Ranibizumab for diabetic macular oedema

Report for NICE rapid review

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Table of Contents

List of Tables and Figures

Tables

Figures

List of abbreviations

AC	Appraisal Committee
ACD	Appraisal Consultation Document
AMD	Age-related Macular Degeneration
ARMD	Age Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BSE	Better-Seeing Eye
CRT	Central Retinal Thickness
DMO	Diabetic Macular Oedema
DRCR.net	Diabetic Retinopathy Clinical Research Network
EQ-5D	EuroQoL-5D
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAD	Final Appraisal Determination
FEI	Fellow Eye Involvement
HbA1c	Glycated Haemoglobin
HRQoL	Health Related Qualify of Life
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
NRRS	Novartis Rapid Review Submission
OCT	Optical Coherence Tomography
PAS	Patient Access Scheme
QALY	Quality Adjusted Life Year
RR	Relative Risk
SA	Sensitivity Analysis
SG	Standard Gamble
STA	Single Technology Appraisal
TA	Technology Appraisal
TPM	Transition Probability Matrix
TTO	Time Trade Off
VA	Visual Acuity
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
WSE	Worse-Seeing Eye

1 Background

NICE issued guidance (TA 237)[1] on ranibizumab for diabetic macular oedema in November 2011, saying that: "Ranibizumab is not recommended for the treatment of visual impairment due to diabetic macular oedema." The reason for not recommending ranibizumab was that it was not considered cost-effective compared to laser photocoagulation. [redacted]

2 Manufacturer revisions to economic modelling and results in the light of the NICE FAD

Novartis has submitted three sets of modelling. The first was in the original industry submission. The second was as part of a substantial response to the negative recommendation in the ACD. The third is the recent submission to the rapid review.

This section of the ERG report for the rapid review is based upon a comparison of the second Novartis model, submitted in the light of the ACD, and the Novartis rapid review model. The rapid review modelling takes account of the concerns raised about cost-effectiveness in the FAD. This section draws upon the 12th May 2011 ERG review of the second Novartis model submitted in the light of the ACD, and follows a similar format. We start with the second post-ACD Novartis model and assess the effect of the changes that are introduced in the Novartis rapid review submission (NRRS).

Given the PAS price discount of [redacted] Novartis has estimated annual savings of [redacted] from reduced treatment costs amongst wet AMD patients. This estimate has not been reviewed by the ERG. The impact the PAS might have upon the overall cost effectiveness estimate of ranibizumab across the treatment of both wet AMD and diabetic macular oedema (DMO) has not been considered by the ERG.

2.1 ERG summary of the FAD and the Novartis response

The FAD raised a number of issues around the economic modelling. In this section we summarise the issues in the FAD, and how Novartis have responded in the NRRS. Paragraph numbers refer to the FAD.

Paragraph 4.16 There was no need to consider age weighting of utilities due to the limited impact this had upon results. The first meeting of the Appraisal Committee had considered that the original model over-estimated the HRQoL of people with diabetic macular oedema as they grew older.

- In the NRRS, Novartis does not age weight the utilities. This is in line with the 2nd Novartis submission base case.

Paragraph 4.18.The Committee considered that a 2.45 relative risk of death compared to the general public was more realistic than that used in the original model.

- In the NRRS, Novartis applies the 2.45 relative risk. This is in line with the 2nd Novartis submission base case.

- Novartis also apply a 2.0 relative risk as a sensitivity analysis which improves the NRRS base case BSE ICER from £14,137 per QALY to £13,758 per QALY, with these figures increasing to £21,205 per QALY and £20,636 per QALY respectively when conditioned by the 1.5 bilateral treatment uplift.

- Novartis does not carry out a sensitivity analysis with a higher figure. For reasons outlined later, the ERG considers that it is possible that 2.45 may be too low. An ERG sensitivity analysis of a relative risk of 3.50 worsens the NRRS base case BSE ICER from £14,137 per QALY to £15,023 per QALY, with these figures increasing to £21,205 per QALY and £22,534 per QALY respectively when conditioned by the 1.5 bilateral treatment uplift.

Paragraph 4.19.The stopping rule in the first Novartis submission was that treatment should stop once a BCVA of 76 letters has been achieved. The Committee thought this should be removed on the grounds that ophthalmologists would aim at best possible vision.

- In the NRRS, Novartis does not apply the stopping rule. This is in line with the 2nd Novartis submission base case.

Paragraph 4.20.The Committee and the ERG considered that ranibizumab would be given as an outpatient procedure and that the £150 administration cost per ranibizumab injection was reasonable.

- In the NRRS, Novartis applies a £150 administration cost for ranibizumab. This is in line with the 2nd Novartis submission base case.

Paragraph 4.21.The clinical experts attending the AC experts expected a bilateral treatment rate of at least 25% to 30%, with Novartis providing a scenario analysis of 35% bilateral treatment.

- In the NRRS, Novartis does not explicitly consider the rate of bilateral treatment, even as a sensitivity analysis. This is in line with the 2nd Novartis submission base case.

Paragraphs 4.22 and 4.23.The Committee thought that the utility values applied covered a broader range than would usually be reflected for changes in the BCVA of the WSE. The manufacturer model

correcting for covariates was preferred to the model not correcting for covariates, but the range of utility values remained surprisingly large.

- In the NRRS, Novartis draw BSE utilities from the Czoski-Murray paper,[2] written in conjunction with, among others, Brazier. This estimated time trade off (TTO) values from applying contact lenses to members of the public, and is reviewed in more detail later in this document. The 2nd Novartis submission base case drew utility values from EQ-5D values collected during RESTORE.

Paragraph 4.24.The Committee regarded an assumption of only the BSE being treated as invalid. The 1.5 multiplier applied in TA155[3] was noted. If TA155[3] was seen as a precedent it would be necessary to not only model treatment of the BSE but to perform an adjustment to the resulting ICER. Note that the FAD did not explicitly accept TA155 as creating a precedent and did not endorse the 1.5 multiplier.

- In the NRRS, Novartis applies the1.5 ICER multiplier. This is in line with the 2nd Novartis submission base case.

Paragraph 4.25. The Committee felt that drawing ranibizumab retreatment rates from the DRCR.net trial would be likely to underestimate these, since the DRCR.net also permitted laser, which would tend to be ranibizumab sparing. Assuming within the extrapolation that one injection of ranibizumab per year would have the same clinical effect as three injections per year was also seen as not credible.

- In the NRRS, Novartis revises the number of ranibizumab treatments to be in line with the pivotal trial including the now completed extension phase, which yields 3 years' data and estimates of 7, 4 and 3 injections in years 1, 2 and 3. The rapid review base case also assumes 0 ranibizumab injections in year 4, to give a total of 14 ranibizumab injections. This compares with the 7, 3, 2 and 1 injections which were assumed for years 1, 2, 3 and 4 in the Novartis 2nd submission base case, and gave a total of 13 ranibizumab injections.

- The NRRS also provides a sensitivity analysis around the number of ranibizumab injections that would be acceptable given a threshold of £30,000 per QALY. Novartis estimate that another 4 injections could be added in years 4 to 9, making a total of 18 injections in the 10 years. The ERG has cross checked that an additional 4 ranibizumab administrations can be added to the NRRS base case to take the BSE ICER to £19,777 per QALY, which when conditioned by the 1.5 bilateral multiplier increases this to £29,666 per QALY.

- Note that due to the NRRS assuming all treatment will cease in at the end of year 3 the extrapolation assumptions have also been slightly revised. The Novartis 2nd submission base

case assumed 3.0% of patients would improve by one health state and 3.0% of patients would worsen by one health state every quarter during years 2, 3 and 4. From year 5 it was assumed that 2.5% of patients would improve by one health state and 3.5% of patients would worsen by one health state every quarter. The NRRS revises this to the 3.0% improving and worsening each quarter occurring in years 2 and 3, with the 2.5% improving and 3.5% worsening each quarter occurring from year 4.

