Aflibercept for treating diabetic macular oedema

Produced by Aberdeen HTA Group

Authors Shona Fielding[1]
Ewen Cummins[2]
Moira Cruickshank[3]
Cynthia Fraser[3]
Noemi Lois[4]
Miriam Brazzelli[3]

1 Medical Statistics Team, University of Aberdeen
2 McMDC Ltd. Health Economics, Glasgow, UK
3 Health Services Research Unit, University of Aberdeen
4 Centre for Vision and Vascular Science, Queen's University Belfast

Correspondence to: Miriam Brazzelli
Health Services Research Unit, University of Aberdeen
2nd Floor, Health Sciences Building, Foresterhill
Aberdeen, AB25 2ZD

Date completed: 12 December 2014

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/10/01.

Declared competing interests of the authors

None

Acknowledgements

The authors are grateful to Graham MacLennan for his advice on the methods used for the indirect and mixed treatment comparisons, to David Cooper for his comments on an early draft of the clinical effectiveness chapter and to Lara Kemp for her secretarial support.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Fielding S, Cummins E, Cruickshank M, Fraser C, Lois N, Brazzelli M. Aflibercept for the treatment of diabetic macular oedema: a single technology appraisal. Aberdeen HTA Group, 2014.

Contributions of authors

Shona Fielding acted as statistician, critiqued the statistical methods presented in the submission, checked all the numerical results, tables, and figures related to the review of the clinical effectiveness evidence, conducted further statistical analyses. Ewen Cummins acted as health economist, critiqued and reviewed the cost-effectiveness evidence presented in the submission, checked and rebuilt the economic model, and carried out further sensitivity analyses. Moira Cruickshank acted as systematic reviewer, critiqued the clinical effectiveness methods. Cynthia Fraser acted as information scientist, critiqued the methods used for identifying relevant studies in the literature and conducted additional searches. Noemi Lois acted as clinical expert, provided clinical advice and general guidance. Miriam Brazzelli acted as project lead for this appraisal, critiqued and reviewed the clinical effectiveness methods, and

supervised the work throughout the project. All authors contributed to the writing of the report and approved its final version.

Table of contents

1	**SUMMARY**	**1**
1.1	***Scope of the submission***	**1**
1.2	***Summary of clinical effectiveness evidence submitted by the company***	**1**
1.3	***Summary of ERG's critique of clinical effectiveness evidence submitted***	**2**
1.4	***Summary of cost-effectiveness submitted evidence by the company***	**3**
1.5	***Summary of the ERG critique of cost-effectiveness evidence submitted***	**5**
1.6	***ERG commentary on the robustness of evidence submitted by the company***	**7**
1.6.1	**Strengths**	**7**
1.6.2	**Weaknesses and areas of uncertainty**	**7**
1.7	***Summary of exploratory and sensitivity analyses undertaken by the ERG***	**8**
2	**BACKGROUND**	**10**
2.1	***Critique of company's description of underlying health problem***	**13**
2.2	***Critique of company's overview of current service provision***	**15**
3	**CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM**	**16**
3.1	***Population***	**16**
3.2	***Intervention***	**16**
3.3	***Comparators***	**16**
3.4	***Outcomes***	**17**
3.5	***Other relevant factors***	**18**

4	**CLINICAL EFFECTIVENESS**	**21**
4.1	***Critique of the methods of review(s)***	**21**
4.1.1	**Searches**	**21**
4.1.2	**Inclusion criteria**	**22**
4.1.3	**Identified Studies**	**24**
4.1.4	**Characteristics of included RCTs**	**24**
4.1.5	**Critique of data extraction**	**34**
4.1.6	**Quality assessment**	**35**
4.2	***Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)***	**36**
4.2.1	**Aflibercept 2Q4 or aflibercept 2Q8 versus laser**	**39**
4.2.2	**Adverse events**	**46**
4.2.3	**Meta-analysis of VIVD and VISTA**	**47**
4.2.4	**Critique of submitted evidence**	**49**
4.3	***Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison***	**50**
4.4	***Critique of the indirect comparison and/or multiple treatment comparison***	**54**
4.4.1	**Indirect comparison**	**54**
4.4.2	**Network meta-analysis**	**61**
4.4.3	**Critique of network meta-analysis**	**64**
4.5	***Additional work on clinical effectiveness undertaken by the ERG***	**66**
4.6	***Conclusions of the clinical effectiveness section***	**69**

5	**COST-EFFECTIVENESS**	**70**
5.1	***ERG comment on company's review of cost-effectiveness evidence***	**70**
5.1.1	**Objectives of the cost-effectiveness review**	**70**
5.1.2	**Inclusion/exclusion criteria of the cost-effectiveness review**	**70**
5.1.3	**Studies included in the cost-effectiveness review**	**71**
5.1.4	**Main conclusions of the cost-effectiveness review**	**71**
5.2	***Summary and critique of company's submitted economic evaluation by the ERG***	**73**
5.2.1	**NICE reference case checklist**	**73**
5.2.2	**Model structure**	**75**
5.2.3	**Population**	**76**
5.2.4	**Interventions and comparators**	**76**
5.2.5	**Perspective, time horizon and discounting**	**77**
5.2.6	**Treatment effectiveness and extrapolation**	**77**
5.2.7	**Health related quality of life**	**80**
5.2.8	**Resources and costs**	**83**
5.2.9	**Cost-effectiveness results**	**85**
5.2.10	**Sensitivity analyses**	**88**
5.2.11	**Scenario analyses: other comparators**	**91**
5.2.12	**Scenario analyses: CRT ≥ 400µm**	**93**
5.2.13	**Model validation and face validity check**	**94**

5.3	*ERG cross check and critique*	**95**
5.3.1	**Base case results**	**95**
5.3.2	**Data inputs: correspondence between written submission and sources cited**	**96**
5.3.3	**Data inputs: correspondence between written submission and electronic model**	**105**
5.3.4	**ERG commentary on model structure, assumption and data inputs**	**106**
5.4	*Exploratory and sensitivity analyses undertaken by the ERG*	**123**
5.5	*Conclusions of the cost-effectiveness section*	**136**
6	**IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG**	**139**
7	**OVERALL CONCLUSIONS**	**141**
7.1	*Implications for research*	**142**
8	**REFERENCES**	**144**
9	**APPENDICES**	**151**
	Appendix 1 Published studies involving bevacizumab and laser photocoagulation therapy for DMO	

List of tables

Table 1	**Base case numbers of treatments and monitoring visits**	**4**
Table 2	**Comparison of NICE final scope and decision problem addressed by company**	**19**
Table 3	**Inclusion criteria used in systematic review of clinical effectiveness**	**22**
Table 4	**Characteristics of the VISTA and VIVID RCTs**	**26**
Table 5	**Baseline demographics and disease characteristics of the patients population in the VISTA and VIVID trials**	**30**
Table 6	**Quality assessment of the company's systematic review of evidence**	**36**
Table 7	**Analysis of change in BCVA from baseline to week 52 (FAS)**	**40**
Table 8	**Analysis of secondary endpoints from baseline to week 52 (FAS, LOCF)**	**43**
Table 9	**Analysis of additional endpoints from baseline to week 52 (FAS, LOCF): VISTA and VIVID**	**44**
Table 10	**Meta-analysis – effects estimates by inverse variance fixed and random effects models for BCVA mean change from baseline**	**48**
Table 11	**Meta-analysis – effects estimates by Mantel-Haenszel fixed and random effects models for binary secondary endpoints – risk ratio**	**48**
Table 12	**Risk of bias of trials included in indirect and mixed treatment comparisons**	**52**
Table 13	**Meta-analysis and indirect comparison results for 12 months continuous outcomes**	**57**
Table 14	**Meta-analysis and indirect comparison results for 12 month secondary outcomes – risk ratios**	**58**
Table 15	**Meta-analysis and indirect comparison results for 12 month safety outcomes – risk ratios**	**59**

Table 16	**Meta-analysis and indirect comparison results for 12 month outcomes: aflibercept versus demexathone – risk ratios**	**60**
Table 17	**Network meta-analysis results for aflibercept 2Q8 versus ranibizumab 0.5PRN for 12 month outcomes**	**63**
Table 18	**Network meta-analysis – comparison of ERG and company findings**	**65**
Table 19	**Network meta-analysis – sensitivity analysis carried out by ERG**	**68**
Table 20	**Haig et al (2014) treatment and monitoring**	**72**
Table 21	**NICE reference case checklist**	**73**
Table 22	**Individual eye health states**	**75**
Table 23	**Eyes' baseline distribution between health states**	**76**
Table 24	**Relative risks applied within the model during year 1**	**78**
Table 25	**Monthly transition probabilities applied within the model during year 1**	**78**
Table 26	**Monthly rates of discontinuation and adverse events on treatment**	**79**
Table 27	**VIVID/VISTA EQ-5D OLS regression**	**80**
Table 28	**Bilateral quality of life: VIVID/VISTA EQ-5D OLS**	**81**
Table 29	**BCVA quality of life: value from the literature**	**81**
Table 30	**Bilateral quality of life: Czoski-Murray**	**82**
Table 31	**Bilateral quality of life: Brown 1999**	**82**
Table 32	**Bilateral quality of life: Brown 2000**	**82**
Table 33	**QALY decrements associated with adverse events**	**83**
Table 34	**Treatment and monitoring visits: base case**	**84**
Table 35	**Treatment and dedicated monitoring visits: base case**	**84**
Table 36	**Adverse event costs: company estimates**	**85**
Table 37	**Company base case results aflibercept vs laser: including aflibercept PAS**	**86**
Table 38	**Company base case results aflibercept vs ranibizumab: including aflibercept PAS**	**87**

Table 39	**Base case results: aflibercept versus ranibizumab: ranibizumab PAS discounts**	**88**
Table 40	**One way sensitivity analyses: aflibercept versus laser**	**89**
Table 41	**One way sensitivity analyses: aflibercept versus ranibizumab**	**90**
Table 42	**Sensitivity analyses around the source of utilities: aflibercept versus laser**	**91**
Table 43	**Aflibercept vs dexamethasone: no dexamethasone PAS**	**92**
Table 44	**Aflibercept vs dexamethasone: various dexamethasone PAS**	**92**
Table 45	**Aflibercept vs fluocinolone: all patients: no fluocinolone PAS**	**92**
Table 46	**Aflibercept vs fluocinolone: pseudophakic patients: no fluocinolone PAS**	**93**
Table 47	**Aflibercept vs fluocinolone: pseudophakic patients: various fluocinolone PAS**	**93**
Table 48	**Laser monthly probabilities for all patients and CRT ≥ 400µm subgroup**	**93**
Table 49	**CRT ≥ 400µm subgroup: aflibercept vs laser**	**94**
Table 50	**CRT ≥ 400µm subgroup: aflibercept vs ranibizumab**	**94**
Table 51	**52 week model validation data: mean letters change in BCVA**	**94**
Table 52	**Company deterministic results and ERG cross check rebuild**	**95**
Table 53	**Christ et al mortality hazard ratios: model and alternative interpretations**	**99**
Table 54	**TTO HRQoL by BSE: Brown 1999 and Brown 2000**	**100**
Table 55	**ERG base case dosing**	**102**
Table 56	**Adverse event costs: revised NHS reference costs**	**104**
Table 57	**Relative risk of adverse events applied within the electronic model**	**105**
Table 58	**Treatment and monitoring visits: medical radar**	**106**

Table 59	**Pooled laser arm probabilities between baseline and week 52: all patients**	**107**
Table 60	**Pooled laser arm transitions between baseline and week 52: all patients**	**111**
Table 61	**Pooled laser arm transitions between baseline and week 52: CRT ≥ 400µm**	**112**
Table 62	**Pooled laser arm transitions between baseline and week 52: CRT < 400µm**	**112**
Table 63	**Patient numbers changing by a given number of health states**	**113**
Table 64	**Patient proportions changing by a given number of health states**	**113**
Table 65	**Bilateral distribution for those with DMO FEI at baseline: patient numbers**	**114**
Table 66	**Bilateral distribution for those without DMO FEI at baseline: patient numbers**	**114**
Table 67	**Bilateral distribution for those with DMO FEI at baseline: percentages**	**115**
Table 68	**Bilateral distribution for those without DMO FEI at baseline: percentages**	**115**
Table 69	**Pooled bilateral distribution and percentage FEI at baseline**	**116**
Table 70	**Additional VIVD/VISTA EQ-5D models**	**119**
Table 71	**Bilateral quality of life: VIVID/VISTA EQ-5D random effects**	**120**
Table 72	**Bilateral quality of life: VIVID/VISTA EQ-5D GEE**	**120**
Table 73	**ERG base case results aflibercept vs laser: including aflibercept PAS**	**126**
Table 74	**ERG base case results aflibercept vs ranibizumab: including aflibercept PAS**	**126**
Table 75	**ERG base case results: aflibercept versus ranibizumab: ranibizumab PAS discounts**	**127**

Table 76	**ERG sensitivity analyses: aflibercept vs laser - including aflibercept PAS**	**128**
Table 77	**ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 5% to 20%**	**131**
Table 78	**ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 25% to 40%**	**132**
Table 79	**ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 45% to 60%**	**133**
Table 80	**ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 65% to 80%**	**134**
Table 81	**ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 85% to 100%**	**135**

List of figures

Figure 1	**Mean change from baseline in BCVA in ETDRS letter score at week 52 for the integrated analysis of VISTA and VIVID (FAS, LOCF), source Figure 9, CS.**	**41**
Figure 2	**Available network at 12 months (Source Figure 18, company submission)**	**61**

List of abbreviations

aLOCF	Additional last observation carried forward (missing data were imputed using LOCF but data obtained after initiating additional treatment were retained)
aOC	Additional observed case (all observed values were used for analysis, including measurements taken after initiating additional treatment)
AE	Adverse event
AIC	Academic in confidence
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BNF	British national formulary
BSE	Best seeing eye
CFT	Central foveal thickness
CI	Confidence interval
CIC	Commercial in confidence
CMT	Central macular thickness
CNV	Choroidal neovascularization
CRD	(York) Centre for reviews and dissemination
CrI	Credible interval
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CS	Company's submission
CSMO	Clinically significant macular oedema
CVA	Cerebrovascular accident
DMO	Diabetic macular oedema
DRSS	Diabetic Retinopathy Severity Scale
EMA	European Medicines Agency
EQ-5D	Euroqol 5 dimensions
ERG	Evidence review group
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAS	Full analysis set
FCE	Finished consultant episode
FCT	Foveal centre thickness

FEI	Fellow eye involvement
GEE	Generalised estimating equation
HRQoL	Health-related quality of life
HS	Health state
HUI3	Health utilities index mark 3
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure
ITC	Indirect treatment comparison
IV	Inverse variance
IVB	Intravitreal bevacizumab
IVR	Intravitreal ranibizumab
LOCF	Last observation carried forward
M-H	Mantel-Haenszel
MTA	Multiple technology appraisal
MTC	Multiple treatment comparison
NEI VFQ-25	National eye institute visual functioning questionnaire - 25
NHB	Net health benefit
NHS	National Health Service
NHIS	National health interview survey
NICE	National Institute for health and Care Excellence
NMA	Network meta-analysis
NPDR	Non-proliferative diabetic retinopathy
OC	Observed case analysis (only observed, non-censored values were used for analysis)
OCT	Ocular coherence tomography
OLS	Ordinary least squares
OP	Outpatient
OR	Odds ratio
PAS	Patient access scheme
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy
PPS	Per protocol set
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRN	Pro re nata

PSS	Personal social services
PSSRU	Personal social service research unit
QALY	Quality adjusted life year
QoL	Quality of life
RPE	Retinal pigment epithelial/epithelium
RCT	Randomised controlled trial
RR	Risk ratio
SAF	Safety set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Structured event equation model
SG	Standard gamble
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TPM	Transition probability matrix
TTO	Time trade off
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WESDR	Wisconsin epidemiologic study of diabetic retinopathy
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health
WSE	Worse seeing eye
WTP	Willingness to pay

1 SUMMARY

1.1 Scope of the submission

The company's submission from Bayer Pharma addressed the use of aflibercept solution for injection, within its licensed indication, for the treatment of diabetic macular oedema (DMO) in adults. Aflibercept solution gained marketing authorisation in the UK for the treatment of DMO in August 2014. It is also licensed in the UK for the treatment of adults with neovascular wet age-related macular degeneration and macular oedema secondary to central retinal vein occlusion.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company consists primarily of two phase-three RCTs, VISTA and VIVID, which compared aflibercept with laser photocoagulation therapy for DMO. Comparisons were made between aflibercept 2Q4 (2mg every four weeks) and laser, and between aflibercept 2Q8 (2mg every eight weeks) and laser. This report focuses primarily on the aflibercept 2Q8 results, which reflect current license indication. The primary endpoint of mean change from baseline in BCVA was measured at 52 weeks, with preliminary, academic in confidence, data available at 100 weeks. The company provided also data from two RCTs, RESTORE and REVEAL, comparing ranibizumab, a licensed anti-VEGF agent for DMO, with laser photocoagulation therapy. In addition, results of a network meta-analysis, which included a total of 11 studies, were provided to assess the effects of aflibercept versus ranibizumab and aflibercept versus dexamethasone.

