93*
35 to 44	*0.91*
45 to 54	*0.85*
55 to 64	*0.80*
65 to 74	*0.78*
75 and over	*0.73*

The utilities in the model were drawn from Brown 1999. The mean age in that study was 67.5 years. Therefore, Table 17 can be 'standardised' to show an index for that group set at 1.0 (Table 18). As can be observed, a very slight downwards adjustment would be needed for utility values after the cohort reaches 75 years and a slight upwards adjustment for the initial years of the cohort in the model. Given that this minor adjustment would have a minimal impact on the cost effectiveness results and, moreover, suggests an adjustment over and above that required by the NICE reference case and the NICE methods guide an updated model is not provided.

Table 18: Utility index by age

Age	*Utility index (67.5 years = 1.00)*
<25	*1.21*
25 to 34	*1.19*
35 to 44	*1.17*
45 to 54	*1.09*
55 to 64	*1.03*
65 to 74	*1.00*
75 and over	*0.94*

B8. Please clarify the rationale for including stroke in the economic model, when there is no difference in incidence between treatment arms.

The model structure was developed before a complete exploration of the evidence through the reviews described in the submission. Thus, the development of the model did not presuppose the outcome of the review of evidence which determined there was no additional risk of stroke associated with ranibizumab compared to other treatments in a wet AMD population. Given that an assumption has been made that this evidence is applicable to the RVO population (as described in section 5.9.2), in line with standard modelling practice when parameters are uncertain, this input was retained in the model to allow sensitivity analysis.

B9. Brazier 2009 has been approved in TA155 as the best source of visual acuity related utility. Please provide further information as to why the visual acuity utility data from Brazier 2009, which was used in TA155, has not been used to inform health state utilities.

The utilities provided in the Brazier study were specific to patients with visual impairment arising from wet AMD. As such, it was not considered that these were the most appropriate source for this cost effectiveness analysis. However, the Brazier utilities have been entered into the model and have generated the results presented in Table 19 and Table 20.

Table 19: Cost effectiveness of ranibizumab versus standard care (laser) in BRVO

Technologies	*Total costs (£)*	*Total QALYs*	*Incremental costs (£)*	*Incremental QALYs*	*ICER (£) incremental (QALYs)*
Laser	*£11,990*	*7.884*	*-*	*-*	*-*
Ranibizumab	*£18,717*	[redacted]	*£6,727*	[redacted]	***£29,277***

Table 20: Cost effectiveness of ranibizumab versus standard care in CRVO

Technologies	***Total costs (£)***	***Total QALYs***	***Incremental costs (£)***	***Incremental QALYs***	***ICER (£) incremental (QALYs)***
Best supportive care	*£20,727*	*7.392*	*-*	*-*	*-*
Ranibizumab	*£26,327*	[redacted]	*£5,600*	[redacted]	***£13,717***

B10. Please provide a detailed description with a worked example of where the probability manipulation method described on page 245 of the submission is used in the model.

This probability manipulation approach was undertaken on the probabilistic probabilities associated with the transition probabilities. This can be seen in cells N12 to O28 in the 'Selected Effectiveness' sheet. The model is driven by these cells, rather than the cells in the 'main' effectiveness screen. When the deterministic model is selected, the 'adjusted' cells remain the same. When the probabilistic model is selected, the 'adjusted' cells are manipulated to ensure that the total is exactly 100%. This is done by dividing the value of each 'generated' probabilistic input by the sum of all generated probabilistic inputs. For example, the adjusted probability of gaining at least 4 lines whilst on ranibizumab (cell N12) is divided by the sum of the probabilities of any progression (or no change) whilst on ranibizumab (cells D12 to D16).

B11. Please clarify why the administration cost of laser therapy used in the model (£110.59) differs from that reported on page 235 of the submission (£192).

The cost of laser treatment is adjusted (in the model) to account for the fact that not all patients in the control arm received laser therapy. 57% of control patients received laser in BRAVO and, therefore, the cost in the model is 57% that of the value specified per treatment in the submission (page 235). This percentage is noted in table B59 (page 235) of the submission. It is noted that, during the first 6 months of the SCORE study, 80% of patients in the laser arm were treated. An adjustment of 57% may therefore be conservative, but would be expected to have minimal impact on the results.

B12. Page 248 of the submission states that there are slight differences between the BCVA of the trials and the model. Please explain why this is the case.

There are two reasons for the slight differences. The first is that the model results are based on the 'half-cycle' correction values. As such, they are based on the average VA during the first months (as opposed to exactly at baseline). Secondly, because patients are grouped into distinct VA bands in the model, each patient's exact VA is not recorded. It is assumed that their VA score is equivalent to the mid-point of the band. For example, all patients in the '46 to 55' band are assumed to have a VA of 50.

B13. Please clarify why the number of follow up visits for 3+ years used in the model (4), differs from that reported in the submission on pages 192 and 237 (2).

Having revisited the submission and executable excel file submitted, it has not been possible to identify any discrepancy. The number of follow up visits in years 3+ for patients with BRVO is 2 both in the model and in the submission. The number of follow up visits in years 3+ for patients with CRVO is 4, both in the model and in the submission.

B14. In section C of the submission, table C1 reports that 50% of BRVO patients experience visual impairment. Please clarify how this number was used in the calculation of the number of patients with visual impairment due to MO secondary to BRVO.

In the budget impact analysis, it was assumed that 50% of patients with BRVO experience visual impairment. As such, those who do not experience visual impairment would be unlikely to receive treatment. Therefore, the number with MO was multiplied by 50% to give the number eligible for treatment.

B15. When fellow eye involvement (FEI) is considered in the model, the different methods of drug cost calculations used before and after the assumed maximum treatment duration suggests that the drug costs may be underestimated. Patients experiencing FEI at, for example 23 months, have the cost of only one treatment applied, whereas patients experiencing FEI after the assumed maximum duration of treatment have the full 2 year cost of treatment in the fellow eye applied. Please confirm if this is an error. Please also correct this error so that all patients who experience FEI have the full cost of treatment applied.

The ERG is correct to identify an error in the calculation of the fellow eye involvement costs. This has now been corrected, by applying a fixed cost to each new case of FEI throughout the model, rather than to existing cases within the first two years and new cases thereafter. The base case model did not include FEI and, as such, the base case results do not change. However, when FEI is included, the results changed as presented in Table 21.

Table 21: FEI scenario analysis results

Scenario	***ICER (original model)***	***ICER (corrected model)***
BRVO – Ranibizumab v grid laser (standard care)	*£26,772*	*£28,632*
BRVO – Ranibizumab v dexamethasone implant	*£11,383*	*£9,979*
CRVO – Ranibizumab v best supportive care	*£12,871*	*£13,942*
CRVO – Ranibizumab v dexamethasone implant	*£12,687*	*£11,278*

As can be seen, the ICER is increased in comparisons against supportive care, but reduces in comparisons against dexamethasone implant. This is because the cost of dexamethasone implant is greater than the cost of ranibizumab and, as such, the increase in the rate of FEI incurs a greater cost in the dexamethasone arm.