Paragraph 4.26.The Committee were concerned about the assumed changes in vision beyond year 4 of the model, when ranibizumab treatment was assumed to end. Sensitivity analyses around the model duration could proxy for sensitivity analyses around the duration of benefit.

- In the NRRS, Novartis revises the base case time horizon to 10 years, with the absolute BCVA benefit from ranibizumab over laser being maintained for this period. This compares with the 15 years Novartis 2nd submission base case.

- The NRRS also presents a threshold analysis that applies a 2.5% quarterly proportion improving and a 5.5% quarterly proportion worsening in the ranibizumab arm from year 4, compared to a 2.5% quarterly proportion improving and a 3.5% quarterly proportion worsening in the laser arm. This is presented in figure 1 of the NRRS. An ERG cross check of this confirms the BSE ICER of £19,862 per QALY, which when conditioned by the 1.5 bilateral multiplier increases this to £29,793 per QALY.

Paragraph 4.27.Novartis assumed that an administration visit for ranibizumab could double as a monitoring visit but that laser would require separate visits for treatment and monitoring, without providing an explanation for this assumption.

- In the NRRS, Novartis revises the laser visit schedule to permit treatment visits to double as monitoring visits. This compares with the Novartis 2nd submission base case assuming that laser treatment visits could not double as monitoring visits.

Paragraph 4.28. Due to the trial excluding patients with very poor glycaemic control, coupled with the HbA1c subgroup data provided by Novartis, the ICER would in practice tend to be worse than that estimated from the trial population because patients with very poor glycaemic control would be treated.

- In the NRRS, Novartis does not address this in the rapid review on the grounds of small patient numbers with key transition probabilities within the subgroups being determined by a single patient in many cases. This is in line with the Novartis 2nd submission.

Paragraph 4.32.The subgroup analyses around retinal thickness while biologically plausible resulted in erratic ICERs. Due to this and the small sample sizes these subgroup analyses were not considered sufficiently robust to support recommendations to the NHS.

- In the NRRS, Novartis revises the measurement of retinal thickness to be based upon the central retinal thickness (CRT). The additional analyses of the Novartis 2nd submission based these analyses upon the central foveal thickness (CVT).

2.2 Brief ERG commentary on Novartis revisions and their impacts

The Novartis revisions in the light of the FAD 4.25 and 4.27 results in the following changes to the numbers of treatments and outpatient visits (Table 1 and Table 2).

Table 1. Treatments, treatment visits and monitoring visits Novartis second submission

Novartis second submission	Year 1	Year 2	Year 3	Year 4	Total
ranibizumab injections	7	3	2	1	13
OP treatment visit	7	3	2	1	13
OP dedicated monitoring visit	5	7	2	3	17
OP total visits	12	10	4	4	30
laser treatments	2	1	1	1	5
OP treatment visit	2	1	1	1	5
OP dedicated monitoring visit	4	4	4	4	16
OP total visits	6	5	5	5	21

Table 2. Treatments, treatment visits and monitoring visits Novartis rapid review submission

Novartis second submission	Year 1	Year 2	Year 3	Year 4	Total
ranibizumab injections	7	4	3	0	14
OP treatment visit	7	4	3	0	14
OP dedicated monitoring visit	5	4	3	2	14
OP total visits	12	8	6	2	28
laser treatments	2	1	1	0	4
OP treatment visit	2	1	1	0	4
OP dedicated monitoring visit	2	3	3	2	10
OP total visits	4	4	4	2	14

The revision to the number of ranibizumab injections in years 1, 2 and 3 is as per Table 1 of the NRRS, which is in turn drawn from the extension study. Given the increased requirement for 3 ranibizumab injections in year 3 compared with the 2 ranibizumab injections previously assumed in the Novartis second submission, it is unclear why the NRRS has reduced the assumed number of ranibizumab injections in year 4 from 1 to 0.

The revised Royal College of Ophthalmologists guidelines have been circulated for consultation. These state that for laser follow up should be quarterly, though they do not specify the duration. For anti-VEGF these state that there should be between 4 and 6 monthly loading doses with monthly optical coherence tomography (OCT) follow up until dry for the first year. After this the follow up interval can be gradually increase to between 3 and 4 monthly.

The impact of each of the Novartis changes to the model of the cost effectiveness of ranibizumab monotherapy compared to laser for treatment of the BSE of a patient can be applied individually to the Novartis 2nd submission base case within which the ICER without the PAS was £36,812 per QALY.

Note that the ERG may have identified an error in the derivation of the Czoski-Murray utilities. This is presented in greater detail later in this document, but the impact of the ERG cross check of the Czoski-Murray utilities[2] is presented below for ease of reference (Table 3).

Table 3. Individual impacts of Novartis model changes

PAS percentage	0%	[redacted]	[redacted]
Novartis 2nd submission base case	£36,812	[redacted]	[redacted]
SA1 BCVA declines from year 4	£36,399	[redacted]	[redacted]
SA2 10 year horizon	£50,206	[redacted]	[redacted]
SA3 Ranibizumab dosing	£40,949	[redacted]	[redacted]
SA4 Laser admin and monitoring	£39,609	[redacted]	[redacted]
SA5 Novartis Czoski-Murray utilities	£15,277	[redacted]	[redacted]
SA1 to SA5 simultaneously	£23,730	[redacted]	[redacted]
1.5 uplift for bilateral treatment	£35,595	[redacted]	[redacted]
ERG Revision to Czoski-Murray utilities			
SA1 to SA4 + ERG Czoski-Murray utilities simultaneously	£24,295	[redacted]	[redacted]
1.5 uplift for bilateral treatment	£36,443	[redacted]	[redacted]

The £30,198 per QALY with the previous [redacted] PAS and the £21,206 per QALY with the revised [redacted] PAS cross check with the values given in Tables 6 and 7 of the Novartis rapid review submission.

Within the submitted economics, of the outstanding issues that remain that the ERG can provide some further commentary upon the following.

- The HRQoL values applied relate to the BCVA of the BSE.
    - There may be an error in the Novartis calculation of the HRQoL values drawn from the Czoski-Murray paper.

- Are these values reasonable for the patients who only have their BSE treated?
- What values should be applied to those who only have their WSE treated?
- What should be assumed for those who have both their BSE and their WSE treated?

- The model assumes that only one eye is treated. Some patients will only have their BSE treated, some will only have their WSE treated, and some will have both their BSE and WSE treated.
    - What proportions of the patient population fall into each group?
    - Given a model of only one eye being treated, how should each group be modelled?

2.3 Revised source for HRQoL values

Czoski-Murray and colleagues,[2] these colleagues including Brazier, explored the feasibility of using contact lenses to simulate the severity of three different BCVAs of ARMD: LogMARs of 0.6 from Lens1, 1.0 from Lens2 and 1.4 from Lens3. 107 respondents were recruited to the study: 107 had a BSE BCVA of LogMAR≤30 (≥20/40) and 104 wore all three sets of contact lenses. HRQoL was measured using TTO, with this being anchored at full health and immediate death. Given patient characteristics this enabled the mean HRQoL to be estimated over four ranges of BCVA in the BSE as summarised below (Table 4).