The results of VIVD and VISTA indicated that aflibercept had more significant visual improvements over laser photocoagulation therapy. There was a 10.5 (95% CI 7.7 to 13.2) increase in mean change from baseline in BCVA within participants receiving aflibercept in VISTA and a 9.1 (95% CI 6.4 to 11.8) letter change within participants receiving aflibercept in VIVID. A higher proportion of patients gained ≥ 15 letters over 12 months in the aflibercept 2Q8 arm compared with laser (23.3; 95% CI 13.5 to 33.1 in VISTA; 24.2 95% CI 13.5 to 34.9 in VIVID). Improvements were maintained through week 100. There were no significant differences in the incidence of ocular or non-ocular TEAEs between aflibercept and laser therapy. A greater number of deaths,

but not significantly greater, was observed among participants treated with aflibercept (5 deaths) than laser (0 deaths).

The network meta-analysis showed that, compared to ranibizumab, aflibercept significantly improved the mean change from baseline in BCVA. No significant differences were observed between aflibercept and ranibizumab in other visual acuity otucomes (gain of ≥10 letters, gain of ≥15 letters, loss of ≥10, and loss of ≥15 letters). Aflibercept was significantly more effective than dexamethasone for the outcome 'gain of ≥10 letters'. A comparison of aflibercept with fluocinolone was not possible due to lack of a common comparator to allow indirect analysis.

SUPERSEDED BY ERRATUM

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company's submission appears to be complete in that it included the two main trials comparing aflibercept with laser. No head-to-head trials were available for the comparison between aflibercept and ranibizumab. The company did include bevacizumab as a comparator event though it was listed in the NICE final scope. The company presented data from VIVID and VISTA separately as well as directly pooled together (integrated analyses). The ERG were concerned at the direct pooling of results due to significant differences between trials at baseline in central retinal thickness and in the proportion of patients who received previous anti-VEGF treatments. A meta-analysis of VIVID and VISTA results was undertaken, followed by a network meta-analysis of studies involving laser and ranibizumab as well as dexamethasone and laser.

The company presented both fixed and random effects estimates for the network meta-analysis. The ERG were concerned by the fixed effect results and were unable to replicate them. This could be due to an error in the model code, or because of the process of running the model. The company did not provide information on initial values used, number of iterations for burn-in, number of updated samples and whether a thinning parameter was used. Despite this, the ERG were able to reasonably replicate the random effects models, which were used to populate the economic model and therefore regarded as more relevant for the purpose of the submission.

1.4 Summary of cost-effectiveness submitted evidence by the company

A de novo Markov model with a monthly cycle was developed by the company. This is a bilateral vision model with each eye falling in one of eight mutually exclusive visual acuity health states defined by the 10 ETDRS letters read. The model features a total of 64 possible health states and one absorbing health state representing death. Patients enter the model having at least one eye being treated for DMO. Of these patients 46.5% are assumed to be bilateral at baseline. An additional 10% of the remainder develop fellow eye DMO involvement at the start of years 2, 3, 4 and 5. It is assumed that 50% of the fellow eyes with DMO at baseline will be treated at baseline, and that 50% of incident fellow eye DMO will be treated at incidence. The other 50% of fellow eyes with DMO are assumed not to be treated.

For eyes that are treated there is an initial efficacy phase of one year followed by a maintenance phase of 4 years. Treatments are associated with a treatment specific discontinuation rate during the first 5 years of treatment. After five years all treatment stops.

The clinical effectiveness estimates for the efficacy phase are based upon applying the relative risks of the network meta-analysis to the rates of improving and worsening by at least two health states and by one health state in the pooled VIVID/VISTA laser arm.

During the four year maintenance phase treatment is assumed to continue. Eyes that remain on treatment retain stable vision.

When treatment stops, due to either discontinuation or the end of the maintenance phase, the eye is subject to a monthly 1.15% probability of deteriorating by one health state. This is based upon the 3-month 3.5% rate of deterioration used within the TA274 ranibizumab for DMO.

Non-DMO eyes are subject to a monthly 0.17% probability of deteriorating by one health state.

Quality of life values for the base case are drawn from the Czoski-Murray (2009) paper, which reported the time trade off values from an experimental study in which members of the general public had their BCVA reduced over the course of an hour through wearing contact lenses. A bilateral quality of life function derived from the VIVID/VISTA EQ-5D data is used for a sensitivity analysis.

The number of treatment administrations and monitoring visits are shown in Table 1. It is assumed that all treatment visits can double as monitoring visits.

Table 1 Base case numbers of treatments and monitoring visits

	Administrations					Monitoring visits				
	Afli.	Rani.	Dexa.	Fluo.	Laser	Afli.	Rani.	Dexa.	Fluo.	Laser
Year 1	8.00	7.93	3.00	1.00	2.40	8.00	12.00	5.00	4.00	4.00
Year 2	4.00	4.00	2.00	0.00	1.00	6.30	6.30	4.00	4.00	4.00
Year 3	2.30	2.30	2.00	1.00	0.80	4.00	4.00	4.00	4.00	2.60
Year 4	1.20	1.20	0.00	0.00	0.40	4.00	4.00	4.00	4.00	2.20
Year 5	1.00	1.00	0.00	0.00	0.30	2.00	2.00	4.00	4.00	1.90

The £816 list price of aflibercept has a PAS of [redacted] resulting in a with PAS price of [redacted]. Ranibizumab is associated with a list price of £742, dexamethasone with a list price of £870 and fluocinolone with a list price of £5,500, all these being drawn from the BNF. Sensitivity analyses for ranibizumab PAS percentages from 5% to 100% in 5% increments are presented.

Administration costs of £194 are applied to aflibercept, ranibizumab and fluocinolone, based upon the TA283 aflibercept for CRVO. Dexamethasone is associated with a higher administration cost of £218, though the source for this is not given. Laser is associated with a total cost per administration of £256.

For the base case comparison with laser, aflibercept is estimated to result in an additional 0.390 QALYs and to save £2,438, and so to dominate laser. The cost savings arise mainly due to a £13,046 offset in the costs of blindness. Sensitivity analyses do not change the conclusion of dominance, but the QALY gains are sensitive to the source of the quality of life data.

For the base case comparison with ranibizumab, aflibercept is estimated to result in an additional 0.092 QALYs. With no ranibizumab PAS aflibercept is estimated to save £8,911 and so to dominate ranibizumab. Aflibercept ceases to be cost saving with a ranibizumab PAS of 65%. For a ranibizumab PAS of 75% aflibercept is estimated to have a cost-effectiveness of £22,103 per QALY gained, while for a ranibizumab PAS of 80% aflibercept is estimated to have a cost-effectiveness of £30,043 per QALY gained.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

There is always uncertainty as to how well trials' results transfer to clinical practice. One concern is that often patients seen in ophthalmic clinical practice have worse control of their HbA1c than the average participants enrolled in clinical trials.

There are general concerns with the modelling approach that has been adopted. The model developed by the company makes a number of implicit assumptions that are not necessarily justified:

- The likelihood of a letters gain (loss) is the same regardless of the health state the treated eye is in.
- It is appropriate to infer monthly probabilities from annual probabilities in a manner analogous to compounding interest rates.
- The monthly rates of gain (loss) are constant over the first year.
- It is appropriate to apply 12 month relative risks to monthly quantities.
- It is appropriate to apply the relative risks of improving by 10 or more letters to the probability of improving by 10 letters.

These concerns may be part of the reason why the modelled results after one year show a relatively poor correspondence with the pooled VIVID/VISTA results. This suggests that the model underestimates the benefit from aflibercept over laser.

The company submission assumptions around dosing for both aflibercept and ranibizumab are not in line with those suggested by the trials' data, and the aflibercept dosing in year 1 also appears to be slightly out of line with the SmPC. The trials also appear to suggest a higher dosing rate for aflibercept than for ranibizumab in the

second year. It is possible that this is more a reflection of the differences between the trials than any difference that will apply in the real world.

The ranibizumab SmPC has been recently revised to permit a monitoring schedule in the first year that is more flexible and is more in line with that of aflibercept. In the short to medium term the number of ranibizumab monitoring visits in the first year may tend to converge with that of aflibercept.

Results are sensitive to the source of quality of life values. The NICE guide to the methods of technology appraisal suggests that the EQ-5D values should be preferred for the base case. These greatly reduce the anticipated QALY gains from aflibercept. But previous assessments of treatments for eye diseases have frequently relied upon the values of Czoski-Murray and Brown. There may be an argument for using these for the base case if comparability of results with those of previous assessments is required.

The analysis for the CRT ≥ 400μm subgroup only changes the probabilities of improving and worsening within the laser arm. The relative risks of the NMA are retained. But the point estimates of the integrated VIVID/VISTA results may suggest a smaller gain for those with a CRT < 400μm than for those with a CRT ≥ 400μm. This is hampered by the relatively small number of patients with a CRT < 400μm. It may not be possible to perform a NMA for the CRT ≥ 400μm subgroup. The company, however, has the VIVID/VISTA data for the comparison of aflibercept with laser for the CRT ≥ 400μm subgroup. It may be difficult to make formal estimates of the cost-effectiveness of aflibercept versus laser for the CRT < 400μm, but some inference might be possible from the all-patient analysis if combined with a CRT ≥ 400μm subgroup analysis.

The model has the facility to base the analysis upon the 4 weekly TPMs of the VIVID/VISTA trial. This modelling may be a sounder basis for the comparison of aflibercept with laser, and at a minimum it would seem sensible to present this as structural sensitivity analysis. The ERG has not examined this aspect of the model.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The report was written in a clear manner and included relevant studies to address the objectives of this assessment.

The clinical effectiveness methods were appropriate.

The company submitted a genuinely bilateral economic model to assess the cost-effectiveness of aflibercept in patients with DMO in the UK.

This included an analysis of the VIVD/VISTA EQ-5D quality of life data that explicitly modelled bilateral vision. This is a major step forward compared to a number of other NICE STAs assessing various treatments for eye diseases.

1.6.2 Weaknesses and areas of uncertainty

The ERG has a number of concerns about the model structure and possible errors within it. The ERG revisions to the mode, which aim to address these concerns, are outlined in more detail in section 5.4.

In brief, the model structure does not take into account the impact of discontinuations upon the mean number of doses each year. This suggests that the model may underestimate the costs of treatment by around 5%.

While the company applies the 3-monthly 3.5% rate of worsening of the TA274 ranibizumab for DMO, which is off treatment, does not apply the corresponding 3-monthly 2.5% rate of improvement.

The mortality multiplier for DMO remains uncertain, but the most appropriate value for the base case would seem to be that used in TA274 ranibizumab for DMO.

There may be a major error in the handling of the costs of blindness. This is at the root of the company estimating aflibercept to dominate laser, while the ERG estimates suggest it may not be cost effective compared with laser.

The ERG has not been able to run the company model probabilistically.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Clinical effectiveness analysis

The ERG were concerned that the company did not include REVEAL for the mortality meta-analysis when the relevant data were available. The company presented the fixed effects result for RESTORE only (ranibizumab versus laser) as risk ratio of 0.96 (95% CI 0.14 to 6.67). The ERG repeated the analyses including both RESTORE and REVEAL mortality data and obtained a risk ratio of 1.34 (95% CI 0.27 to 6.72). The company did not undertake an indirect comparison to obtain an estimate for aflibercept versus ranibizumab but the ERG did so and obtained a risk ratio of 1.77 (95% CI 0.07 to 44.24) using RESTORE only and of 1.32 (95% CI 0.06 to 28.06) using RESTORE and REVEAL in combination with VISTA and VIVID.

With regard to the NMA, the ERG undertook sensitivity analyses by excluding VISTA, excluding REVEAL and excluding both VISTA and REVEAL. In each case there was some change in the point estimates of aflibercept versus ranibizumab and the 95% credible intervals tended to be wider, but in each case no difference between aflibercept and ranibizumab was found.

Cost-effectiveness analysis

For the comparison of aflibercept with laser the base case suggests a gain of 0.381 QALYs, a net cost inclusive of the aflibercept PAS of £12,931 and a cost-effectiveness estimate of £33,921 per QALY gained.

Results are sensitive to the source of the quality of life estimates. Using the VIVID/VISTA EQ-5D data worsens the cost-effectiveness estimate to £117,222 for the ERG preferred GEE analysis. The Brown 1999 quality of life values worsen the cost-effectiveness estimate to £45,024 per QALY gained, while those of Brown 2000 improve it to £29,915 per QALY gained.

Reducing the proportion of treatment visits that double as monitoring visits to 50% worsens the cost-effectiveness estimate to £36,117 per QALY gained. Removing the blindness mortality multiplier when one eye falls into blindness has a similar effect, revising the cost-effectiveness estimate to £36,063 per QALY gained.

With no ranibizumab PAS it is estimated that aflibercept results in cost savings of £4,390 and a 0.091 QALY gain, so dominates ranibizumab. A ranibizumab PAS of 25% causes the cost savings to turn into additional costs of £195. A ranibizumab PAS of 35% results in a cost-effectiveness estimate of £22,224 per QALY gained, while a ranibizumab PAS of 40% results in a cost-effectiveness estimate of £32,269 per QALY gained.

The pattern of sensitivities is similar to those for the comparison of aflibercept with laser, but for the comparison of aflibercept with ranibizumab the inclusion and exclusion of studies from the NMA has a more noticeable effect. Excluding VISTA from the NMA causes the gain from aflibercept to fall to 0.073 QALYs. A ranibizumab PAS of 35% results in a cost-effectiveness estimate of £29,205 per QALY gained. Excluding the REVEAL trial from the NMA causes the gain from aflibercept to rise to 0.152 QALYs. A ranibizumab PAS of 45% results in a cost-effectiveness estimate of £29,320 per QALY gained.

Applying the VIVID/VISTA EQ-5D quality of life estimates greatly reduces the anticipated gains. Using the VIVID/VISTA EQ-5D data and the GEE analysis causes the gain from aflibercept to fall to only 0.008 QALYs. A ranibizumab PAS of 25% results in a cost-effectiveness estimate of £24,195 per QALY gained, while a ranibizumab PAS of 30% results in a cost-effectiveness estimate of £138,058 per QALY gained.

2 BACKGROUND

Diabetes mellitus is one of the most common chronic diseases worldwide, with numbers rising due to the decrease in physical activity and increase in obesity inherent in contemporary lifestyles.[1,2] The world prevalence of diabetes in 2013 was estimated to be 382 million people[3] (International Diabetes Federation; with an estimate of 439 million adults (7.7%) by 2030.[2]

Diabetes is one of the principal causes of blindness in people of working age in industrialised countries.[4] Diabetes causes both neuroretinal dysfunction and retinal vascular damage, known as diabetic retinopathy,[4] the commonest and most serious ocular complication associated with diabetes.[5] In 2010, there were around 748,000 people in England with early signs of diabetic retinopathy and a further 85,000 people with more advanced retinopathy (i.e. non-proliferative or proliferative retinopathy). The number of people with early signs of diabetic retinopathy in England is expected to increase to 938,000 people by 2020.[6]

Diabetic macular oedema (DMO) is a complication of type 1 and type 2 diabetes.[7] DMO is more prevalent in type 2 disease[8] and proliferative diabetic retinopathy (PDR) is more common in type 1 diabetes. A recent meta-analysis of individual patient data showed similar worldwide prevalence of DMO and PDR.[9] DMO involves swelling of the retina in the vicinity of, or incorporating, the centre of the macula[1,4] and arises from capillaries in the eye becoming abnormally permeable and leaking fluid into the retina.[7] Diabetic macular oedema impacts heavily upon quality of life and affects reading, driving and various other aspects of daily life.[10]

Diabetic macular oedema is responsible for around three-quarters of vision loss related to diabetes.[4] In England in 2010, an estimated 7% of people over 12 years of age with diabetes had DMO in at least one eye; of these, around 4% had clinically significant disease with visual acuity poorer than 6/6.[11]

Diabetic macular oedema is commonly classed as focal DMO or diffuse DMO[12] but definitions of these terms are not clear and their use across the literature is inconsistent. In any case, evidence that the putative underlying characteristics of these

terms explain differences in visual acuity or response to treatment is lacking. The question remains, therefore, whether conceptualising DMO as focal or diffuse is clinically useful.[13]

Clinically significant macular oedema (CSMO) is a potentially blinding complication of diabetic retinopathy that can develop at any stage of the disease. It is characterised by the presence of one or more of the following, as determined by slit-lamp biomicroscopy: "retinal thickening within 500 μm from centre of macula; hard exudates within 500 μm from centre of macula if associated with adjacent retinal thickening; retinal thickening of more than one optic disc area within one optic disc diameter from centre of macula".[5] The ETDRS demonstrated that eyes with clinically significant macular oedema benefited from focal or grid laser treatment.[14] Although the definition of CSMO has been widely used, it has been somewhat superseded by that of central involvement DMO, which emerged with the advent of optical coherence tomography (OCT) and is widely used in the context of anti-VEGF therapy. OCT allows retinal thickness to be assessed precisely and is able to detect structural changes,[5] not always observed by slit-lamp biomicroscopy, thereby allowing diagnosis of sub-clinical DMO.[15-17]

A number of risk factors for DMO have been identified. Strong risk factors are hyperglycaemia, hypertension (both modifiable factors) and diabetes duration (non-modifiable). Further modifiable risk factors are dislipidaemia, nephropathy and anaemia. Further non-modifiable risk factors include duration of diabetes, puberty, pregnancy and ethnicity.[8,10,18]

Laser photocoagulation has been the cornerstone of DMO treatment since publication of the Early Treatment of Diabetic Retinopathy study (ETDRS) in 1985, which showed around a 50% reduction in risk of losing 15 letters after 3 years.[14] However, evidence has since emerged that not all cases of DMO responded to laser treatment[19] and indeed some people experience advancing vision loss despite laser treatment.[20] In addition, standard laser treatment can cause collateral neuroretinal damage, resulting in reduced contrast sensitivity and retinal sensitivity.[21] New laser treatment strategies and new laser modalities have, however, reduced the risks of laser treatment. Small randomised controlled trials have recently demonstrated the safety (i.e. lack of an

effect in the retinal pigment epithelium demonstrated by fundus autofluorescence imaging and improved retinal sensitivity determined by microperimetry) following micropulse subthreshold laser.[22,23]

Intravitreal corticosteroids have more recently been used to treat DMO.[1,24] due to their anti-inflammatory, angiostatic and antipermeability properties.[25] These include Triamcinolone acetonide (Kenalog, Bristol-Myers Squibb; not licensed in the UK for treating DMO), Fluocinolone acetonide (Iluvien, Alimera Sciences; UK marketing authorisation for treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies; recommended by NICE, TA271, for people who are pseudophakic and unresponsive to other treatment) and Dexamethasone (Ozurdex, Allergan Ltd; UK marketing authorisation for visual impairment due to DMO in people who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy; currently under review by NICE).

Vascular endothelial growth factor (VEGF) is involved in the pathogenesis of DMO,[15,18,26] with VEGF-A playing a particular role.[15,26] Since 2006, anti-VEGF treatments for DMO have been investigated due to the action of VEGF in DMO and retinal neovascularisation[1] and have revolutionised the treatment of people with DMO.[25] A recent systematic review of anti-VEGF and laser treatment for DMO showed that between 37.4% and 60.8% of participants treated with ranibizumab or aflibercept gained at least 10 letters from baseline at 12 months.[27] Therefore, a proportion of people do not respond to anti-VEGF treatments. In addition, anti-VEGF treatments require multiple injections (for example, mean 9 injections in the DRCR.net study)[28] and there is a risk of potentially devastating consequences, for example, endophthalmitis, although these are rare.[24] Anti-VEGF treatments currently in use worldwide are ranibizumab, aflibercept and pegaptanib.[20] Bevacizumab was used off-label in the UK for years but its use in treating DMO has essentially ceased following the licensing of ranibizumab in 2013 for this indication (TA274).

Ranibizumab (Lucentis, Novartis, UK) inhibits the action of VEGF, thereby leading to regression of the DMO. Ranibizumab has UK marketing authorisation for the treatment of visual impairment due to DMO, neovascular (wet) age-related macular

degeneration, visual impairment due to macular oedema secondary to retinal vein occlusion and visual impairment due to choroidal neovascularisation secondary to pathological myopia.

Aflibercept (Eylea, Bayer PLC, UK) is an engineered protein that blocks VEGF-A, thereby reducing the growth of blood vessels and controlling any leakage and swelling.[29] Aflibercept has UK marketing authorisation for neovascular wet age-related macular degeneration, visual impairment due to macular oedema secondary to central retinal vein occlusion, and visual impairment due to DMO.

Pegaptanib (Macugen, Pfizer Limited, UK) is a ribonucleic acid aptamer that binds to the major pathological VEGF protein in the eye.[25] Pegaptanib has UK marketing authorisation for treatment of neovascular wet age-related macular degeneration in adults but is explicitly not recommended by NICE for that indication (TA155).[30]

Bevacizumab (Avastin, Roche Products Limited, UK) is an inexpensive, full-length monoclonal antibody that binds and inhibits all isoforms of anti-VEGF A. It is currently unlicensed for all eye conditions but has been used off-label in the NHS for the treatment of age related macular degeneration (AMD), neovascular glaucoma, exudative AMD, and macular oedema. To the best knowledge of the ERG, bevacizumab is not currently used for the treatment of AMD, exudative AMD, or macular oedema related to either retinal vein occlusion (RVO) or DMO since ranibizumab is now available in the NHS for these clinical indications.

All four anti-VEGF treatments are administered as injections into the vitreous cavity (the space in the centre of the eye), so called “intravitreal injections”.

2.1 Critique of company’s description of underlying health problem

The company’s description of visual impairment due to DMO appears to be, on the whole, accurate, but the ERG has identified some inaccuracies therein. For example, the ERG disagrees with the company’s statement that “laser treatment has limited effect on improving vision” (company’s submission, page 9). In the DRCR.net trial, 28% of participants in the sham + prompt laser treatment group showed improvement of visual acuity of 10 or more letters at one year follow-up, with 15% of these

showing an improvement of at least 15 letters. Furthermore, 32% of participants met the "success criteria" (i.e. visual acuity score of >84 ETDRS letters or OCT central subfield <250 microns).[28] In addition, the proportion of participants in the laser groups of VISTA and VIVID who gained at least 10 letters were 19.5% and 25.8%, respectively, at one year. Thus, there is a group of patients that do respond to laser treatment.

The ERG questions the statement that aflibercept *"is a potent specific inhibitor of VEGF that interferes with the growth of new blood vessels that leads to retinal oedema, ischaemia and haemorrhage in diseases of ocular neovascularization"* (company's submission, page 13, section 1.2). The ERG maintains that DMO is caused by increased vascular leakage rather than growth of new blood vessels. The company's statement that *"Eventually the leaking fluid can cause swelling and scar tissue on the macula and permanent loss of central vision"* (company's submission, page 19, section 2.1) is disputed by the ERG. Retinal scarring is not a main feature of DMO and retinal atrophy, not retinal scarring, may result from untreated fluid.

The company stated that *"More modern laser machines are available (PASCAL, NAVILAS) but require capital investment, maintenance, and additional training. Even so, expert opinion indicates that there remain practical issues, such as positioning the patient appropriately and the additional time that is required for this"* (company's submission, page 23, section 2.6). The ERG considers that there is no strong evidence from RCTs showing the superiority of these laser techniques over any others. The ERG clinical adviser (an ophthalmologist with expertise in diabetic retinopathy and who deals with DMO patients regularly) considers that it takes seconds for an individual to be positioned in the slit-lamp prior to laser treatment, certainly not longer than it takes to be position a patient on a couch, flat, for an intravitreal injection. It worth noting that the latter also requires the eye to be cleaned with a disinfectant at least 5 minutes before the injection, drapes are usually placed to keep the area clean, a speculum inserted in the eye to prevent blinking and then anaesthesia given. It is the ERG's opinion that the combined time for all these processes required prior to an intravitreal injection is likely to exceed the preparation time for laser photocoagulation therapy.

2.2 Critique of company's overview of current service provision

The company identified that there are currently two sets of NICE guidelines for treating DMO:

TA274[15] Ranibizumab for treating DMO (rapid review of technology appraisal guidance 237), April 2013:

- 1.1 Ranibizumab is recommended as an option for treating visual impairment due to DMO only if:
    - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
    - the company provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.
- 1.2 People currently receiving ranibizumab for treating visual impairment due to DMO whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

TA301[31] Fluocinolone acetonide intravitreal implant for treating chronic DMO after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271), November 2013:

- 1.1 Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic DMO that is insufficiently responsive to available therapies only if:
    - the implant is to be used in an eye with an intraocular (pseudophakic) lens and
    - the company provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme.

The company acknowledged that the recent granting of UK marketing authorisation for dexamethasone (for treatment of adults with visual impairment due to DMO who are pseudophakic or are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy) may result in change of routine practice in the NHS. The company also acknowledged the off-label use of bevacizumab for the relevant indication. However, they did not include bevacizumab as a comparator, contrary to the final scope issued by NICE.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

3.1 Population

The company's submission states that aflibercept is indicated for treating adults with visual impairment due to diabetic macular oedema (DMO). This population is in line with the NICE final scope for this assessment and the licensed indication for aflibercept.

3.2 Intervention

Aflibercept is a soluble decoy receptor formed by fusing protein of portions of human VEGF receptor 1 and 2 extracellular domains and the Fc portion of human IgG1. It has a longer half-life in the eye than ranibizumab or bevacizumab and a higher binding affinity to VEGF-A, as well as other VEGF variants, including placental growth factors 1 and 2.[25,32] These features mean that aflibercept can inhibit the binding and activation of these related VEGF receptors.[32]

Aflibercept is formulated as a solution for intravitreal injection. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept, providing a usable amount for a single dose of 50 microlitres containing 2 mg aflibercept (SPC). For treating DMO, the recommended dose of aflibercept is 2 mg, equivalent to 50 microlitres. Treatment commences with one injection per month for five consecutive doses, then one injection every two months. Monitoring between injections is not required. After the first 12 months treatment, the treatment interval may be extended, depending on visual and anatomical outcomes. If these outcomes indicate no benefit from continued treatment, aflibercept should be discontinued. A schedule for monitoring after the first year of treatment should be decided by the treating clinician (SPC).

Aflibercept has regulatory approval in the UK, Europe, and USA for the treatment of visual impairment due to DMO in adults.

3.3 Comparators

The comparators specified in the NICE scope for this assessment are laser photocoagulation alone as well as the following technologies alone or in combination with laser photocoagulation: ranibizumab, corticosteroids (including fluocinolone

acetonide intravitreal implant and dexamethasone) and bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable). The company's submission differs from the scope in that bevacizumab was not considered as a comparator. The company argued that bevacizumab is an unlicensed treatment for treating visual impairment due to DMO and has not been appraised by NICE. As such, it was used to treat DMO in the period before ranibizumab and fluocinolone were licensed (TA274 and TA301, respectively).[15,31] The company drew a comparison with the situation with AMD treatment, in which the use of bevacizumab decreased following NICE guidance recommending ranibizumab. They maintained that the clinical use of bevacizumab for DMO will also decline in light of the two currently licensed treatments and, therefore, they chose not to consider bevacizumab as routine or best practice in the NHS for the treatment of DMO.

The company further noted that bevacizumab was not used as a comparator in the cost-effectiveness analysis for either of the two NICE guidance documents (TA274 and TA301).[15,31] NICE guidance TA274 (ranibizumab for treating DMO) states that information about the balance and harms associated with bevacizumab was not readily available for people with DMO and, therefore, they were not able to investigate a comparison between ranibizumab and bevacizumab. However, they further suggested that research directly comparing the clinical and cost-effectiveness of ranibizumab versus bevacizumab in people with DMO would reduce some of these uncertainties (NICE TA274, page 51).

Literature searches of MEDLINE and EMBASE performed by the ERG showed that a number of studies involving bevacizumab versus laser therapy for people with DMO have been conducted (see Appendix 1 for further details). Dosage of bevacizumab intravitreal injections was 1.25mg for the majority of the identified studies (dosage was not clearly reported in two trials: Mansourian 2011[33] and Zhang 2013[34]). It is worth noting that the DRCR.net 2007 trial also included a 2.5mg bevacizumab arm.[35]

3.4 Outcomes

The outcomes considered by the company were best corrected visual acuity (BCVA) in affected eye and both eyes, central retinal thickness, mortality, need for cataract surgery, adverse effects of treatment and health-related quality of life (HRQoL),

including effects of changes in visual acuity. The company considered central foveal subfield thickness (as stated in the NICE final scope) in terms of thickness of the central 1mm of the retina. The company did not consider central contrast sensitivity, which was in the final scope for this assessment issued by NICE. The company explained that the outcomes in the final scope had been amended, following the pre-invitation (post-workshop) scope, without further consultation and that they considered some outcomes (e.g. cataract-related) to be more appropriate for appraising corticosteroids. The company further stated that the two RCTs central to the submission, VIVID and VISTA, included change in central retinal thickness as a secondary outcome and that contrast sensitivity was not measured.

3.5 Other relevant factors

Table 2 summarises the differences between the NICE final scope and the decision problem addressed by the company.

Table 2 Comparison of NICE final scope and decision problem addressed by company

	Final scope issued by NICE	Decision problem addressed in the submission
Population	• People with visual impairment because of diabetic macular oedema	• Adults with visual impairment due to diabetic macular oedema
Intervention	• Aflibercept	• Aflibercept
Comparator(s)	• Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: • Ranibizumab • Corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone) • Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable)	• **Laser photocoagulation alone** **The following technologies alone or in combination with laser photocoagulation:** • **Ranibizumab** • **Corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone)**
Outcomes	• Best corrected visual acuity (affected eye) • Best corrected visual acuity (both eyes) • Central foveal subfield thickness • Contrast sensitivity • Mortality • Need for cataract surgery • Adverse effects of treatment, including cataract formation and	• Best corrected visual acuity (affected eye) • Best corrected visual acuity (both eyes) • **Central retinal thickness** • Mortality • Need for cataract surgery • Adverse effects of treatment

	glaucoma • Health-related quality of life, including the effects of changes in visual acuity	• Health-related quality of life, including the effects of changes in visual acuity
Economic analysis	• Incremental cost per quality-adjusted life year • Time horizon should be sufficiently long to reflect differences in costs or outcomes between technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • Availability of any patient access schemes for the intervention or comparator technologies should be taken into account • Cost-effectiveness analysis should include consideration of the benefit in the best and worst seeing eye	• Incremental cost per quality-adjusted life year • **Lifetime horizon** • Costs were considered from an NHS and Personal Social Services perspective • Patient access schemes for aflibercept, ranibizumab, and fluocinolone acetonide intravitreal implant were taken into account

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company states that literature searches were undertaken in October 2013and updated in August 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, PubMed and CENTRAL as well as the major clinical trials registers and relevant conference proceedings for the last six years. Full details of the search strategies are included in Appendix 10.2 of the company's submission and are reproducible.