Table 4. Czoski-Murray HRQoL values

	Lens1		Lens2		Lens3		Overall	
LogMAR	n	HRQoL	n	HRQoL	n	HRQoL	n	HRQoL
≤0.3	18	0.778	23	0.649	0		41	0.706
0.31-0.60	40	0.731	40	0.649	9	0.603	89	0.681
0.61-1.30	46	0.653	41	0.486	38	0.366	125	0.511
≥1.31	0		0		56	0.314	56	0.314
Total	104	0.705	104	0.585	103	0.358	311	0.550

This resulted in two regression equations, one controlling for age and the other not. These were also compared with similar regression equations derived from a patient survey among ARMD patients undertaken by Espallargues and colleagues (2005),[4] these colleagues including Czoski-Murray. Espallargues measured TTO, HU13 and EQ-5D among 209 UK ARMD patients and related these to the VA of the BSE. Valuation of the EQ-5D data was based upon the UK social tariff, while valuation of the HU13 index was apparently based upon the VAS and standard gamble conducted among a sample of the Canadian public. Note that the regression models reported below are only reported in Czoski-Murray[2] (Table 5).

Table 5. Czoski-Murray HRQoL models

	Lens study		Survey of ARMD patients					
Method	TTO		TTO		HUI3		EQ-5D	
Models	coef	s.e.	coef	s.e.	coef	s.e.	coef	s.e.
Not controlling for Age								
Constant	0.828	0.039	0.753	0.038	0.479	0.033	0.745	0.027
VA LogMAR	-0.359	0.045	-0.087	0.031	-0.140	0.027	-0.027	0.023
Adjusted R^2	0.171		0.032		0.110		0.002	
Controlling for Age								
Constant	0.860	0.068	1.737	0.217	1.078	0.198	0.753	0.164
VA LogMAR	-0.368	0.046	-0.036	0.032	-0.109	0.028	-0.027	0.024
Age	-0.001	0.002	-0.013	0.013	-0.008	0.003	0.000	0.002
Adjusted R^2	0.172		0.121		0.147		0.003	

Czoski-Murray noted that the coefficient from TTO values obtained from the lenses study within the model not correcting for age was "*over four times the size of the patients' own TTO coefficients and 13 times the coefficient for the EQ-5D*".[2] In other words, for a given LogMAR change in the BCVA of the BSE the Lens TTO coefficient suggests this will have four times the HRQoL impact compared to the coefficient estimated using the TTO among ARMD patients. Czoski-Murray also noted that controlling for age "*increased the differences between the coefficients on the VA for the TTO values*".[2]

In the discussion it is further noted that "*By comparing our sample with a patient sample, we have drawn attention to the potential use of a simulation method; however, the nature of the sample and the problems encountered with the lenses themselves makes any true comparison impossible at this stage*", and that "*Our sample was considerable younger than the patient study and therefore comorbidities in the older population may be an issue*".[2] The paper concludes with "*Further validation work comparing or combining vignettes and contact lens simulation methods may make it possible to use this method in the future to obtain general population values for an important health condition*".[2]

The revised modelling uses the lenses study coefficients from the TTO model controlling for age, and in particular the VA LogMAR coefficient of -0.368. Given an age of 65 and the mapping between ETDRS values and LogMAR values as presented in Table 11 of the NRRS, the HRQoL values cross check with the regression equation.

But the conversion between ETDRS values and LogMAR values as presented in Table 11 appears to be incorrect. In particular, some parts of the Novartis LogMAR range are not continuous while other

parts of the range overlap. ERG expert opinion suggests that the appropriate conversion is as below (Table 6).

Table 6. Mapping from ETDRS to LogMAR

	Novartis LogMAR		ERG LogMAR	
BCVA	Lower	Upper	Lower	Upper
1: 86-100	-0.1	-0.3	0.0	-0.3
2: 76-85	0.2	0.0	0.2	0.0
3: 66-75	0.5	0.3	0.4	0.2
4: 56-65	0.6	0.4	0.6	0.4
5: 46-55	0.8	0.6	0.8	0.6
6: 36-45	1.0	0.8	1.0	0.8
7: 26-35	1.2	1.0	1.2	1.0
8: 0-25	n.a.	1.2	1.6	1.2

Note that Novartis applies a LogMAR of 1.2 for the worst health state and does not average between the lower bound and 1.2. This seems reasonable since the range of the worst health state is 25 letters, though it may tend to understate the HRQoL impact from falling into the worst health state. Along similar lines, it may be reasonable to apply some upper limit to the best health state for the averaging of utilities: 95 letters corresponds with a LogMAR of -0.2.

Retaining the upper bound of 100 letters for the best health state, the NRRS and the ERG cross check of values implied by the age adjusted HRQoL functions presented by Czoski-Murray are outlined below (Table 7).

Table 7. Czoski-Murray HRQoL Age Adjusted Models

	Novartis	ERG cross check			
BCVA	Lens TTO	Lens TTO	Patient TTO	Patient HUI	Patient EQ-5D
1: 86-100	0.869	0.850	0.897	0.574	0.757
2: 76-85	0.758	0.758	0.888	0.547	0.750
3: 66-75	0.648	0.685	0.881	0.525	0.745
4: 56-65	0.611	0.611	0.874	0.504	0.740
5: 46-55	0.537	0.537	0.867	0.482	0.734
6: 36-45	0.464	0.464	0.860	0.460	0.729
7: 26-35	0.390	0.390	0.852	0.438	0.723
8: 0-25	0.353	0.353	0.849	0.427	0.721

Note that limiting the upper bound of the best health state to 95 letters would result in the average from the ERG Lens TTO cross check changing from 0.850 to 0.832.

For completeness, the parallel HRQoL values implied by the non-age adjusted models presented by Czoski-Murray are outlined below (Table 8).

Table 8. Czoski-Murray HRQoL Non-Age Adjusted Models

	Novartis	ERG cross check			
BCVA	Lens TTO	Lens TTO	Patient TTO	Patient HUI	Patient EQ-5D
1: 86-100	0.900	0.882	0.766	0.500	0.749
2: 76-85	0.792	0.792	0.744	0.465	0.742
3: 66-75	0.684	0.720	0.727	0.437	0.737
4: 56-65	0.649	0.649	0.710	0.409	0.732
5: 46-55	0.577	0.577	0.692	0.381	0.726
6: 36-45	0.505	0.505	0.675	0.353	0.721
7: 26-35	0.433	0.433	0.657	0.325	0.715
8: 0-25	0.397	0.397	0.649	0.311	0.713

Note that limiting the upper bound of the best health state to 95 letters would result in the average from the ERG Lens TTO cross check changing from 0.882 to 0.864.

Both Table 7 and Table 8 rely upon the Czoski-Murray derived functions as outlined in Table 5. The TTO HRQoL values for the BSE reported in Espallargues, pooled across contrast sensitivities, are reported below (Table 9).

Table 9. TTO HRQoL values presented by Espallargues

approx. ETDRS	Snellen		n	HRQoL
80-85	20/25	20/20	11	0.810
65-75	20/50	20/30	32	0.760
50-60	20/100	20/60	35	0.580
20-35	20/400	20/200	54	0.640
<20		<20/400	76	0.580

These values differ from those estimated using the Czoski-Murray functional form for the patient TTO age adjusted model of Table 7 above. In particular the HRQoL values estimated using the Czoski-Murray patient TTO function are somewhat better for the worse health states than those reported in Espallargues. The reasons for this are not clear. Table 9 could be taken to provide some

support for the Czoski-Murray Lens TTO values with which they are more closely aligned for the better health states, but this alignment tails off with the worse health states. For these, the Lens TTO values may still tend to overstate the detrimental HRQoL impact of poor eyesight, possibly due to patients with poor eyesight adjusting to it over time. But there is a reasonable accord between the TTO HRQoL values of Espallargues[4] and those reported by Brown 1999,[5] summarised in Table 12 below. The range reported and approximate slope of the HRQoL function of Espallargues is less than that of Brown 1999,[5] but the values appear to be more in line than the comparison with the Czoski-Murray Lens TTO values.

The above HRQoL values can be read alongside the HRQoL values presented over the course of the assessment (Table 10).

Table 10. HRQoL values presented over the course of the assessment

		RESTORE		Lloyd	
BCVA	Czoski-Murray	Unadjusted	Adjusted	Unadjusted	Adjusted
1: 86-100	0.869	0.860	0.849	0.830	0.830
2: 76-85	0.758	0.860	0.849	0.750	0.750
3: 66-75	0.648	0.813	0.806	0.625	0.750
4: 56-65	0.611	0.802	0.796	0.500	0.715
5: 46-55	0.537	0.770	0.770	0.680	0.680
6: 36-45	0.464	0.760	0.768	0.605	0.680
7: 26-35	0.390	0.681	0.686	0.530	0.530
8: 0-25	0.353	0.547	0.556	0.340	0.340

The RESTORE EQ-5D data remains a potential source of HRQoL values provided that:

- the data is analysed with due regard to whether it is the BCVA of the BSE or the BCVA of the WSE that is changing from baseline, with this possibly having to take into account patients' whose WSE becomes their BSE once treated, and
- the impact of the BCVA in the untreated eye, coupled with other comorbidities, does not drive results, possibly through analysing changes in the BCVA of the treated eye against changes in the EQ-5D.

2.4 BSE and WSE HRQoL

Brown et al (1999)[5] employed TTO and Standard Gamble (SG) to assess the HRQoL among 325 US patients with impaired vision of at least 20/40 in at least one eye. Note that the patient group was not specific to patients with diabetes, though one third had diabetes and there was no apparent relationship between the cause of visual impairment and its impact. There were 78 patients with good

vision of 20/20 to 20/25 in one eye. These patients were subdivided by the BCVA in the fellow eye into 5 groups with TTO and SG being applied to them. This resulted in the following patient distribution and HRQoL estimates (Table 11).

Table 11. HRQoL by BCVA in WSE among patients with good vision in BSE: Brown et al 1999

BCVA in WSE	n	TTO	SG
20/40-20/50	18	0.860	0.930
20/70-20/100	12	0.900	0.960
20/200-20/400	13	0.950	0.940
≤ 20/800 (CF)	28	0.880	0.920
≤ 20/1600 (HM/NLP)	7	0.810	0.950
CF: Counting fingers HM: Detecting hand movement NLP: No light perception			

As can be seen from the above, among the patients who had good vision in their BSE eye there was no strong relationship between HRQoL and vision in the WSE. Based upon TTO the above could be taken to indicate that given good vision in one eye, the other eye has to drop to levels below 20/400 for there to be an impact upon HRQoL values.

Brown et al[5] subdivided the BSEs into 12 BCVA groups, with TTO and SG suggesting the following HRQoL values (Table 12).

Table 12. HRQoL by BCVA in BSE: Brown et al 1999

BCVA in BSE	n	TTO	SG
20/20	32	0.920	0.960
20/25	50	0.870	0.920
20/30	44	0.840	0.910
20/40	54	0.800	0.890
20/50	31	0.770	0.830
20/70	40	0.740	0.800
20/100	18	0.670	0.820
20/200	16	0.660	0.800
20/300	13	0.630	0.780
20/400	9	0.540	0.590
≤20/800 (CF)	12	0.520	0.650
≤20/1600 (HM/NLP)	6	0.350	0.490

From the introduction it appears that the BCVAs stated in Brown et al 1999[5] form the upper bound of the range and extend down to the upper bound of the next best range. The ERG has assumed this in what follows. There is not an exact mapping between the categories and for both HS1 and HS2 the ERG has applied a value of 0.920. For HS8 of the model the HRQoL value of 0.540 for 20/400 will be applied, though it could be argued that the value of 0.630 for 20/300 might be more reasonable.

In another paper Brown et al (2000)[6] report the HRQoL values measured among 72 US ARMD patients with impaired vision of at least 20/40 in at least one eye. In the light of this, these may be a subset of the patients of the Brown et al (1999)[5] paper summarised above (Table 13).

Table 13. HRQoL by BCVA in BSE: Brown et al 2000

BCVA in BSE	TTO	SG
20/20 to 20/25	0.890	0.960
20/30 to 20/50	0.810	0.880
20/60 to 20/100	0.570	0.690
20/200 to 20/400	0.520	0.710
CF to LP	0.400	0.550

The mapping between the BCVA bands of Brown et al (2000)[6] and the health states of the model is worse than that for Brown et al (1999),[5] and grosser assumptions have to be made. As for the Brown et al (1999)[5] paper, the best two health states of the model have been assigned the same 0.890 HRQoL value when using Brown et al (2000).[6] The worst health state of the model requires a value for less than 25 letters, or 20/320 on the Snellen scale. The worst health state of Brown et al (2000)[6] corresponds to 20/800 or only 5 letters. In the light of this, the bottom two health states of the model have been assigned the same 0.520 HRQoL value when using Brown et al (2000),[6] though it could be argued that the worst health state might be assigned a 0.400 HRQoL value.

The above values, while not a comprehensive literature review, suggest a range of possible sources for HRQoL values for changes to the BCVA of the BSE for the model, as outlined below (Table 14).

Table 14. HRQoL by BSE: TTO Czoski-Murray, Brown 1999 and Brown 2000

			HRQoL values		
State	**ETDRS**	**Snellen**	**Czoski-Murray**	**Brown 1999**	**Brown 2000**
HS1	86-100	>20/20	0.850	0.920	0.890
HS2	76-85	>20/32 to ≤20/20	0.758	0.920	0.890
HS3	66-75	>20/50 to ≤20/32	0.685	0.840	0.810
HS4	56-65	>20/80 to ≤20/50	0.611	0.770	0.570
HS5	46-55	>20/125 to ≤20/80	0.537	0.740	0.570
HS6	36-45	>20/200 to ≤20/125	0.464	0.670	0.570
HS7	26-35	>20/320 to ≤20/200	0.390	0.660	0.520
HS8	0-25	≤20/320	0.353	0.540	0.520

The range covered by the Czoski-Murray lenses TTO values is broader than that of both Brown 1999[5] and Brown 2000[6] (Figure 1). Brown 1999[5] and Brown 2000[6] have roughly the same range between the best and the worst health state, but Brown 1999[5] has the benefit of a finer gradation and being based upon somewhat larger patient numbers than Brown 2000.[6] Given this, the analysis focusses upon Czoski-Murray and Brown 1999.[5] The ERG recognises that there is a wider literature upon HRQoL related to vision but has not reviewed it given the constraints of the STA process.