The searches were designed to identify all trials for diabetic retinal disease without specifying aflibercept or any of the relevant comparators. As such the search was very broad and therefore would be expected to be highly sensitive. The search strategies followed the same structure: a combination of the search facets *Diabetes Mellitus* with *Macular Degeneration* or *Macular Oedema* and then addition of the *Diabetic Retinopathy* facet using the Boolean operator OR. Appropriate RCT filters were used in MEDLINE and EMBASE. Specific additional searches for adverse events were not undertaken.

There is some concern, however, that only "oedema" was used throughout the searches and not the most commonly used spelling 'edema". In MEDLINE, the correct MeSH is "Macular Edema"/. However, the company's search used "Macular Oedema". This term returned 0 hits when replicated by the ERG. Nevertheless, the submission indicates that 4542 hits were returned in the initial MEDLINE search and it is unclear how this was achieved. In EMBASE the incorrect term was again used but was automatically mapped to the correct term. This error was also applied to the text word searching throughout the searches in all databases and conference abstract searches. This error could have affected the sensitivity of the search. However, apart for this error, a comprehensive list of search terms and combinations were used and, to some extent, may have compensated for this omission.

4.1.2 Inclusion criteria

The inclusion criteria used in the company's systematic review of clinical effectiveness are presented in Table 3.

Table 3 Inclusion criteria used in systematic review of clinical effectiveness

Population	• Patients with diabetic macular oedema
Intervention	• Eylea (VEGF Trap Eye/Aflibercept/ AFB) • Anti-VEGF treatments (Any including Ranibizumab/Lucentis/ RBZ, bevacizumab/Avastin/BVZ, pegaptanib/macugen) • Intravitreal steroids (Any including Triamcinolone, Fluocinolone [Iluvien], dexamethasone [Ozurdex] and implants) • Laser treatments • NOTE the intervention should be to treat the DMO not to treat cataracts • The above interventions can be included if combined with other treatments (e.g. eye drops) except the exclusions
Comparator	• Placebo, best standard care, masked control, sham, eye drops • Any intervention (from those listed as interventions) • NOTE this can be a single treatment/ implant
Outcomes	• No. injections/treatments • No. visits/assessments • Best corrected visual acuity (BCVA) (Mean change from baseline, mean average change from baseline, as measured by ETDRS score or Snellen equivalent). Visual acuity (% of patients who gain/lose outcome vs. baseline): - loss of ≤ 15 letters in ETDRS score (maintained vision) - loss of ≥ 30 letters ETDRS score (severe vision loss) - loss of ≥ 15 letters ETDRS score (moderate vision loss). - gain of ≥ 15 letters

	- 20/40 vision or better (Snellen chart) - 20/200 or worse (Snellen chart) - Gain ≥ 0 letters - Gain ≥ 10 letters - Gain ≥ 30 letters • Reduction in laser use • Contrast sensitivity • Change in Choroidal neovascularisation (CNV) • Optic disc area • Area of lesion • Size of leakage • Greatest linear dimension • Fluid on OCT • Presence of dye leakage • Eyes with dry lesion • Change in total lesion size • Change in central foveal thickness, mean change from baseline • Health-related quality of life (EQ 5D, NEI VFQ-25, other scales) • Treatment discontinuations • Serious adverse effects (all SAE, all ocular SAE, death, endophthalmitis, uveitis, retinal tear, diabetic macular/retinal oedema, reduced visual acuity, vitreous haemorrhage, corneal abrasion, any others) • Adverse events (all AE, all ocular AE, all non-ocular AE, retinal detachment, retinal ischaemia, lens damage, all grades ocular inflammation, eye pain, increased ocular pressure, retinal degradation, macular oedema, cataract, neovascularisation, any others). • Serious non-ocular adverse events (all, non-fatal cardiac infarction, non-fatal stroke, non-ocular haemorrhage,

	hypertension, serious systemic events, arterial thrombotic events, venous thrombotic events).
Study design	• Published and unpublished randomised controlled prospective clinical trials • Dose or frequency comparison trials • Ad-hoc analyses of RCT data • Crossover RCTs
Language restriction	None

It is worth noting that some of the listed outcomes (i.e. change in choroidal neovascularisation; optic disc area; area of lesion; size of leakage; greatest linear dimension; change in total lesion size) seem to relate to other condition (exudative AMD) and not to DMO. Furthermore, *retinal degradation*, in the list of adverse events, does not describe a retinal disease or complication and it is a term not commonly used in current ophthalmic clinical practice.

4.1.3 Identified studies

The company's submission included two RCTs, VISTA and VIVID,[36] comparing aflibercept (2mg every 4 weeks or every 8 weeks after five initial monthly doses) versus focal laser photocoagulation. The two trials (VISTA and VIVID) were conducted by the same investigators and were sponsored by Regeneron Pharmaceutical, Inc,, Tarrytown, NY, United States and Bayer HealthCare, Berlin, Germany. The sponsors participated in the design and conduct of the trials, analysis of the data, and preparation of the written manuscript.

4.1.4 Characteristics of included RCTs

VISTA and VIVID were phase three, double masked, 148-week RCTs conducted in Europe, North America, Japan, and Australia. Participants with centre involvement DMO, based on OCT, were recruited and randomised in a 1:1:1 ratio to 2mg intravitreal aflibercept injection either every 4 weeks (2q4) or every 8 weeks (2q8) after five initial monthly doses with sham injections on non-treatment visits (2q8) or macular laser photocoagulation at baseline and sham injections at every visit (laser

control group). In addition, the two aflibercept groups (2q4 and 2q8) were given sham laser treatment at baseline and at subsequent visits where laser re-treatment criteria were met. Laser re-treatment criteria were applicable when it was expected that the patient would benefit from a further laser treatment and at least one of the following conditions occurred (i.e. clinically significant macular oedema, CSMO, developed): (1) thickening of the retina at, or within, 500µm of the centre of the macula, or (2) hard exudates at, or within, 500µm of the centre of the macula, if associated with thickening of adjacent retina, or (3) zone(s) of retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula. From week 24, where additional treatment criteria were met,

[redacted]

. Additional treatment criteria involved one or both of the following conditions: i) loss of ≥ 15 letters from the previous measurement, but actual BCVA not better than baseline at any study visit, or ii) loss of ≥ 10 letters from the best previous measurement, but actual BCVA not better than baseline at any study visit, confirmed at a consecutive (possibly unscheduled) visit at least seven days later. Table 4 presents the characteristics of the VISTA and VIVID RCTs.

Table 4 Characteristics of the VISTA and VIVID RCTs

	VISTA	VIVID
Study duration	148 weeks	148 weeks
Number of participants randomised	459	403
Country	54 sites in USA	73 sites in Japan, Europe (Austria, Czech Republic, Denmark, France, Germany, Hungary, Poland, Spain), Australia
Intervention & comparator	Intravitreal aflibercept injections (2mg every 4 or 8 weeks) versus macular laser photocoagulation	Intravitreal aflibercept injections (2mg every 4 or 8 weeks) versus macular laser photocoagulation
Inclusion criteria	• Adults ≥ 18 years with type 1 or type 2 diabetes mellitus • DMO secondary to diabetes involving the centre of the macula • Decrease in vision determined to be primarily the result of DMO in the study eye • BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye • Willing and able to comply with	• Adults ≥ 18 years with type 1 or type 2 diabetes mellitus • DMO secondary to diabetes involving the centre of the macula • Decrease in vision determined to be primarily the result of DMO in the study eye • BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye • Retinal thickness of ≥ 300μm as

	clinic visits and study-related procedures [redacted]	assessed by OCT in the study eye • Willing and able to comply with clinic visits and study-related procedures • [redacted]
Main exclusion criteria	• Previous treatment of DMO in the 3 months prior to study entry including laser photocoagulation (panretinal or macular) • Cataract surgery or any other intraocular surgery in the study eye within 90 days prior to study entry • Patients deemed unlikely to benefit from additional macular photocoagulation • Prior use of intraocular or periocular corticosteroids in the study eye within 120 days of study entry • Previous treatment with anti-angiogenic drugs in the study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab) within 90 days of study entry.	• Previous treatment of DMO in the 3 months prior to study entry including laser photocoagulation (panretinal or macular) • Cataract surgery or any other intraocular surgery in the study eye within 90 days prior to study entry • Previous vitreoretinal surgery (and/or including scleral buckling), in the study eye • Patients deemed unlikely to benefit from additional macular photocoagulation • More than 2 previous macular laser treatments in the study eye • Prior use of intraocular or periocular corticosteroids in the study eye within 120 days of study entry • Previous treatment with anti-angiogenic drugs in the study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab) within 90 days of study entry.
Prima	Mean change in BCVA from baseline to week 52	

ry outcome	
Other outcomes	• Proportion of patients gaining ≥ 10 ETDRS letters from baseline to week 52 • Proportion of patients gaining ≥ 15 ETDRS letters from baseline to week 52 • Proportion of patients who achieved ≥2-step improvement on the ETDRS DRSS from baseline to week 52 • Mean change in central retinal thickness (CRT) from baseline to week 52, as assessed on OCT • Vision-related quality of life (QoL): Mean changes in NEI VFQ-25 near activities subscale score from baseline to week 52. • Vision-related quality of life (QoL): Mean changes in NEI VFQ-25 distance activities subscale score from baseline to week 52. • Safety: Ocular and non-ocular adverse events (AEs), and serious adverse events (SAEs)[redacted] • Quality of life: Overall state of health was assessed by EuroQol 5 dimensions health questionnaire (EQ-5D)

For VIVID, the company's definition of retinal thickness specified in the above inclusion criteria (i.e. "*Retinal thickness of ≥ 300µm as assessed by OCT in the study eye*") lacks information on the type of OCT used to determine retinal thickness (time domain or spectral domain), which it is important as the measurements obtained with different instruments are not the same. Besides, as this criterion was specified in VIVID but not in VISTA, participants enrolled in VIVID were more likely to have thicker retinas than those enrolled in VISTA (see Table 5).

Table 5 shows the baseline demographics and disease characteristics of the patient population in the VISTA and VIVID RCTs.

Table 5 Baseline demographics and disease characteristics of the patient population in the VISTA and VIVID trials

Characteristic	VISTA			VIVID		
	2q4 (n=154)	**2q8 (n=151)**	**Laser (n=154)**	**2q4 (n=136)**	**2q8 (n=135)**	**Laser (n=132)**
Mean age, years	62.0 (11.2)	63.1 (9.4)	61.7 (8.7)	62.6 (8.6)	64.2 (7.8)	63.9 (8.6)
Sex, n (%)						
Male	87 (56.5)	78 (51.7)	85 (55.2)	83 (61)	88 (65.2)	78 (59.1)
Female	67 (43.5)	73 (48.3)	69 (44.8)	53 (39)	47 (34.8)	54 (40.9)
Ethnic information, n (%)						
White	128 (83.1)	125 (82.8)	131 (85.1)	109 (80.1)	106 (78.5)	106 (80.3)
Black or African American	16 (10.4)	19 (12.6)	16 (10.4)	0 (0)	1 (0.7)	1 (0.8)
Asian	5 (3.2)	2 (1.3)	3 (1.9)	27 (19.9)	27 (20.0)	25 (18.9)
Other	5 (3.2)	5 (3.3)	4 (2.6)	0 (0)	1 (0.7)	0 (0)
Prior anti-VEGF treatment, n (%)	66 (42.9)	68 (45.0)	63 (40.9)	8 (5.9)	15 (11.1)	13 (9.8)
Prior laser photocoagulation (in study eye)	[redacted]	[redacted]	[redacted]	NR[b]	NR[b]	NR[b]
Mean duration of diabetes, years (SD)	16.5 (9.9)	17.6 (11.5)	17.2 (9.5)	14.3 (9.2)	14.1 (8.9)	14.5 (9.8)
Pseudophakic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][d]

Characteristic	VISTA			VIVID		
	2q4 (n=154)	**2q8 (n=151)**	**Laser (n=154)**	**2q4 (n=136)**	**2q8 (n=135)**	**Laser (n=132)**
Mean HbA1c, % (SD)	7.9 (1.6)	7.9 (1.6)	7.6 (1.7)	7.8 (1.5)	7.7 (1.4)	7.7 (1.3)
Mean BMI, kg/m^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BCVA letters (SD)	58.9 (10.8)	59.4 (10.9)	59.7 (10.9)	60.8 (10.7)	58.8 (11.2)	60.8 (10.6)`
Mean CRT, µm (SD)	485 (157)	479 (154)	483 (153)	502 (144)	518 (147)	540 (152)
Mean IOP, mmHg (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean NEI-VFQ (SD)						
Total	69.5 (19.9)	70.5 (17.1)	68.7 (18.1)	77.3 (16.2)	71.2 (17.8)	77.5 (15.2)
Near	60.1 (23.9)	58.1 (22.9)	56.6 (23.1)	68.0 (22.9)	60.8 (23.5)	67.4 (22.2)
Distance	65.3 (23.5)	66.8 (22.5)	63.7 (23.3)	76.7 (21.8)	67.8 (22.9)	77.0 (20.9)
DRSS score, n (%)						
10	4 (2.6)	4 (2.6)	1 (0.6)	0	0	0
20	5 (3.2)	3 (2.0)	3 (1.9)	0	0	1 (0.8)
35	7 (4.5)	9 (6.0)	5 (3.2)	0	1 (0.7)	2 (1.5)
43	49 (31.8)	52 (34.4)	60 (39.0)	31 (22.8)	28 (20.7)	36 (27.3)
47	26 (16.9)	32 (21.2)	26 (16.9)	18 (13.2)	27 (20.0)	24 (18.2)
53	52 (33.8)	40 (26.5)	42 (27.3)	44 (32.4)	42 (31.1)	35 (26.6)
61	1 (0.6)	2 (1.3)	1 (0.6)	2 (1.5)	2 (1.5)	1 (0.8)
65	4 (2.6)	5 (3.3)	10 (6.5)	2 (1.5)	1 (0.7)	0
71	4 (2.6)	1 (0.7)	1 (0.6)	0	0	0
75	0	0	1 (0.6)	0	0	0

Characteristic	VISTA			VIVID		
	2q4 (n=154)	2q8 (n=151)	Laser (n=154)	2q4 (n=136)	2q8 (n=135)	Laser (n=132)
Could not grade	2 (1.3)[e]	3 (2.0)	4 (2.6)	39 (28.7)	34 (25.2)	33 (25.0)

SD: standard deviation; BMI: body mass index; BCVA: best corrected visual acuity; CRT: central retinal thickness; IOP: intraocular pressure; NEI-VFQ: National eye institute visual functioning questionnaire; DRSS: Diabetic Retinopathy Severity Scale;

[a] Reported in VISTA 1-year clinical study report, Table 12
[b] Number of participants with prior laser treatment reported in VISTA but not VIVID. Total number over both studies reported in Tables 22 to 26 of the company's submission. Subtracting VISTA numbers from totals gives number of participants with prior laser treatment as 122 (aflibercept 2Q4), 143 (aflibercept 2Q8), 130 (laser). Peculiarly, 143 is greater than the total number of participants in the VIVID aflibercept 2Q8 group (n=135). These data have not been added to the table above as they may be inaccurate.
[c] "Intraocular lens implant" (VISTA year 1 clinical study report, Table 15)
[d] "Lens therapeutic procedures" (VIVID year 1 clinical study report, Table 17)
[e] [redacted]

The company regarded the patients' demographic and disease characteristics among intervention groups in the VISTA and VIVID trials as "fairly well balanced".