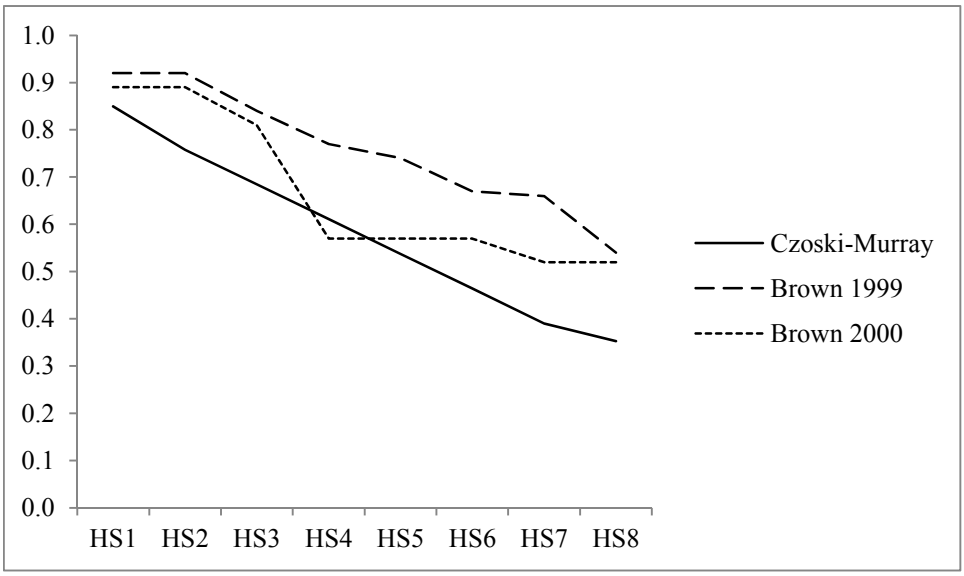

Figure 1. HRQoL by BSE: TTO Czoski-Murray, Brown 1999 and Brown 2000

Both the Czoski-Murray[2] and the Brown 1999[5] utility functions are reasonably linear in the health states of the model, with the slope of each also being reasonably similar Brown 1999[5] is slightly flatter.

Brown 1999[5] could be taken as suggesting that changes in the BCVA of the WSE typically have minimal impact upon HRQoL. But there is limited data on this. In the light of this, a range of scenario analyses can be presented which simplistically considers the range of utility values over the best to the worst health state for the BCVA of the BSE and apportions a percentage of this to changes in the BCVA of the WSE. While crude, this enables the range of possible alternatives to be explored through six sensitivity analyses which apply percentages of:

- SA1 0%,
- SA2 15%,
- SA3 30%,
- SA4 50%,
- SA5 75% and
- SA6 100%.

These are provided for illustration and the ERG is not suggesting that all are possible, though given that DMO is frequently bilateral, and given also that patients with DMO often have other forms of diabetic retinopathy, there is always the danger of visual loss in the original BSE, for example after a bleed into the vitreous, and it could then become the WSE. Similarly, if there is little difference at baseline, it is possible that a unilaterally treated WSE could improve sufficiently to become the BSE. These scenarios cannot be addressed within the current modelling framework, and to do so would require a genuinely bilateral model of patients' BCVAs in both eyes. But for the subgroups of patients in which a former WSE becomes the BSE after treatment, or in which the former BSE deteriorates to become the WSE, SA6 may be the most reasonable to assume within the current modelling framework, though this may tend to slightly overstate the overall QALY gain.

To illustrate, the step between best and worst health state for the BSE from the Czoski-Murray lenses TTO values is 0.850-0.353=0.497. The scenario exploring the WSE having 30% of the HRQoL impact of the BSE reduces this step to 0.497*30%=0.149. This results in the patient HRQoL ranging from 0.850 when the WSE is in HS1, down to 0.850-0.149=0.701 when the WSE is in HS8. The intermediate health states assume a linear utility function for the WSE, which appears reasonable given the broadly linear utility functions of the utility functions for the BSE.

2.5 Unilateral BSE treatment, unilateral WSE treatment and bilateral treatment

Section 5.3.1 of the ERG report notes that in the RESTORE "[redacted] *had visual impairment and DMO in one eye. The* [redacted] *had visual impairment and DMO in both eyes at baseline."* and that "*At baseline,* [redacted] *of patients in the RESTORE trial had their worst seeing eye treated, this again being largely driven by the trial protocol*".

Section 5.5.1 of the ERG report notes that

- in the RESTORE trial "*given the trial protocol only* [redacted] *of patients had their BSE treated*"
- in the RESTORE trial "[redacted] *of patients had FEI DMO at baseline*"
- in the RESTORE trial "*the proportion of patients with FEI DMO and FEI visual impairment of ≤ 78 letters at baseline was* [redacted]
- in the RESOLVE trial "*the proportion of patients with FEI DMO and FEI visual impairment of ≤ 78 letters at baseline was…* [redacted]
- in the Welsh screening programme "*at first presentation among patients with clinically significant DMO in one eye 61% had visual impairment in the other eye with 38% having visual impairment in the fellow eye due to DMO*".

Table 23 of section 5.5.1 of the ERG report goes on to summarise Novartis experts as suggesting that most if not all patients with visual impairment due to DMO in one eye will go on to develop visual impairment due to DMO in the fellow eye at some point.

Section 4.21 of the FAD notes that AC experts suggest that at least 25% to 30% of patients will require treatment in both eyes.

On the assumption that the [redacted] of patients in RESTORE who had their BSE treated would not be eligible for bilateral treatment and that this is representative of the broader patient population, this suggests that the remaining [redacted] of patients will be split between those having only their WSE treated and those having both eyes treated. Given the Novartis figure of [redacted] being likely to receive bilateral treatment this appears to suggest a figure of [redacted] having only their WSE treated.

Due to the model being only a one eye model, rather than performing an ad hoc 1.5 multiplier to the BSE ICER, it may be more appropriate to model one eye being treated with explicit assumptions as to costs and QALYs as required for adapting it to modelling bilateral treatment:

- Patients having only their BSE treated, with an associated BSE HRQoL function and the model as submitted complete with the costs of blindness.
- Patients having only their WSE treated, with an associated WSE HRQoL function[1] and the costs of blindness removed[2].

[1] Implemented in *Current_Markov_Inputs* worksheet by changing the values in R27:R34 to be equal to those in cells B15:B22 of the ERG inserted *ERG* worksheet and selecting Czoski-Murray et al as the source of utilities within the *CEA_Start* worksheet. Note that this method can also draw upon the Brown 1999 HRQoL values and the Brown 2000 HRQoL values as given within the *ERG* worksheet, the selection of Czoski-Murray et al as the source of utilities within the *CEA_Start* worksheet simply being a means of inserting these values into the

- Patients having both eyes treated with an associated BSE HRQoL function coupled with assumptions around the additional HRQoL benefit from having the WSE bilaterally treated. In the absence of bilateral HRQoL data, the simplest assumption for the WSE being treated under the bilateral scenario is that the same absolute QALY impact results from changes in the BCVA of the WSE when it is being bilaterally treated as when it is being unilaterally treated: i.e. draw the additional HRQoL impacts for treatment of the WSE from the modelling performed under the preceding bullet and simply add these to the QALYs modelled using the BSE HRQoL function[3]. Treatment costs would be doubled[4] and the costs of blindness retained.
- Combine the cost estimates from each of the above bullets as a weighted average with a [redacted] split; similarly combine the QALY estimates as a weighted average; and, calculate the resultant pooled ICER.

Note that in line with the bilateral treatment sensitivity analysis of the Novartis 1st submission, treatment and monitoring visits have not been increased for bilateral treatments. This may quite significantly favour ranibizumab given the increasing importance of these in the light of the [redacted] PAS, and the greater number of treatment and monitoring visits required for ranibizumab compared to laser.

None of the above takes into account the possible disutility from the fear of blindness. This may apply even to the WSE, since if treatment improves vision, it may reduce the fear of blindness, especially since patients will be aware of the likelihood of developing DMO in both eyes.

Note that for the above approach to be correct it would be necessary to apply the baseline BCVA distribution specific to those having their BSE treated at baseline, and the baseline BCVA distribution to those having their WSE treated at baseline. The former would be anticipated to be better than the latter. The ERG has not been able to apply this due to a lack of data. The probable impact of this upon the overall pooled results cannot be determined.

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correct cells of the *Current_Markov_Inputs* worksheet. Also note that where Czoski-Murray et al HRQoL values are being applied these are those calculated by the ERG rather than those calculated by Novartis.

[2] Implemented in the *Appendix_1* worksheet by setting cells E113:E114 to zero.

[3] Implemented separately with the ERG inserted *Bilaterl_XXX* worksheets

[4] Implemented in line with the stated Novartis 2nd submission scenario analysis by doubling the values in cell B6 of the *Appendix_1* worksheet. Note that this only doubles the number of ranibizumab injections, and does not increase the administration cost for either ranibizumab or laser, as per the bilateral sensitivity analysis of the original Novartis submission. Adverse event rates and monitoring visits are also unaffected.

3 ERG additional sensitivity analyses around the base case

The following analyses apply the [redacted] PAS (Table 15 and Table 16). Also, for the scenario using the Czoski-Murray HRQoL values the ERG calculation of these has been used rather than those submitted by Novartis. Note that these analyses cannot take into account the proportion of patients initially treated in their WSE where this eye subsequently becoming their BSE.

Table 15. Unilateral BSE, unilateral WSE and 35% bilateral treatment with Czoski-Murray utilities

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	WSE	Bilateral	Mean	BSE	WSE	Bilateral	Mean	Net	ICERs
	[redacted]	[redacted]	35%		[redacted]	[redacted]	35%			
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
QALYs										
SA1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,712
SA2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,843
SA3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,999
SA4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,398
SA5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,411
SA6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,585

Table 16. Unilateral BSE, unilateral WSE and 35% bilateral treatment with Brown 1999 utilities

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	WSE	Bilateral	Mean	BSE	WSE	Bilateral	Mean	Net	ICERs
	[redacted]	[redacted]	35%		[redacted]	[redacted]	35%			
Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
QALYs										
SA1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,879
SA2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,227
SA3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,089
SA4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,231
SA5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,131
SA6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,504

The RESTORE trial had [redacted] of patients with FEI DMO and FEI visual impairment of ≤ 78 letters at baseline (**Table 17** and Table 18).

Table 17. Unilateral BSE, unilateral WSE and [redacted] bilateral treatment with Czoski-Murray utilities

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	WSE	Bilateral	Mean	BSE	WSE	Bilateral	Mean	Net	ICERs
	[redacted]									
Cost	[redacted]									
QALYs										
SA1	[redacted]									£29,868
SA2	[redacted]									£26,193
SA3	[redacted]									£23,324
SA4	[redacted]									£20,351
SA5	[redacted]									£17,554
SA6	[redacted]									£15,433

Table 18. Unilateral BSE, unilateral WSE and [redacted] bilateral treatment with Brown 1999 utilities

	Ranibizumab monotherapy				Laser monotherapy					
	BSE	WSE	Bilateral	Mean	BSE	WSE	Bilateral	Mean	Net	ICERs
	[redacted]									
Cost	[redacted]									
QALYs										
SA1	[redacted]									£38,267
SA2	[redacted]									£33,643
SA3	[redacted]									£30,016
SA4	[redacted]									£26,244
SA5	[redacted]									£22,681
SA6	[redacted]									£19,970

In the light of the above, the key uncertainties remaining appear to be:

- The most appropriate source from the literature for HRQoL values for changes in the BCVA of the BSE.
- In the absence of data on the HRQoL values for changes in the BCVA of the WSE, the proportion of the HRQoL values for changes in the BCVA of the BSE it is most reasonable to apply; i.e. which of SA1 to SA6. The Brown 1999 study suggests that the WSE has little effect on utility, which would suggest that SAs 4, 5 and 6 are unlikely. However there was some effect so perhaps SA1 can also be discounted.
- The proportion of patients who will only have their WSE treated, while will in turn be related to the rate of fellow eye involvement at baseline and over time. Involvement over time is not readily inferred from the above, as additional treatment and monitoring visits will definitely be required compared to the current assumption of no additional visits being required.

- What is reasonable to assume in terms of treatment visits and monitoring visits for those being treated bilaterally from baseline, and over time.
- What utility gain to apply from reduced fear of blindness if the WSE improves with treatment but remains the WSE.
- How these factors would affect ICERs in subgroups by retinal thickness.

3.1 CRST and HbA1c subgroup analyses

Due to the following section being largely a cross check of the manufacturer submission, the manufacturer derived Czoski-Murray utilities are used.

Novartis argue that due to small patient numbers within the HbA1c subgroups, coupled with a number of cells within the 8*8 transition probability matrices (TPMs) being populated by only one patient, the results of any HbA1c subgroup analyses are subject to considerable uncertainty and should be seen as exploratory. This needs to be viewed against the CRST[5] subgroup analyses presented in section 6.3 of the NRRS. The subgroup patient numbers and the number and proportion of cells within the four TPMs that are populated by only one patient are presented below (Table 19).

Table 19. Subgroup patient numbers and TPM cells populated by only one patient

	Ranibizumab monotherapy					Laser monotherapy				
HbA1c	n	TPM1	TPM2	TPM3	TPM4	n	TPM1	TPM2	TPM3	TPM4
<8%	[redacted]					[redacted]				
≥8%	[redacted]					[redacted]				
CRST	n	TPM1	TPM2	TPM3	TPM4	n	TPM1	TPM2	TPM3	TPM4
>400	[redacted]					[redacted]				
<400	[redacted]					[redacted]				
300-400	[redacted]					[redacted]				
<300	[redacted]					[redacted]				
TPM1: 0-3 months TPM2: 3-6 months TPM3: 6-9 months TPM4:9-12 months										

[5] Within the electronic copy of the model CRST has been used throughout. This is assumed by the ERG to be synonymous with CRT.

The CRST≥400µm:CRST<400µm criterion splits the trial into roughly equal parts: [redacted]. The split from the HbA1c<8%: HbA1c≥8% criterion of [redacted] is not as equal with the number with poor glycaemic control within the trial being roughly only [redacted] of the trial population. But the proportions of cells within the TPMs that are populated by only one patient are not dissimilar between the groups, and could be argued to be higher in the CRST subgroup analyses.

Note that the above only outlines the number of cells within the TPMs which are populated by a single patient. The converse of the number of empty cells which might have been populated by one patient had the trial been larger has not been presented. This aspect is not easily addressable within the deterministic modelling. It could be addressed within the probabilistic modelling by the addition of an uninformed prior to each of the TPMs. This was the approach adopted by Novartis in the first model submitted, but it appeared to lead to bias with the central distributions of patients simulated probabilistically tending to reduce the difference between ranibizumab and laser compared to the deterministic distributions, the latter being drawn directly from the trial. This effect would be probably be larger for the sub-group modelling, since the same amount of weight from the uninformed prior would be being added to a smaller subgroup population. In the light of this, the ERG is unsure whether the addition of an uninformed prior to the TPMs within the probabilistic modelling would much help matters.

But probabilistic modelling is perhaps the most obvious means of formally assessing the reasonableness of the sub-group modelling. Rather than rely upon counts of the number single patients populating cells within the TPMs, probabilistic modelling that samples the TPMs is the obvious means of addressing these concerns. Note that the following probabilistic modelling has not applied any uninformed priors to the TPMs.

The approximations of the previous section for unilateral BSE treatment, unilateral WSE and bilateral treatment had to assume that all eyes had the same baseline BCVA distribution. A parallel consideration applies for the CRST subgroup analysis. The NRRS model assumes that the BSE is being treated, and as a consequence also assumes that the baseline BCVA distribution for the CRST subgroup drawn from the trial as a whole is equally applicable to those having their BSE treated.