VISTA, however, included a greater proportion of female participants, and Black or African American participants while VIVID included a greater proportion of Asian participants. In VISTA participants had also a longer duration of diabetes and higher BMI. In VIVID more participants could not be graded on DRSS score.

Participants in VIVID had a significantly higher mean CRT than those in VISTA for the laser and aflibercept 2Q8 groups. This may be important as there is evidence that clinical effectiveness of anti-VEGF treatment for DMO can vary according to baseline CRT measurements.[15,37-39]

In particular, in VIVID participants in the laser group had a higher mean CRT than those in each aflibercept group. Nevertheless, a further analysis, provided by the company during the clarification process, indicated that the observed difference was not statistically significant.

More eyes in VISTA received prior anti-VEGF treatment than eyes in VIVID (42.9% versus 8.9%, respectively).[36] The company explained that the main reason for this difference was the relative lack of availability of anti-VEGF treatments in the countries where the VIVID trial was conducted (i.e. Japan, Europe and Australia). About half of the VISTA participants received also previous laser photocoagulation treatment in the study eye. It seems quite plausible that an eye that initially failed to respond to laser therapy may respond to a subsequent anti-VEGF treatment but it is less obvious that an eye that initially failed to respond to laser therapy may respond to the same treatment if administered again. However, eyes unlikely to respond to laser were excluded from the VISTA and VIVID trials. It is worth mentioning, nonetheless, that there is currently no evidence to indicate which eyes are more likely to respond to one treatment or another. It is, therefore, not clear on which basis and criteria clinicians would determine that eyes that had received prior laser would still benefit from further laser.

In the early days of macular laser treatment for DMO, more intense laser burns were applied to the retina (macula) and side effects included expansion of the laser scars into fixation could occur. A deleterious effect in vision was seen in some patients, in particular those where the leak was close to the centre of the macula. Current lighter laser techniques and new laser modalities, such as subthreshold micropulse laser, seem to have reduced or eliminated these complications (for instance, accidental foveal laser burns do not occur when using subthreshold micropulse laser), as some small RCTs available evaluating subthreshold micropulse laser have demonstrated. Therefore, it may be important to consider "previous laser treatment" into account due to its potential impact upon baseline BCVA and on any further treatment.

[redacted]

Mean HbA1c across VISTA and VIVID was between 7.6 and 7.9. In the experience of the ERG, the vast majority of patients with DMO attending NHS clinics have, however, higher HbA1c levels (over 8 or 9 being common). Therefore, it is possible that in clinical practice the proposed treatment will not have the same benefits as shown by the findings of the included trials, unless people with diabetes become well-controlled.

4.1.5 Critique of data extraction

The company used the methods recommended by the German Institute for Quality and Efficacy in Health Care (IQWiG), the Cochrane Collaboration and the University of York Centre for Reviews and Dissemination (CRD) to assess current evidence. The methods described in these publications are, in general, considered appropriate.

Title/abstract screening, full-text screening, and quality assessment were all carried out by two independent reviewers with a third reviewer acting as arbitrator, where necessary. Data extraction was carried out by one reviewer and checked by a second reviewer. These procedures are all considered appropriate. The information and data extracted from the included studies are detailed in the company's submission and considered appropriate, even though it is not clear whether they were specified *a priori*.

4.1.6 Quality assessment

The company adopted the criteria specified by the CRD for the assessment of the risk of bias in the VISTA and VIVID RCTs. The criteria, which involve assessment of selection bias, performance bias, detection bias, attrition bias and reporting bias, are considered appropriate by the ERG.

The VISTA and VIVID RCTs were based on the same methodology, the quality of which is considered adequate. In particular, the randomisation process is appropriate and has proved to be successful (i.e. baseline demographics and disease characteristics were balanced across the intervention groups). The company maintain *that concealment was adequate based upon randomisation being via IVRS/IWRS and the study being double masked* (Table 132 of the company's submission). This information is considered insufficient to assess whether concealment of treatment allocation was performed adequately. Study personnel and participants were masked throughout the trials, with the exception of the unmasked personnel who administered the study drug but took no other part in the study. The ERG consider this masking strategy appropriate.

An intention-to-treat approach was not undertaken. Primary efficacy analyses included all randomised participants who received any study medication and had a baseline assessment and at least one BCVA assessment after baseline. Participants were analysed as randomised. Missing data were dealt with using a last observation carried forward (LOCF) approach except for eyes that had received additional treatment, in which case, the last measurement, before additional treatment, was used. This is considered an acceptable approach by the ERG. In general, in each trial the number of participants dropping out was balanced across the interventions arms at 52

weeks and 100 weeks (31, 27 and 23 for VISTA 2q4, 2q8 and laser, respectively; 21, 25, 30 for VIVID 2q4, 2q8 and laser, respectively). The company reported sensitivity analyses for VIVID exploring the impact of the higher levels of discontinuation of laser participants at 52 weeks and 76 weeks. No impact on outcomes was evident at either time point. The ERG note that the data presented by the company for 52 week withdrawals concurs with data presented in the company's submission and the clinical study report but the source of the 76 week data is unclear. Equivalent sensitivity analyses for VISTA were not reported and the data presented for 100 week discontinuations did not reflect the data reported in company's submission or the CSR.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 6.

Table 6 Quality assessment of the company's systematic review of evidence

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	**Yes**
2. Is there evidence of a substantial effort to search for all of the relevant research?	**Yes**
3. Is the validity of included studies adequately assessed?	**Yes**
4. Are sufficient details of the individual studies presented?	**Yes**
5. Are the primary studies summarised appropriately?	**Yes**

Overall, the systematic review conducted by the company was of good quality with no major concerns in any of the specified quality areas.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company present the results of the VIVID and VISTA trials for the comparison of aflibercept versus laser photocoagulation therapy for DMO. In both trials aflibercept

2mg was administrated either once every 4 weeks (2Q4) or once every eight weeks after five initial monthly doses (2Q8) and compared with laser treatment.

The primary efficacy endpoint was change from baseline in BCVA in ETDRS letter score at week 52. Secondary endpoints for change from baseline to week 52 were proportion of patients gaining ≥ 10 letters, proportion of patients gaining ≥ 15 letters, proportion of patients who achieved ≥ 2-step improvement on the ETDRS DRSS, mean change in central retinal thickness (CRT), mean change in NEI VFQ-25 near activities subscale and mean change in NEI VFQ-25 distance activities subscale. In addition, safety outcomes of ocular and non-ocular adverse events and serious adverse events were assessed. Overall quality of life was assessed using the EuroQol five dimension health questionnaire (EQ5D).

The company defined a number of datasets:

- **The full analysis set (FAS):** all randomised patients who received any study medication and had a baseline measurement and at least one BCVA assessment after baseline. Analysed as randomised.
- **The per protocol set (PPS):** all patients in the FAS who did not have any major protocol violations during the first 52 weeks. Analysed as treated.
- **Safety (SAF):** all randomised patients who received any study medication (active or sham). Analysed as treated.

In both VISTA and VIVID the primary endpoint was evaluated using both the FAS and the PPS, with the FAS being the primary analysis. In VISTA, but not VIVID, secondary endpoints were analysed using the PPS in addition to the FAS.

In all analyses for the primary and secondary endpoints, the LOCF approach was used for missing measurements. Baseline values were not carried forwards. Measurements obtained after initiation of additional treatments were censored with missing or censored values imputed using LOCF. Several sensitivity analyses were presented by the company to assess the impact of these missing data. They were:

- **Observed case (OC)** analysis: only observed, non-censored values were used for analysis. Measurements taken after additional treatment were censored.

- **aLOCF**: missing data were imputed using LOCF but data obtained after initiating additional treatment were retained.
- **aOC**: all observed values were used for analysis, including measurements taken after initiating additional treatment.

In both trials, VISTA and VIVID, the pre-planned subgroup analyses conducted by the company were:

- gender
- age (<55 years, ≥ 55 to < 65 years, ≥ 65 to < 75 years, ≥ 75 years)
- race (VISTA: White, Black, African American, Other; VIVD: White, Asian)
- geographic region (VIVID: Japan, Europe/Australia)
- ethnicity (Hispanic of Latino no/yes)
- HbA1c (≤8%, >8%)
- baseline VA category (efficacy analyses only: < 40 letters, ≥ 40 to < 55 letters, ≥ 55 to < 65 letters, ≥ 65 letters)
- history of hypertension
- history of CVA/stroke
- history of ischaemic heart disease
- renal function
- hepatic impairment

The company indicated that they carried out some additional subgroup analyses in order to respond appropriately to the NICE scope/decision problem. These *post hoc* analyses were:

- baseline central retinal thickness
- prior laser
- prior cataract surgery (presence of pseudophakic lens) and
- prior anti-VEGF therapy (yes/no)

Unless otherwise indicated, all results in this report relate to the full analysis set (FAS). Results of sensitivity analyses are only provided if they show a difference to the FAS approach. The company presented results for the VISTA and VIVID trials i) separately and ii) directly pooled together (integrated analysis) and, later in the

submission, iii) combined in a standard meta-analysis. As previously highlighted in section 4.1.2, the VISTA and VIVID trials differed significantly in the proportion of participants who received previous anti VEGF treatment. The mean CRT was also significantly different between the two trials (Table 5). For these reasons the ERG does not regard the integrated analysis (i.e. results directly pooled from the two trials to form a single data set) favourably. Moreover, all integrated analyses of secondary endpoints were defined as exploratory - with no control for multiplicity - in the company submission. Consequently, the ERG chose to avoid highlighting the results of the integrated analysis, unless necessary. For all treatment comparisons the company presented both risk ratios and odds ratios (that showed consistent estimates). The ERG opted for presenting results expressed as risk ratios because these effect estimates were used in the cost-effectiveness analyses.

4.2.1 Aflibercept 2Q4 or aflibercept 2Q8 versus laser

Primary endpoint: BCVA change from baseline to week 52

The primary analysis used a 2-sided test at 2.5% significance to assess the two comparisons (aflibercept 2Q4 versus laser and aflibercept 2Q8 versus laser). Analyses were adjusted for history of myocardial infarction (and or cerebrovascular accident CVA - VISTA only), geographic region, and baseline BCVA, but not for baseline CRT. Table 7 presents the results for each of the aflibercept to laser comparisons in both VIVD and VISTA. Both aflibercept regimens were found to be superior to laser in terms of change in BCVA with larger changes occurring in the aflibercept groups. Figure 1 shows the mean change from baseline in BCVA to week 52 for the integrated analysis and shows the profile of the change is similar in the aflibercept groups (source Figure 9, page 71 of the company's submission).

Table 7 Analysis of change in BCVA from baseline to week 52 (FAS)

	AFB 2Q4		Laser		Treatment difference [a]		
	N	Mean (SD)	N	Mean (SD)	Mean	97.5% CI	p-value
VISTA	154	12.5 (9.54)	154	0.2 (12.53)	12.19	(9.35, 15.04)	<0.0001
VIVID	136	10.5 (9.55)	132	1.2 (10.65)	9.25	(6.49, 12.02)	<0.0001

	AFB 2Q8		Laser		Treatment difference [a]		
	N	Mean (SD)	N	Mean (SD)	Mean	97.5% CI	p-value
VISTA	151	10.7 (8.21)	154	0.2 (12.53)	10.45	(7.73, 13.17)	<0.0001
VIVID	135	10.7 (9.32)	132	1.2 (10.65)	9.05	(6.35, 11.76)	<0.0001

[a] From ANCOVA model

[redacted] Forest plots summarising these results are presented in Figure 10 and 11 of the company submission.

Table 8 shows the results of the secondary efficacy outcomes for the VISTA and VIVID trials. Clinical and statistically significant differences in favour of aflibercept treatment over laser therapy were found in both trials for the following outcomes: proportion of patients gaining ≥10 letters, proportion of patients gaining ≥15 letters, proportion of patients with ≥2-step ETDRS improvement and mean change in CRT. For the NEI-VFQ-25, the VISTA trial showed a significant advantage with aflibercept 2Q4 (but not with aflibercept 2Q8) on the near activities subscale compared with laser. No differences were observed for each aflibercept regimen versus laser within VIVID. No statistical differences were observed in either trial for the NEI-VFQ-25 distance activities subscale.

[redacted]

[redacted].

[redacted] The results are presented in Tables 23 to 26 of the company's submission.

FIGURE ACADEMIC IN CONFIDENCE

BCVA=best corrected visual acuity; VTE = intravitreal aflibercept; 2Q4 = 2mg aflibercept every 4 weeks; 2Q8 = 2mg aflibercept every 8 weeks, after 5 initial monthly doses;

Figure 1 Mean BCVA change from baseline in ETDRS letter score at week 52 for the integrated analysis of the VISTA and VIVID trials (FAS, LOCF), source Figure 9, company's submission

Secondary endpoint: additional efficacy variables

Table 9 shows the results for the additional secondary endpoints assessed using the FAS, LOCF approach. Overall, the results were consistent between trials. Clinically and significant differences in favour of the aflibercept treatment (both regimens) were observed for the majority of the secondary outcomes. The two aflibercept groups were numerically superior to the laser group for the NEI VFQ-25 total score at week 52 in both trials, [redacted]

There were minimal changes from baseline in EQ5D total score in each of the three treatment groups. No statistical comparisons were reported. No subgroup analyses

were deemed feasible for loss of ≥10 and ≥15 letters as such a decline was rarely observed in participants treated with aflibercept.

Week 100 results

The two-year results for both VIVID and VISTA were not finalised at the time the company's submission was completed. Nevertheless, the company included some preliminary results. In VISTA the improvement from baseline in BCVA was maintained at week 100 in participants receiving aflibercept 2Q4 and 2Q8 compared with those receiving laser therapy. After two years patients receiving aflibercept 2Q8 had a mean change from baseline in BCVA of 11.5 letters compared to 12.5 letters at 52 weeks. Patients receiving aflibercept 2Q8 had a mean change from baseline of 11.1 letters (10.7 letters at 52 weeks) while those treated with laser had a mean change from baseline of 0.9 letters (0.2 letters at 52 weeks). In VIVID, the mean change from baseline at week 100 was 11.4 letters in the aflibercept 2Q4 group; 9.4 letters in the aflibercept 2Q8 group; and 0.7 letters in the laser group. This compared to a mean change from baseline of 10.5, 10.7 and 1.2 letters, respectively, at week 52.

In both trials for the [redacted] the sustained favourable differences to laser were statistically significant for both aflibercept groups at week 100. Results for other secondary endpoints at week 100 were consistent with those observed at week 52.