A parallel consideration also applies to the CRST subgroup given the 1.5 bilateral ICER uplift. In a sense, the ad hoc 1.5 multiplier for bilateral treatment assumes that the fellow eye being treated has the same CRST thickness as the CRST thickness of the BSE that is being treated. The degree of correlation between a patient's eyes' CRSTs when both are eligible for treatment cannot be addressed by the ERG. Also, it is possible that the eye with the thicker CRST at baseline may be less likely to be the patients' BSE, making the NRRS assumption of the main model being a BSE model less tenable.

In what follows only the BSE ICERs are reported; i.e. the ICER that is estimated to apply when only the BSE is treated. The Novartis 1.5 adjustment for bilateral treatment would increase all these ICERs by 50%, but this adjustment is ad hoc and given the previous section this adjustment may be questionable. While only the BSE ICERs are reported in the following, this still enables a cross check of the model and its outputs as reported in the NRRS and some consideration of the impact of sample sizes and subgroups upon the uncertainty surrounding the BSE ICERs.

The ERG has replicated the results for CRST≥400µm and CRST<400µm in Tables 15 and 16 of the NRRS. But note that while the modelling for CRST≥400µm restricts the patient baseline BCVA distribution to <=75 letters, the modelling for CRST<400µm does not. This is a relatively minor oversight, and restricting the baseline BCVA distribution of <=75 letters for the CRST<400µm modelling revises the BSE ICER from £28,861 per QALY to £29,666 per QALY.

The ERG has not been able to exactly replicate the results for the 300µm ≤CRST<400µm subgroup of Table 17. Revising the patient baseline BCVA distribution to the pooled baseline distribution among those receiving either ranibizumab monotherapy or laser monotherapy with both 300µm ≤CRST<400µm and ≤75 letters at baseline[6] results in a BSE ICER of £25,653 per QALY compared to the £25,665 per QALY of Table 17.

The ERG attempt to replicate the results for CRST<300µm subgroup of Table 18 is rather further out. Adopting the parallel approach for the CRST<300 subgroup modelling[7] results in a BSE ICER of £66,453 per QALY compared to the £47,030 per QALY of Table 18. It may be more reasonable to include the ranibizumab combination arm in the baseline BCVA distribution. Applying this[8] results in a BSE ICER of £54,794 per QALY. But this is still somewhat different from the £47,030 per QALY of Table 18 and may be the result of an error by the ERG.

This underlines the importance of applying the subgroup specific baseline BCVA distribution within the CRST subgroup analyses. The impact of this upon any modelling of HbA1c subgroups is, however, less pronounced since the baseline BCVA distributions for the HbA1c<8% subgroup and the HbA1c ≥8% subgroup are not that different. For the HbA1c<8% subgroup applying the subgroup specific BCVA baseline distribution results in a BSE ICER of £12,777 per QALY, compared to £12,594 per QALY if the pooled BCVA baseline distribution overall patient population is applied. For the HbA1c≥8% the subgroup specific BCVA baseline results in a BSE ICER of £21,656 per

[6] As drawn from *Library_Of_Transition_Matrices* worksheet cells BT60:CA60 and CP60:CW60.
[7] As drawn from *Library_Of_Transition_Matrices* worksheet cells EH60:EO60 and FD60:FK60.
[8] As drawn from *Library_Of_Transition_Matrices* worksheet cells EH60:EO60, ES60:EZ60 and FD60:FK60.

QALY, compared to £21,780 per QALY when the pooled patient population BCVA distribution is applied.

Running the model probabilistically over 5,000 iterations results in the following central estimates and probabilities of ranibizumab being cost effective compared to laser (Table 20). Note that these are all BSE ICERs and have not had any bilateral uplift applied to them.

Table 20. Subgroup analyses and probabilistic results

	All patients	CRST				HbA1c	
	≤75 letters	≥400µm	<400µm	≥300µm <400µm	<300µm	<8%	≥8%
Deterministic	£14,137	£8,881	£28,681	£25,652	£66,453	£12,777	£21,656
Probabilistic	£14,065	£8,954	£29,136	£25,734	£64,579	£12,895	£21,560
Likelihood of c/e at							
£0 per QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£10k per QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£20k per QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£30k per QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£40k per QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£50k per QALY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The main ERG intention behind presenting all the subgroup CEACs in one figure [redacted] is not to enable a review of their relative positions, but rather to enable a review of their broad shape and steepness. This is to facilitate consideration of the uncertainty around the central estimates of the individual subgroups. As it happens, the curves grouped by their central cost effectiveness estimates are also broadly similar in terms of their shape and steepness.

The CEACs for the subgroup with a baseline CRST ≥400µm, the subgroup with a baseline HbA1c<8% and all patients with ≤75 letters at baseline are the three curves towards the left, and are of similar shape to one another. Those for the subgroups with a baseline HbA1c≥8%, a baseline CRST <400µm and a baseline 300<CRST ≤400µm are grouped in the centre of the figure, and are of also similar shape to one another. In the light of this, the probabilistic modelling does not particularly distinguish between the subgroup modelling that applies the CRST≥400µm:CRST<400µm split and the subgroup modelling that applies the HbA1c<8%: HbA1c≥8% split. The uncertainty around the two appears to be broadly similar.

Only the CEAC for the subgroup with a baseline CRST<300µm forms an obvious outlier in terms of shape with a noticeably flat CEAC. This is possibly due to the small patient numbers involved, but is possibly also due to incorrect implementation by the ERG.

4 Other issues

4.1 Mortality in people with diabetic retinopathy

In the ranibizumab STA, assumptions about mortality had a significant effect on ICERs, of up to £4,660 per QALY. If people get benefit from treatment of DMO, the total QALY gain depends on, inter alia, how long they live for. Mortality is increased amongst people with diabetes, and further amongst those with diabetes and retinopathy.

In Table 10 of the NRRS, a relative risk of 2.0 for mortality is used as a sensitivity analysis. The RR used in the first Novartis submission was 1.27. The RR of 2.45 was used in the second Novartis submission, post-ACD, in response to the ERG's comments. That was based on two studies. One by Mulnier and colleagues[7] from the UK provided the RR for people with diabetes versus the general population. They estimated that people with type 2 diabetes had a relative risk of dying of 1.93 (compared to the general population).

The other by Hirai et al[8] gave the RR for people with diabetes and DMO versus those with diabetes but no DMO. Hirai and colleagues estimated that the excess risk in those diagnosed over the age of 30 (i.e. mostly type 2) with DMO to be 1.27, which combined gives those with diabetes and DMO a RR of 2.45.

Because that figure was based on only two studies, the ERG has done a wider search for data on mortality in people with DMO, and concludes that the RR might be higher than 2.45. Details are given in Appendix 1.

In the fluocinolone STA, the ERG used a RR of 3.5 in a sensitivity analysis. That worsened the ICER, though only by about £3000 per QALY.

The range of studies suggests that;

- Mortality is higher in people with diabetes, compared to the general population
- In those with diabetes, mortality is much higher in those with advanced retinopathy, with RRs in the range 3 to 4.

This provides the justification for the ERG's sensitivity analysis using an RR of 3.5.

4.2 Retinal thickness

In the STA of ranibizumab, the ICERs by band of retinal thickness looked odd, with the middle band having very high ICERs. Given the reduced efficacy of laser treatment in thicker retinas, it was not surprising that ranibizumab ICERs over laser would be lower. But we would expect the ICERs to show linearity, which in the first submission, was not the case.

In the current submission from Novartis, a different method of measuring thickness has been used. The results look more credible, and the ERG's clinical opinion accepts the new method.

The Table below is reproduced from the submission (Table 21).

Table 21. Proportion of patients with ≥10 letters change in BCVA from baseline, at M12

	Ranibizumab 0.5 mg	Laser
Proportion of patients with at least 10 letter improvement		
Full RESTORE population	37.4%	15.5%
CRT < 400µm	[redacted]	[redacted]
CRT ≥ 400µm	[redacted]	[redacted]
Proportion of patients with at least 10 letter deterioration		
Full RESTORE population	3.5%	13.7%
CRT < 400µm	[redacted]	[redacted]
CRT ≥ 400µm	[redacted]	[redacted]

So the difference between laser and ranibizumab is much less with thinner retinas, because laser is less effective in thicker retinas. One effect is that ranibizumab has higher ICERs than would normally be acceptable with thinner retinas, with the implication that its use might be targeted based on OCT results.

4.3 Number of follow-up visits

The number of follow-up visits depends on local policies. If it is considered, as by the ERG, that fluorescein angiography (FA) is needed prior to laser (i.e. to decide which areas to treat) then, a fluorescein angiogram needs to be obtained. Laser tends not to be done on the same day as the angiogram. However, if laser is done without angiography (as in the DRCR.net trial) then laser could be done on the same visit.

The process in the NHS may be as follows. If a patient is referred with possible macular oedema, it is likely that in the first visit the ophthalmologist will see him/her and organise images (FA, OCT). Once

the diagnosis is established, depending on the hospital, there may be time or not to do the treatment on the same visit.

Thus, first visit will be confirming diagnosis and counselling the patient and then patient will return to get treatment (and that may be the same for both, laser and anti-VEGF). However, after that, in most hospitals, patients would just return for injections - they would get the OCT and if there is no oedema, no injection is given. If there is oedema, an injection is given. If there is a response after 4 months from the initial laser, that will be assessed at the clinic, and patients will be followed every 4 months.

In some hospitals, there may not be both "injection clinics" where patients are not examined at these clinics, but just treated, and laser clinics" , used more to do panretinal photocoagulation.

If laser works and the macular oedema resolves, then patients are followed usually every 4 months. If all is stable, they will be probably checked twice a year. So ERG expects visits every 4 months for first year after treatment and if controlled every 4-6 months thereafter.

The Royal College of Ophthalmologists guidelines, out for consultation (Lois personal communication), recommend follow-up after laser every 4 months (though they do not specify duration). For anti-VEGF they suggest 4-6 loading injections monthly, then monthly follow-up with OCT until the macula is dry for the first year. After year 1 the period of time between appointments can be gradually increased up to 3-4 months for the year 2 and 3.

4.4 Setting for treatment

Table 10 of the NRRS includes a sensitivity analysis with 25% of treatments given as “day care”. The ERG assumes that this means day case. Our assumption remains that we expect ranibizumab to be given in Outpatient clinics, and charged as such.

5 Some uncertainties

One of the key factors is the utility gain from treating the WSE. There are several uncertainties around this.

Utility is determined mainly by the BSE, and so the first uncertainty, discussed earlier, is how much utility arises from treating the WSE.

The second uncertainty is the future of the original BSE, given that DMO is frequently bilateral, and also frequently associated with other forms of possible sight-threatening retinopathy, and with other forms of eye disease. For example, cataract is very common in diabetes.

The third uncertainty is about utility from reduced fear of blindness. It is said that the complication most feared by people with diabetes, is blindness. It is possible that successful treatment of a WSE might reduce anxiety and fear of blindness, and hence provide a utility gain that is not captured by utilities based on BCVA. We have no data on this at present. The nearest example might be from diabetes appraisals where a reduction in chronic fear of hypoglycaemic episodes, was estimated by the assessment group to provide 0.01 QALYs per annum.

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Appendix 1. Mortality studies.

The RR of 1.93 in the Mulnier study[7] (which was of high quality) was for all ages. However people having treatment for DMO are older than the average in the Mulnier study.[7] The RRs for the age range 55-64 in the Mulnier study were 2.21 for men and 3.28 for women. The overall RR of 1.93 is affected by the much lower RRs seen in the over 75 age groups.

Caveats are necessary when applying mortality rates from older studies, to present day modelling. The cohort in the Mulnier study[7] was recruited on 1st January 1992. No details on duration of diabetes are given in the paper, but most would have had diabetes for some years. Mortality was based on deaths in the years 1992 to 1998. The reported prevalence of diabetes was only 1.5% - much less than now. It is likely that outcomes for people with diabetes may have improved since then, for example with more use of the statins in diabetes, and better control of blood pressure. So mortality may be lower now. Gulliford and Charlton using General Practice Research Database (GPRD) data, showed that the RR for overall mortality declined from 1.38 in 1997 to 1.27 in 2006 in men, and from 1.62 to 1.44 in women.[9] In Scotland, the Scottish Diabetes Research Network[10] reports RRs in type 2 diabetes of 1.4 in men and 1.7 in women.

Targher and colleagues followed up a cohort of 2103 people with type 2 diabetes in Italy.[11] All were initially free of diagnosed cardiovascular disease. The risk of new CVD was higher in those with retinopathy, especially in those who had more advanced retinopathy such as proliferative or previously laser treated. The RRs for those with advanced retinopathy were 3.75 for men and 3.81 for women. Even after adjustment for a range of other variables, RRs remained high at 2.08 for men and 2.41 for women.

Other studies have also reported increased mortality amongst people with advanced retinopathy. Juutilainen et al reported that patients with proliferative retinopathy had (after adjustment for a range of variables) a RR of 3.06 ($p<0.001$) for all-cause mortality, relative to those with no retinopathy.[12]

Rajala et al compared mortality in several groups. People with visual impairment due to diabetic retinopathy had a RR compared to the general non-diabetic population of 5.1.[13]

In type 1 diabetes, van Hecke et al[14] reported an adjusted hazard ratio in patients with proliferative retinopathy of 4.2, compared to those without retinopathy at baseline. The increased mortality was mainly explained by cardiovascular risk factors. Patients with proliferative retinopathy also had much more hypertension (38% vs. 5% in diabetic people without retinopathy) and prior CVD. At 8 year follow-up, 10% of the group with proliferative retinopathy had died compared to 1.5% of the group with no retinopathy.

In a Danish cohort of patients with type 1 diabetes, Grauslund et al reported that 55% of all patients survived to a 25-year follow-up, but that amongst those with proliferative retinopathy and proteinuria, only 22%5 survived for 10 years.[15]

From the Beijing Eye Study, Xu and colleagues reported that the presence of retinopathy doubled the mortality rate.[16]

Cusick and colleagues (ETDRS 27) reported that severe non-proliferative diabetic retinopathy conferred a 1.7 (crude) or 1.48 (adjusted) relative risk of mortality compared to those with no or only mild background retinopathy.[17]

The association between retinopathy and mortality is because cardiovascular risk factors are also risk factors for the development of retinopathy.[14]

Hence a range of studies suggest that;

- Mortality is higher in people with diabetes, compared to the general population
- In those with diabetes, mortality is much higher in those with advanced retinopathy, with RRs in the range 3 to 4.

One problem is that many studies report associations with proliferative retinopathy, rather than macular oedema. This is usually because they rely on 2-dimensional retinal photographs which cannot detect oedema. However there is a high correlation between DMO and proliferative retinopathy.

We could use the RR of 5.1 from the Rajala 2000 study,[13] which compares mortality in people with visual impairment due to diabetic retinopathy, with that in the general non-diabetic population. That is the comparison we need. However numbers in that study were quite small.

Or we could take the Cusick[17] and Xu[16] figures for the excess risk in those with more severe retinopathy, averaged to 1.75, and apply that to the excess risk amongst those with diabetes versus the general population – using the 2.3 from the AusDiab study[18] or the 1.9 from Mulnier[7] – to give the relative risk of mortality in those with DMO in the range 3.3 to 4.0.

We therefore chose an RR of 3.5 to use in sensitivity analysis