Table 8 Analysis of secondary endpoints from baseline to week 52 (FAS, LOCF)

	AFB 2Q4		AFB 2Q8		Laser		AFB 2Q4 - laser			AFB 2Q8 - laser		
	N	n (%)	N	n (%)	N	n (%)	Adjusted Difference	97.5% CI	p-value	Adjusted Difference	97.5% CI	p-value
Gaining >= 10 letters												
VISTA	154	100 (64.9)	151	88 (58.3)	154	30 (19.5)	45.9	(34.7, 57.0)	<0.0001	38.8	(27.2, 50.3)	<0.0001
VIVID	136	74 (54.4)	135	72 (53.3)	132	34 (25.8)	28.7	(15.8, 46.1)	<0.0001	27.5	(14.6, 40.5)	<0.0001
Gaining >= 15 letters												
VISTA	154	64 (41.6)	151	47 (31.1)	154	12 (7.8)	34.2	(24.1, 44.4)	<0.0001	23.3	(13.5, 33.1)	<0.0001
VIVID	136	44 (32.4)	135	45 (33.3)	132	12 (9.1)	23.3	(12.6, 33.9)	<0.0001	24.2	(13.5, 34.9)	<0.0001
>= 2 step ETDRS improvement	N (evaluable)		N (evaluable)		N (evaluable)							
VISTA	154 (154)	52 (33.8)	151 (151)	44 (29.1)	154 (154)	22 (14.3)	19.7	(9.0, 30.4)	<0.0001	14.9	(4.4, 25.4)	<0.0001
VIVID	136 (81)	27 (33.3)	135 (83)	12 (27.7)	132 (80)	6 (7.5)	25.8	(12.2, 39.4)	<0.0001	19.3	(6.6, 32.1)	<0.0001

	AFB 2Q4		AFB 2Q8		Laser		AFB 2Q4 - laser			AFB 2Q8 - laser		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	Adjusted Difference	97.5% CI	p-value	Adjusted Difference	97.5% CI	p-value
Change in CRT (by OCT)												
VISTA	154	-186 (150.7)	151	-183 (153.5)	154	-73.3 (176.7)	-110.78	(-141.3, -80.2)	<0.0001	-113.47	(-144.2, -82.7)	<0.0001
VIVID	136	-195 (146.6)	135	-192 (149.9)	132	-66.2 (139.0)	-156.98	(-190.9, -123.1)	<0.0001	-142.82	(-179.3, -106.3)	<0.0001
Change in NEI VFQ-25 near activities	N (evaluable)	Mean (SD)	N (evaluable)	Mean (SD)	N (evaluable)	Mean (SD)	Adjusted Difference	97.5% CI	p-value	Adjusted Difference	97.5% CI	p-value
VISTA	154 (146)	9.0 (20.6)	151 (146)	9.4 (18.5)	154 (151)	5.4 (20.4)	5.19	(0.33, 10.0)	0.0168	4.36	(-0.21, 8.93)	0.0323
VIVID	136 (128)	5.7 (18.9)	135 (134)	5.3 (19.1)	132 (120)	3.5 (16.8)	2.41	(-2.01, 6.82)	0.2208	-1.21	(-5.79, 3.37)	0.5537
Change in NEI VFQ-25 distance activities												
VISTA	[redacted]	8.6 (21.0)	[redacted]	7.3 (19.3)	[redacted]	6.7 (19.9)	2.86	(-1.82, 7.54)	0.1702	1.65	(-2.83, 6.13)	0.4067
VIVID	[redacted]	0.9 (16.5)	[redacted]	5.3 (18.5)	[redacted]	2.3 (15.9)	-1.19	(-5.29, 2.91)	0.5138	-0.37	(-4.79, 4.05)	0.8498

Table 9 Analysis of additional endpoints from baseline to week 52 (FAS, LOCF): VISTA and VIVID

	AFB 2Q4		AFB 2Q8		Laser		AFB 2Q4 - laser			AFB 2Q8 - laser		
	N	n (%)	N	n (%)	N	n (%)	Adjusted Difference	97.5% CI	p-value	Adjusted Difference	97.5% CI	p-value
Gaining >= 0 letters												
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136	[redacted]	135	[redacted]	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gaining >= 5 letters		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136	[redacted]	135	[redacted]	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing >= 5 letters		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136	[redacted]	135	[redacted]	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing >= 10 letters		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136	[redacted]	135	[redacted]	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing >= 15 letters		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136	[redacted]	135	[redacted]	132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with >=2step worsening on DRSS		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	81	[redacted]	83	[redacted]	80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with >=3 step worsening on DRSS		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	81	[redacted]	83	[redacted]	80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with >=3 step improvement on DRSS		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154	[redacted]	151	[redacted]	154	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VIVID	81	3 (3.7)	83	2 (2.4)	80	0 (0)	3.7	(-1.1, 8.4)	0.0817	2.3	(-1.4, 6.0)	0.1582
Change in NEI-VFQ-25 total score												
VISTA	154 (146)	[redacted]	151 (147)	[redacted]	154 (151)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136 (128)	[redacted]	135 (134)	[redacted]	132 (120)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ5D total score		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VISTA	154 (146)	[redacted]	151 (147)	[redacted]	154 (151)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	136 (128)	[redacted]	135 (134)	[redacted]	132 (120)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB: Red text indicates possible typographical error by the company. The ERG assume there should be a negative sign in the upper limit of the CI.

4.2.2 Adverse events

The company provides evidence on the safety and tolerability of aflibercept compared with laser using data available from the VIVID and VISTA trials. The company submission reported safety analyses at week 100. An informative summary of the incidence of adverse events is the following: a total of 427 patients (92.6%) in VISTA and 360 (86.6%) in VIVID experienced at least one treatment-emergent adverse event (TEAE) during the first 52 weeks of study treatment.

[redacted]. [redacted] Incidence of all reported event types was similar among treatment groups. Nevertheless, as expected, [redacted].

Overall, the company found that aflibercept compared with laser therapy is well tolerated and has a favourable safety profile out to at least two years.

Mortality

The company present mortality information at both 52 weeks and 100 weeks. Within the submission the company indicate that for VISTA there were no deaths in the aflibercept 2Q8 group, two deaths in the aflibercept 2Q4 group and one death in the laser arm at 52 weeks. In VIVID, there were four deaths recorded within participants in the aflibercept 2Q8 group, none in the aflibercept 2Q4 group or laser group (Figure 6, company submission). However, this does not match the VIVID data (meta-analysis of aflibercept 2Q8 versus laser) presented in Figure 56 of the company's submission. Figure 56 shows that five deaths were observed in the aflibercept 2Q8 group and zero in the laser group rather than five and one, respectively, as for Figure 6. The ERG assessed this further by considering the data presented in the Korobelnik et al publication[36] where two deaths were reported in laser arm (one in each trial), two in the aflibercept 2Q4 arm (unclear how many in each trial) and four in the aflibercept

2Q8 arm. As Korobelnik et al[36] did not present data separately by treatment group, the ERG were not in the position to confirm which source was correct. The ERG underline the inconsistency in the data presented by the company in different sections of the submission.

By week 100, the company indicate that there were four deaths in the laser arm (3 in VISTA, 1 in VIVID), 12 deaths in the aflibercept 2Q4 arm (8 in VISTA, 4 in VIVID) and 10 deaths in the aflibercept 2Q8 arm (4 in VISTA and 6 in VIVID).

A fixed effect meta-analysis presented by the company for the 52 week data for aflibercept 2Q8 versus laser gave a risk ratio of 2.19 (95% CI 0.49 to 9.73) indicating no statistically significant difference between the two treatment groups. The fact that the number of deaths was higher, although not statistically significant higher, among participants who received aflibercept treatment compared with those who received laser therapy it is, in itself, a result that warrants consideration.

4.2.3 Meta-analysis of VIVD and VISTA

The submission includes standard meta-analyses of the results of the VISTA and VIVID trials for a number of relevant outcomes. The results are presented initially in tabular format (Tables 32-34 of the company's submission) using both fixed and random effects models. Some of these results are also presented as forest plots within the indirect comparison section (Figures 19-65 of company submission). The meta-analysis comparisons are made exclusively between aflibercept 2Q8 regimen and laser. This choice is justified by the fact that aflibercept 2Q8 is the licensed aflibercept dose in the UK and that approved by the EMA. Thus, the remainder of the ERG report will focus on the comparisons between aflibercept 2Q8 treatment and laser therapy within the VISTA and VIVID trials.

Tables 7 and 8 show the relevant VISTA and VIVID raw data. Estimates of treatment effect together with 95% CIs for both fixed and random effects models are presented in Table 10 (primary outcome) and Table 11 (secondary endpoints). Results are presented as risk ratios. All estimates of effect favoured aflibercept 2Q8 treatment.

Table 10 Meta-analysis – effect estimates by inverse variance fixed and random effects models for BCVA mean change from baseline

BCVA Mean Change from baseline			
Study ID	**Weight**	**Mean Difference IV, Fixed 95% CI**	**Mean Difference IV, Random 95% CI**
VISTA-DME	50.60%	10.50 [8.13, 12.87]	10.50 [8.13, 12.87]
VIVID-DME	49.40%	9.50 [7.10, 11.90]	9.50 [7.10, 11.90]
Total	**100%**	**10.01 [8.32, 11.69]**	**10.01 [8.32, 11.69]**

Table 11 Meta-analysis – effect estimates by Mantel-Haenszel fixed and random effects models for binary secondary endpoints – risk ratio

Gain of ≥10 ETDRS letters				
Study ID	**Risk Ratio**		**Risk Ratio**	
	Weight	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	46.40%	2.99 [2.11, 4.24]	48.80%	2.99 [2.11, 4.24]
VIVID-DME	53.60%	2.07 [1.49, 2.88]	51.20%	2.07 [1.49, 2.88]
Total	100%	2.50 [1.97, 3.17]	100%	2.48 [1.73, 3.56]
Loss of ≥10 ETDRS letters				
Study ID	**Risk Ratio**		**Risk Ratio**	
	Weight	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	[redacted]	[redacted]	[redacted]	[redacted]
VIVID-DME	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Gain of ≥15 ETDRS letters				
Study ID	**Risk Ratio**		**Risk Ratio**	
	Weight	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	49.50%	3.99 [2.21, 7.23]	49.70%	3.99 [2.21, 7.23]
VIVID-DME	50.50%	3.67 [2.03, 6.61]	50.30%	3.67 [2.03, 6.61]
Total	100%	3.83 [2.52, 5.82]	100%	3.83 [2.52, 5.81]
Loss of ≥15 ETDRS letters				
Study ID	**Risk Ratio**		**Risk Ratio**	
	Weight	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	48.60%	0.07 [0.01, 0.55]	66.00%	0.07 [0.01, 0.55]
VIVID-DME	51.40%	0.03 [0.00, 0.56]	34.00%	0.03 [0.00, 0.56]
Total	100%	0.05 [0.01, 0.27]	100%	0.06 [0.01, 0.29]

Treatment Discontinuation				
Study ID	**Risk Ratio**		**Risk Ratio**	
	Weight	**M-H, Fixed, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	35.30%	0.92 [0.40, 2.11]	36.4	0.92 [0.40, 2.11]
VIVID-DME	64.7	0.75 [0.40, 1.40]	63.6	0.75 [0.40, 1.40]
Total	100%	0.81 [0.49, 1.33]	100%	0.81 [0.49, 1.33]

4.2.4 Critique of submitted evidence

It is worth pointing out that that main entry criterion for VIVID and VISTA was a central retinal thickness in the 1 mm central retina, as assessed by OCT (not determined, in the Korobelnik et al published manuscript[36] or in the company's submission, whether spectral domain or time domain OCT). Thus, at entry, patients may or may not have fulfilled the standard definition of clinically significant macular oedema (CSMO). CSMO was, however, used as re-treatment criterion for laser photocoagulation therapy. Thus, one could argue that the initial laser treatment was not given based on the presence of CSMO while the re-treatments were; the rationale for this is unclear to the ERG. It is not specified either whether fluorescein angiography was obtained prior to laser treatment to guide laser (as recommended by the ETDRS).

The company present a wealth of information for the VIVID and VISTA trials including sensitivity analyses to the main FAS analysis as well as a number of subgroup analyses (see section 4.2 for a list of pre-specified and *post hoc* subgroup analyses). The same analyses were presented in multiple figures and tables making it challenging to navigate through the submission. Nonetheless, the methods used were considered adequate.

In Table 9 of this report, the ERG have noted several possible imprecisions in the company's submission surrounding the exclusion of a minus sign for the upper limit of the reported confidence intervals. As the associated p-value is significant in all cases and the point estimate is negative, both confidence limits should, necessarily, be negative. This was likely to be an oversight by the company and the ERG have assumed that the minus sign needed to be included in all cases.

Within the methods section of the company submission, the company indicate they undertook a sensitivity analysis for missing data within VISTA/VIVID outcomes by employing a repeated measured model and secondly through use of multiple imputation. Details of the results of these approaches were not provided in the company submission. They were, however, provided within the clinical study reports of both trials which were requested by the ERG during the clarification process. The estimates of treatment effect from the repeated measures model/multiple imputation approach were of similar magnitude to the main FAS (LOCF) analysis for VISTA but of slightly smaller magnitude (yet still highly significant) for VIVID.

On the whole, the ERG are satisfied that the results provided by the company are representative of all sensitivity analyses.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company presented initially Mantel-Haenszel meta-analyses comparing aflibercept 2Q8 with laser (VIVID and VISTA trials), ranibizumab with laser (RESTORE and REVEAL trials) and dexamethasone with laser (PLACID trial). Then using the pooled estimates from these meta-analyses, the company reported a Bucher indirect comparison for aflibercept 2Q8 versus ranibizumab as well as aflibercept 2Q8 versus dexamethasone. Subsequently, in the absence of head-to-head data, the company conducted a network meta-analysis to assess the relative treatment differences between aflibercept 2Q8, ranibizumab (0.5mg treatment as needed), fluocinolone acetonide implants or dexamethasone implants on visual and safety outcomes. The company identified all relevant studies for the indirect comparisons of aflibercept versus ranibizumab at 12 months (i.e. VIVID, VISTA, RESTORE, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, LUCIDATE, IBETA, Maia 2009)[36-38,40-45] and aflibercept versus dexamethasone at 12 months (i.e. VIVID, VISTA, and PLACID).[36,46] A total of 11 studies contributed to the network meta-analysis. Table 12 presents a summary of the risk of bias of the included trials using the Cochrane checklist. Where information for a specific domain was lacking, the ERG judged the risk of bias as Unclear. For each study, rating of overall bias for the assessed methodological domains, was made on the basis of the most frequently observed rating (columns 2 to 8 in Table 12).

Overall risk of bias was rated as Low in four trials (VISTA, VIVID, RESTORE, PLACID)[36,38,46] and Unclear (IBETA, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, LUCIDATE, Mia 2009)[37,40-45] in the remaining trials. It is worth noting that the IBETA and REVEAL trials[40,41] were not reported in full but in abstract form only and the details of the RELATION trial were available on the clinicaltrials.gov website. These reports generally contain insufficient information to fully assess risk of bias.

The majority of trials did not provide sufficient information to assess the risk of bias in the random sequence generation (IBETA, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, LUCIDATE, Maia 2009[37,40-45]) or allocation concealment domains (VISTA, VIVID, IBETA, RESTORE, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, Maia 2009, PLACID).[36-38,40,42-46]

Participants in the LUCIDATE and Maia 2009 trials[42,44] were not blinded. IBETA was an open-label trial.[41] The remaining trials were described as being blinded but insufficient information was given on blinding of participants, personnel (REVEAL, RELATION, LRT for DME, LRT for DME for PRP)[37,40,43,45] and outcome assessors (REVEAL, RELATION, LUCIDATE). [40,42,45]

Table 12 Risk of bias of trials included in indirect and mixed treatment comparisons

Study	Random sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other	Appropriate data analysis	Overall rating of bias
VISTA[36]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Not ITT (all randomised patients who received any study medication with at least baseline assessment and 1 post-baseline BCVA assessment); LOCF (primary & secondary outcomes); aLOCF (if additional treatment)	Low Risk
VIVID[36]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Not ITT (as above); LOCF (primary & secondary outcomes); aLOCF (if additional treatment)	Low Risk
IBETA[41]	Unclear Risk	Unclear Risk	High Risk	High Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk
RESTORE[38]	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Not ITT (patients with at least 1 application of treatment and at least 1 post-baseline BCVA assessment);	Low Risk

Study	Random sequence generation	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other	Appropriate data analysis	Overall rating of bias
								LOCF	
REVEAL[40]	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Unclear Risk
RELATION[45]	Unclear Risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	High Risk	Not ITT (patients with at least 1 application of treatment and at least 1 post-baseline BCVA assessment); LOCF for final month data as study terminated early	Unclear Risk
LRT for DME[37]	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	High Risk	ITT for primary outcome; LOCF	Unclear Risk
LRT for DME for PRP[43]	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	High Risk	ITT for primary outcome; LOCF	Unclear Risk
LUCIDATE[42]	Unclear Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	High Risk	Not ITT (patients completing 48-week follow-up)	Unclear Risk
Maia 2009[44]	Unclear Risk	Unclear Risk	High Risk	Low Risk	High Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk
PLACID[46]	Low Risk	Unclear Risk	Low Risk	Low Risk	High Risk	Low Risk	High Risk	ITT; modified ITT; LOCF	Low Risk

For the domain 'incomplete outcome data' most of the trials were considered at Low (VISTA, VIVID, RESTORE, RELATION, LRT for DME, LUCIDATE)[36-38,42,45] or Unclear (IBETA, REVEAL, LRT for DME for PRP)[40,41,43] risk of bias. Two trials were judged to be at High risk of bias due to the exclusion of patients because of adverse events (Maia 2009 - three eyes excluded in the laser group)[44] or to a large number of participants not completing the trial (PLACID).[46]

Selective reporting was at low risk of bias in all trials that reported this information. Other sources of bias related mainly to funding. The majority of trials had either sole industry funding (VISTA, VIVID, RESTORE, REVEAL, RELATION and PLACID)[36,38,40,45,46] or mixed industry/public funding (LRT for DME, LRT for DME for PRP, LUCIDATE)[37,42,43] and were, therefore, rated as High risk of bias. Two trials (IBETA and Maia 2009)[41,44] did not report industry funding.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

4.4.1 Indirect comparison

The company present Mantel-Haenszel meta-analyses comparing aflibercept 2Q8 with laser (VIVID and VISTA trials),[36] ranibizumab with laser (RESTORE and REVEAL trials)[38,40] and dexamethasone with laser (PLACID trial).[46] The meta-analyses results for a number of relevant outcomes were presented graphically, as forest plots (Figures 19 to Figure 65 of the company's submission), as well as in tabular format (Tables 42 to 44 of the company's submission). The company used the Bucher indirect method to synthesise, where possible, efficacy and safety data for aflibercept versus ranibizumab and aflibercept versus dexamethasone. A comparison of aflibercept with fluocinolone was not possible due to lack of a common comparator to allow indirect analysis.

The outcomes considered for the indirect comparison of aflibercept versus ranibizumab are the following:

- Mean change in BCVA from baseline to 12 months
- Mean average change in BCVA from baseline at 12 months
- Proportion of patients gaining ≥ 10 letters of BCVA from baseline at 12 months

- Proportion of patients losing ≥ 10 letters of BCVA from baseline at 12 months
- Proportion of patients gaining ≥ 15 letters of BCVA from baseline at 12 months
- Proportion of patients losing ≥ 15 letters of BCVA from baseline at 12 months
- Treatment discontinuation
- All serious adverse events
- All serious ocular adverse events
- All serious non-ocular adverse events
- All non-ocular adverse events
- All adverse events
- All ocular adverse events
- Eye pain
- Hypertension
- Cataract
- All-cause mortality

An indirect comparison of aflibercept versus dexamethasone is presented for the following outcomes:

- Proportion of patients gaining ≥ 10 letters of BCVA from baseline at 12 months
- Treatment discontinuation
- All ocular adverse events
- Cataract
- Macular Oedema
- Reduced visual acuity
- Vitreous haemorrhage
- Increased intraocular pressure

Tables 13-15 summarise the results of i) the meta-analyses of VIVID and VISTA to obtain a summary estimate of aflibercept 2Q8 versus laser, ii) the meta analysis of RESTORE[38] and REVEAL for a summary estimate of ranibizumab versus laser and finally iii) the result of the indirect comparison using the Bucher method to obtain an estimate of aflibercept 2Q8 versus ranibizumab. Table 13 illustrates the results for the

continuous outcomes, using both fixed and random effects models. Table 14 shows the results for the binary secondary outcomes expressed as risk ratios while Table 15 presents the risk ratio estimates, calculated using both fixed and random effects models, for the safety outcomes. The company present also the odds ratio estimates, which were consistent with the risk ratio estimate, and therefore are not reported here. Table 16 summarises, where possible, the results for the comparison of aflibercept with laser, dexamethasone with laser, and the indirect comparison of aflibercept with dexamethasone.

The analyses showed a significant effect in favour of anti-VEGF treatments (aflibercept and ranibizumab) compared with laser for the BCVA mean change from baseline. The resultant indirect comparison of aflibercept versus ranibizumab was significantly in favour of aflibercept with mean difference of 4.82 (95% CI 2.52 to 7.11). The exclusion of the REVEAL trial, which was based primarily on an Asian population, reduced the size of the effect estimate but did not alter the conclusion (see Table 13).

With regard to the secondary outcomes, for the gain of ≥10 and ≥15 letters both aflibercept and ranibizumab showed a significant improvement, and the tendency to lose fewer letters, over laser. The indirect comparison found that aflibercept and ranibizumab were not different from each other (Table 14). Looking at the safety outcomes presented in Table 15, no obvious differences were found between aflibercept and laser, between ranibizumab and laser and also between aflibercept and ranibizumab. Table 16 show the 12-month results for aflibercept versus dexamethasone. A significant advantage was observed with aflibercept for the gain of ≥10 letters, but no differences in terms of safety outcomes were evident, despite a trend towards fewer adverse events with aflibercept treatment.

Table 13 Meta-analysis and indirect comparison results for 12 month continuous outcomes

		AFB vs laser[a]		RBZ vs laser[b]		AFB vs RBZ		AFB vs RBZ[c]	
		Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
BCVA change from baseline	fixed	10.01	(8.32, 11.69)	5.19	(3.63, 6.75)	4.82	(2.52, 7.11)	4.11	(0.99, 7.22)
	random	10.01	(8.32, 11.69)	5.19	(3.63, 6.75)	4.82	(2.52, 7.11)	4.11	(0.99, 7.22)
BCVA mean average change from baseline	fixed	7.75	(6.43, 9.06)	4.80	(3.59, 6.00)	2.95	(1.17, 4.73)	2.45	(0.07, 4.82)
	random	7.75	(6.43, 9.06)	4.80	(3.59, 6.00)	2.95	(1.17, 4.73)	2.45	(0.07, 4.82)

[a] VISTA and VIVID; [b] REVEAL/RESTORE; [c] excludes REVEAL

Table 14 Meta-analysis and indirect comparison results for 12 month secondary outcomes outcomes – risk ratios

		AFB vs laser[a]		RBZ vs laser[b]		AFB vs RBZ		AFB vs RBZ[c]	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Gain of >=10 ETDRS letters	fixed	2.50	(1.97, 3.98)	2.48	(1.74, 3.54)	0.99	(0.65, 1.52)	1.02	(0.59, 1.77)
	random	2.48	(1.73, 3.56)	2.48	(1.74, 3.54)	1.00	(0.06, 1.66)	1.03	(0.55, 1.90)
Loss of >=10 ETDRS letters	fixed	[redacted]	[redacted]	0.35	(0.16, 0.77)	[redacted]	[redacted]	[redacted]	[redacted]
	random	[redacted]	[redacted]	0.35	(0.16, 0.78)	[redacted]	[redacted]	[redacted]	[redacted]
Gain of >=15 ETDRS letters	fixed	3.83	(2.52, 5.82)	2.58	(1.57, 4.23)	1.49	(0.78, 2.85)	1.39	(0.61, 3.16)
	random	3.83	(2.52, 5.81)	2.57	(1.57, 4.23)	1.49	(0.78, 2.85)	1.39	(0.61, 3.16)
Loss of >=15 ETDRS letters	fixed	0.05	(0.01, 0.27)	0.21	(0.06, 0.71)	0.24	(0.03, 1.90)	0.52	(0.04, 7.27)
	random	0.06	(0.01, 0.29)	0.23	(0.07, 0.84)	0.26	(0.03, 2.11)	0.55	(0.03, 8.77)
Treatment discontinuation	fixed	0.81	(0.49, 1.33)	0.65	(0.40, 1.05)	1.22	(0.60, 2.47)	0.78	(0.33, 1.87)
	random	0.81	(0.49, 1.33)	0.63	(0.24, 1.66)	1.23	(0.45, 3.37)	0.76	(0.29, 2.03)

[a] VISTA and VIVID; [b] REVEAL/RESTORE; [c] excludes REVEAL

Table 15 Meta-analysis and indirect comparison results for 12 month safety outcomes – risk ratios

		AFB vs laser[a]		RBZ vs laser[b]		AFB vs RBZ		AFB vs RBZ[c]	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
All serious adverse events	Fixed	0.93	(0.70, 1.22)	1.17	(0.78, 1.75)	0.78	(0.48, 1.27)	0.71	(0.37, 1.33)
	Random	0.95	(0.62, 1.47)	1.17	(0.78, 1.76)	0.81	(0.45, 1.47)	0.74	(0.36, 1.51)
All serious ocular adverse events	Fixed	0.42	(0.15, 1.17)	1.81	(0.59, 5.62)	0.20	(0.04, 1.11)	2.19	(0.09, 3.94)
	Random	0.42	(0.15, 1.18)	1.15	(0.06, 20.98)	0.39	(0.02, 7.34)	2.21	(0.09, 52.16)
All serious non-ocular adverse events	Fixed	0.99	(0.73, 1.34)	1.47[d]	(0.81, 2.66)	0.66	(0.34, 1.29)	-	-
	Random	1.02	(0.64, 1.64)	1.47[d]	(0.81, 2.66)	0.70	(0.33, 1.48)	-	-
All adverse events	Fixed	1.00	(0.95, 1.06)	1.41	(0.95, 2.09)	0.70	(0.47, 1.04)	0.81	(0.38, 1.71)
	Random	1.00	(0.92, 1.08)	1.42	(0.96, 2.10)	0.70	(0.47, 1.05)	0.82	(0.39, 1.73)
All ocular adverse events	Fixed	0.90	(0.79, 1.03)	1.09[d]	(0.80, 1.49)	0.83	(0.59, 1.16)	-	-
	Random	0.90	(0.79, 1.03)	1.09[d]	(0.80, 1.49)	0.83	(0.59, 1.16)	-	-
All non-ocular adverse events	Fixed	1.02	(0.93, 1.12)	0.94[d]	(0.76, 1.17)	1.04	(0.83, 1.32)	-	-
	Random	1.04	(0.79, 1.36)	0.94[d]	(0.76, 1.17)	1.11	(0.78, 1.57)	-	-
Eye pain	Fixed	1.18	(0.65, 2.14)	1.04[d]	(0.48, 2.27)	1.13	(0.42, 3.01)	-	-
	Random	1.18	(0.65, 2.15)	1.04[d]	(0.48, 2.27)	1.14	(0.43, 3.03)	-	-
Hypertension	Fixed	0.92	(0.64, 1.32)	0.96	(0.48, 1.91)	0.96	(0.44, 2.06)	0.96	(0.37, 2.50)
	Random	0.92	(0.64, 1.32)	0.96	(0.48, 1.91)	0.96	(0.44, 2.06)	0.96	(0.37, 2.51)
Cataract	Fixed	0.93	(0.46, 1.90)	0.27[d]	(0.06, 1.29)	3.42	(0.62, 18.95)	-	-
	Random	0.95	(0.37, 2.41)	0.27[d]	(0.06, 1.29)	3.52	(0.58, 21.23)	-	-
All cause mortality[d]	Fixed	2.19	(0.49, 9.73)	0.96	(0.14, 6.67)	2.25	(0.16, 31.26)	-	-
	Random	1.70	(0.13, 22.2)	0.96	(0.39, 2.32)	1.77	(0.07, 44.10)	-	-

[a] VISTA and VIVID; [b] REVEAL/RESTORE; [c] excludes REVEAL as a sensitivity; [d] outcome only available in RESTORE

Table 16 Meta-analysis and indirect comparison results for 12 month outcomes: aflibercept versus demexathone – risk ratios

		AFB vs laser[a]		DEX vs laser[b]		AFB vs DEX	
		RR	95% CI	RR	95% CI	RR	95% CI
Gain of >=10 ETDRS letters	fixed	2.50	(1.97, 3.98)	1.18	(0.77, 1.79)	2.10	(1.29, 3.40)
	random	2.48	(1.73, 3.56)	1.18	(0.77, 1.79)	2.10	(1.21, 3.66)
Treatment discontinuation	fixed	0.81	0.49, 1.33)	0.70	(0.44, 1.13)	1.15	(0.58, 2.29)
	random	0.81	0.49, 1.33)	0.70	(0.44, 1.13)	1.16	(0.57, 2.34)
Eye pain	fixed	1.18	(0.65, 2.14)	1.47	(0.65, 3.31)	0.80	(0.29, 1.39)
	random	1.18	(0.65, 2.15)	1.47	(0.65, 3.31)	0.78	(0.27, 2.21)
Cataract	fixed	0.93	(0.46, 1.90)	2.20	(0.86, 5.61)	0.42	(0.13, 1.39)
	random	0.95	(0.37, 2.41)	2.20	(0.86, 5.61)	0.43	(0.12, 1.63)
Macular Oedema	one study in each	0.39[c]	(0.08, 2.00)	1.78	(0.53, 5.92)		
Reduce visual acuity	fixed	0.60	(0.32, 1.10)	0.94	(0.45, 1.98)	0.64	(0.24, 1.67)
	random	0.60	(0.32, 1.10)	0.94	(0.45, 1.98)	0.64	(0.17, 2.40)
Vitreous haemorrhage	fixed	0.36	(0.12, 1.13)	1.52	(0.65, 3.60)	0.3	(0.07, 1.39)
	random	0.39	(0.05, 3.07)	1.52	(0.65, 3.60)	0.18	(0.02, 1.65)
Increased ocular pressure	fixed	1.19	(0.53, 2.71)	12.7	(3.07, 52.49)	0.08	(0.02, 0.42)
	random	1.65	(0.18, 14.83)	12.7	(3.07, 52.49)	0.13	(0.01, 1.79)

[a] VISTA and VIVID; [b] PLACID; [c] VIVID only

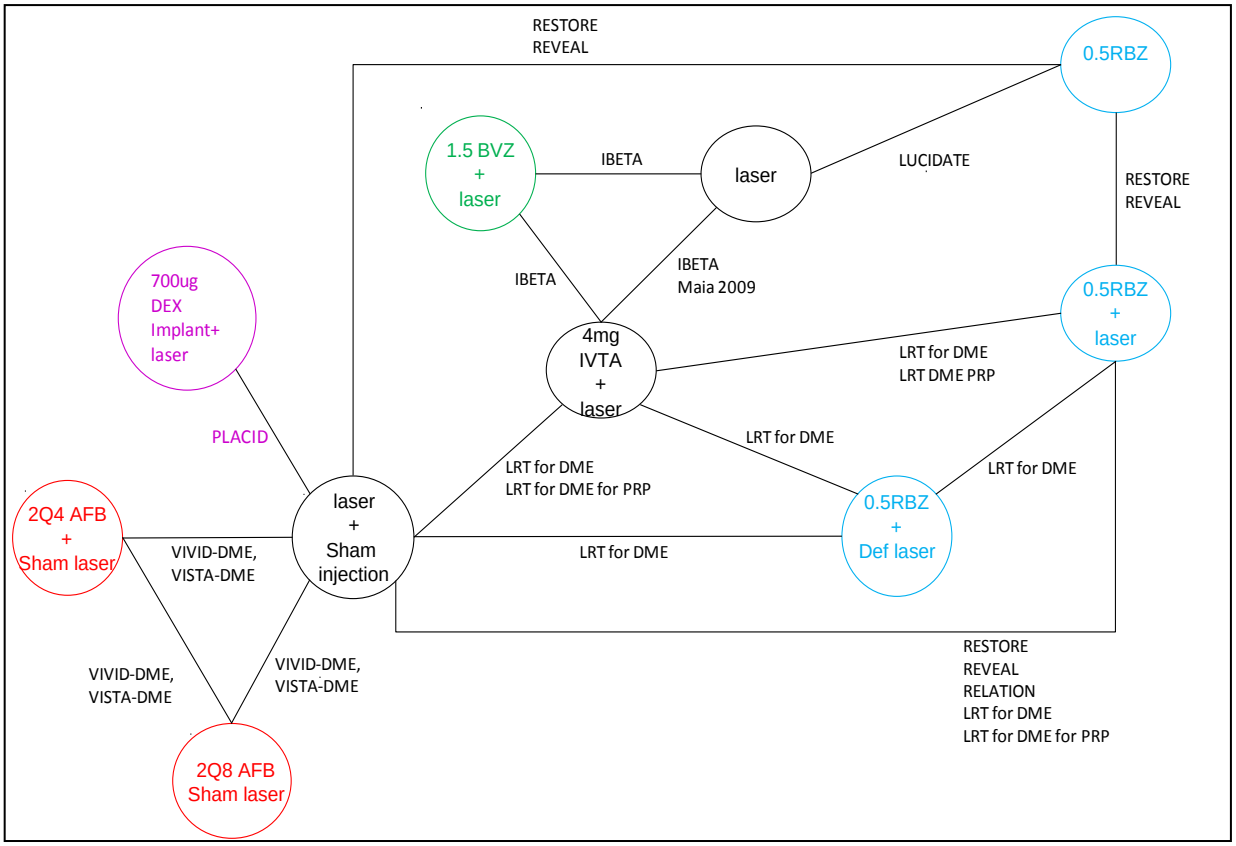

Figure 2 Available network at 12 months (Source Figure 18, company's submission)

4.4.2 Network meta-analysis

Figure 2 reproduces the 12-month network diagram of all relevant studies identified in the company's submission for the indirect comparisons between aflibercept and ranibizumab, and aflibercept and dexamethasone. A comparison between aflibercept and fluocinolone was not possible at 12 months due to the lack of a common comparator. Similarly, a network of studies at 24 months was not possible for the key comparators. Table 17 shows the results of the network meta-analysis expressed as risk ratio estimates. The company indicated that the results of the network meta-analysis showed a significant improvement in the visual acuity outcomes (BCVA mean change from baseline) for aflibercept 2Q8 compared with ranibizumab. However, no differences were observed for other outcomes such as gain of ≥ 10 letters, gain of ≥ 15 letters, loss of ≥ 10 letters, loss of ≥ 15 letters or indeed for the safety outcomes. Aflibercept was associated with a higher likelihood to improve visual acuity of ≥ 10 letters than dexamethasone. The company was concerned over the inclusion of the LRT for DME for PRP study due to differences in the study

protocol. A concern echoed by the ERG. The network meta-analysis was repeated without this study, but the results remained unchanged.

The network meta-analysis of the safety outcomes is also shown in Table 17 (risk ratio estimates). No significant differences were observed between aflibercept 2Q8 and ranibizumab for the nine safety outcomes for which a quantitative analysis was possible. Nevertheless, the proportion of participants who experiences cataracts or died tended to be higher, but not significant higher, with aflibercept treatment. The ERG' opinion is that these trends should be taken into account.

Table 17 Network meta-analysis results for aflibercept 2Q8 versus ranibizumab 0.5PRN for 12 month outcomes

		AFB vs RBZ	
Outcome		**Mean difference**	**95% CrI**
BCVA mean change from baseline	fixed	4.67	(2.45, 6.87)
	random	4.67	(1.85, 7.52)
BCVA mean average change from baseline	fixed	1.87	(0.22, 3.57)
	random	1.93	(-0.65, 4.34)
		Risk ratio	**95% CrI**
Gain of >=10 ETDRS letters	fixed	1.32	(0.98, 1.78)
	random	1.19	(0.90, 1.57)
Loss of >=10 ETDRS letters	fixed	[redacted]	[redacted]
	random	[redacted]	[redacted]
Gain of >=15 ETDRS letters	fixed	1.78	(0.96, 3.29)
	random	1.42	(0.93, 2.24)
Loss of >=15 ETDRS letters	fixed	0.13	(0.004, 1.35)
	random	0.14	(0.007, 1.52)
Treatment discontinuation	fixed	1.12	(0.55, 2.30)
	random	1.09	(0.39, 3.29)
All serious AE	fixed	0.76	(0.47, 1.26)
	random	0.82	(0.47, 1.42)
All serious ocular AE	fixed	0.28	(0.06, 1.24)
	random	0.30	(0.05, 2.49)
All AE	fixed	0.79	(0.55, 1.10)
	random	0.88	(0.64, 1.15)
All Ocular AE	fixed	0.75	(0.54, 1.05)
	random	0.85	(0.58, 1.25)
All serious non-ocular AE	fixed	0.60	(0.32, 1.14)
	random	0.67	(0.29, 1.66)
All non-ocular AE	fixed	1.09	(0.87, 1.40)
	random	1.03	(0.80, 1.56)
Eye pain	fixed	0.98	(0.38, 2.70)
	random	0.96	(0.23, 3.91)
Hypertension	fixed	0.95	(0.44, 2.07)
	random	0.95	(0.37, 2.55)
Cataract	fixed	3.93	(0.77, 32.74)
	random	3.83	(0.52, 43.72)
All-cause mortality	fixed	2.90	(0.20, 50.4)
	random	2.76	(0.13, 79.02)

CrI – Credible intervals

4.4.3 Critique of network meta-analysis

The company provided a network meta-analysis for both fixed and random effects. Although the company provided the WINBUGS codes for the model and the source data, they did not provide information on the initial values used, or the process of running the model. The ERG were able to determine from the model results provided in the submission's Appendices that the company had used a burn-in of 20, 000 iterations, followed by 20,000 iterations, which acted as updates for the model. However, it was not clear if this was 20,000 consecutive updates or say 100,000 using a thinning parameter of five. Models can be sensitive to the initial values and because the company did not provide their initial values or full details on the iterative process, in some cases, the ERG were unable to replicate the results. The ERG independently extracted source data from the references and matched them with those provided by the company.

In the case of continuous outcomes, mean change from baseline in BCVA, the ERG agree with the result presented by the company and consider the results consistent. Nonetheless, for binary secondary outcomes, results for aflibercept versus ranibizumab replicated by the ERG were in the same direction (non-significant) and same magnitude of effect even though some discrepancies in numerical values were observed. The ERG utilised WINBUGS code available from the Decision Support Unit website. The code for the random effects binary outcome matched exactly that used by the company while the code for the fixed effects did not. This inconsistency could explain some of the observed differences. Unless otherwise indicated all ERG models were undertaken with a burn in of 20,000 and 20,000 consecutive updates. Discrepancies could have been caused by differences in burn in or numbers of iteration updates with or without thinning. Strangely, within the fixed effects model, the company estimated risk ratios as a function of the odds ratios.

In particular, the ERG was concerned about the mortality results. Neither the fixed or random effect risk ratios calculated by the ERG were equivalent to those obtained by the company. The ERG speculate that this is a consequence of the choice of the initial values used and because mortality is a rare event. It is likely that the specification of different initial values would result in different estimates. Moreover, the iterative process may have differed between the ERG and company. The between-study

heterogeneity could also explain the observed discrepancies. Despite the numerical differences, the risk ratios estimated by both the company and the ERG were consistent with the data. Section 4.5 details the additional work the ERG undertook to investigate this further.

Table 18 shows the ERG network meta-analysis results for the comparison between aflibercept and ranibizumab together with those presented by the company in their submission. The company used the results of the random effects models to feed into the economic model. Although the ERG express some concern about the estimates of effect calculated using the fixed effect models, they are confident that the results used by the company in the cost-effectiveness analyses (random effects) are appropriate.

Table 18 Network-meta analysis – comparison of ERG and company findings

		Fixed effects		Random effects	
Outcome		RR	95% CrI	RR	95% CrI
Gain of >10 letter	MS	1.32	(0.98, 1.78)	1.19	(0.90, 1.57)
	ERG	1.25	(0.99, 1.95)	1.20	(0.89, 1.59)
Loss of >10 letter	MS	[redacted]	[redacted]	[redacted]	[redacted]
	ERG	[redacted]	[redacted]	[redacted]	[redacted]
Gain of >15 letter	MS	1.78	(0.96, 3.29)	1.42	(0.93, 2.24)
	ERG	1.32	(0.99, 2.34)	1.41	(0.92, 2.30)
Loss of >15 letter	MS	0.13	(0.004, 1.35)	0.14	(0.007, 1.52)
	ERG	0.14	(0.004, 1.40)	0.12	(0.004, 1.91)
Treatment discontinued	MS	1.12	(0.55, 2.30)	1.09	(0.44, 2.77)
	ERG	0.94	(0.47, 1.82)	1.10	(0.41, 2.91)
Mortality	MS	2.90	(0.20, 50.4)	2.76	(0.13, 79.02)
	ERG	1.91	(0.67, 21.8)	2.32	(0.03, 196.1)

CrI – Credible interval

The results indicate that, between aflibercept 2Q8 and ranibizumab, there is no difference in the proportion of patients who gain or lose ≥ 10 or ≥ 15 letters.

Taking into consideration that in VISTA the proportion of patients with prior anti-VEGF treatment was statistically significant higher than in VIVID (see Table 5)[36] and that REVEAL was based primarily on an Asian population,[40] the ERG opted for

repeating the NMA without VISTA, without REVEAL, and without VISTA and REVEAL (sensitivity analyses). The results are presented in section 4.5 of this report.[36,40]

4.5 Additional work on clinical effectiveness undertaken by the ERG

All–cause mortality

The company conducted a fixed effect meta-analysis of the number of deaths at 52 weeks in the VIVID and VISTA trials.[36] The pooled risk ratio calculating using the Mantel-Haenzsel fixed effects was 2.19 (95% CI 0.49 to 9.73) and 1.70 (95% CI 0.13 to 22.2) using the random effects model (undertaken by ERG). Both estimates indicate that the number of deaths was not significantly different between aflibercept 2Q8 and laser.

For the comparison between ranibizumab and laser, the company present mortality data from the RESTORE trial[38] but not from the REVEAL trial,[36,40] maintaining they are not available. The ERG succeeded in deriving these data from the clinical study report and ran a new meta-analysis including mortality data from REVEAL.[36,40] The estimated risk ratio was 1.34 (95% CI 0.27 to 6.72) for the fixed effects model and 1.29 (95% CI 0.24 to 6.78) for the random effects model, which indicated that there was no significant difference in the number of deaths between ranibizumab and laser.

The company did not undertake an indirect comparison of these results to obtain the estimate for aflibercept versus ranibizumab but the ERG calculated result using the Bucher method (based on random effects estimates). By restricting the analysis of the indirect comparison between aflibercept and ranibizumab to VISTA, VIVID, and RESTORE the risk ratio was 1.77 (95% CI 0.07 to 44.24),[38] inclusion of REVEAL[36,40] changed the risk ratio to 1.32 (95% CI 0.06 to 28.06). This indicates that although there was a trend towards a higher risk of mortality with aflibercept, it was not statistically significant. The meta-analysis of the week-100 mortality data from VIVID and VISTA for the comparison between aflibercept and laser, provide a similar conclusion.[36]

Network meta-analysis – all cause mortality

The ERG found some discrepancies in the risk ratio estimates for the outcome of mortality for both fixed and random effects models within the network meta-analysis (Table 18). To assess this, the ERG considered 20,000 burn in and 100,000 updates with a thinning parameter of five. The random effects risk ratio was 2.74 (95% CrI 0.11 to 79.4) compared with 2.76 (95% CrI 0.13 to 79.02) presented by the company. These estimates were more in line with each other than the original ERG estimate of 2.32 (95% CrI 0.03 to 196.1), which was obtained with burn in of 20,000 and 20,000 consecutive updates. In addition, the ERG undertook a revised analysis to include REVEAL in the network. The random effects methods gave a risk ratio of 1.42 (95% CrI 0.06 to 29.96). In all instances, there was a trend to increased mortality among participants treated with aflibercept compared with ranibizumab even though the observed differences were not statistically significant.

Network meta-analysis – outcomes relevant to cost-effectiveness

The ERG felt it appropriate to repeat the network met-analysis without VISTA, without REVEAL, and without both VISTA and REVEAL. These additional analyses were undertaken for the four outcomes that fed into the economic model: gain of ≥ 10 letters, loss of ≥ 10 letters, gain of ≥ 15 letters, loss of ≥ 15 letters, and treatment discontinuation. Table 19 illustrates the results of these analyses including the relative risk for aflibercept 2Q8 versus laser, ranibizumab versus laser and aflibercept versus ranibizumab. Random effect models were used.

Excluding VISTA, REVEAL or both had some impact on the point estimates of aflibercept versus ranibizumab and the 95% credible intervals tend to be wider. However, in each case no significant difference was found. The more apparent differences in results for the outcome ‘loss of ≥ 15 letters’ were due to the fact that in VIVID alone there were no participants experiencing this outcome.

Table 19 Network meta-analysis - sensitivity analysis carried out by ERG

		AFB vs RBZ		AFB vs laser		RBZ vs Laser	
Outcome		RR	95% CrI	RR	95% CrI	RR	95% CrI
Gain of >10 letter	MS	1.19	(0.90, 1.57)	2.07	(1.68, 2.48)	1.74	(1.36, 2.17)
	ERG	1.20	(0.89, 1.59)	2.09	(1.67, 2.50)	1.75	(1.35, 2.20)
	ERG (excl VISTA)	1.08	(0.71, 1.53)	1.89	(1.30, 2.43)	1.75	(1.33, 2.19)
	ERG (excl REVEAL)	1.21	(0.83, 1.95)	2.03	(1.57, 2.46)	1.67	(1.05, 2.28)
	ERG (excl VISTA & REVEAL)	1.11	(0.62, 1.94)	1.84	(1.10, 2.43)	1.66	(0.995, 2.28)
Loss of >10 letter	MS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG (excl VISTA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG (excl REVEAL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG (excl VISTA & REVEAL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain of >15 letter	MS	1.42	(0.93, 2.24)	3.09	(2.20, 4.21)	2.19	(1.47, 3.13)
	ERG	1.41	(0.92, 2.30)	3.06	(2.18, 4.20)	2.15	(1.47, 3.06)
	ERG (excl VISTA)	1.38	(0.79, 2.32)	2.94	(1.82, 4.38)	2.10	(1.44, 3.06)
	ERG (excl REVEAL)	1.40	(0.80, 2.68)	3.06	(2.05, 4.26)	1.22	(2.17, 3.52)
	ERG (excl VISTA & REVEAL)	1.37	(0.64, 2.87)	3.02	(1.61, 4.55)	2.20	(1.14, 3.61)
Loss of >15 letter	MS	0.14	(0.007, 1.52)	0.026	(0.001, 0.16)	0.19	(0.03, 0.63)
	ERG	0.12	(0.004, 1.91)	0.02	(0.001, 0.16)	0.19	(0.03, 0.70)
	ERG (excl VISTA)	0.00	(0.00, 0.09)	0.00	(0.00, 0.015)	0.18	(0.03, 0.63)
	ERG (excl REVEAL)	0.30	(0.004, 12.9)	0.03	(0.00, 0.18)	0.09	(0.004, 0.65)
	ERG (excl VISTA & REVEAL)	0.00	(0.00, 1.36)	0.00	(0.00, 0.04)	0.08	(0.003, 0.61)
Treatment discontinued	MS	1.09	(0.44, 2.77)	0.80	(0.42, 1.55)	0.74	(0.37, 1.36)
	ERG	1.10	(0.41, 2.91)	0.81	(0.39, 1.58)	0.73	(0.35, 1.40)
	ERG (excl VISTA)	1.02	(0.27, 3.26)	0.75	(0.25, 1.89)	0.74	(0.36, 1.42)
	ERG (excl REVEAL)	0.72	(0.26, 2.06)	0.81	(0.40, 1.50)	1.14	(0.47, 2.33)
	ERG (excl VISTA & REVEAL)	0.69	(0.16, 2.79)	0.78	(0.24, 2.01)	1.12	(0.40, 2.59)

CrI – Credible interval

4.6 Conclusions of the clinical effectiveness section

In summary, the company provided detail on two RCTs, VIVID and VISTA, comparing aflibercept treatment (2Q4 and 2Q8) with laser therapy for DMO. Results favoured aflibercept for the main visual acuity outcomes of interest (mean change from baseline in BCVA, proportion of patients gaining ≥10 letters and ≥15 letters). Visual improvements were maintained at week 100. The safety profile of aflibercept was found to be similar to that of laser, albeit with a greater, but not significant, number of deaths. The company provided a meta-analysis of the results of VIVID and VISTA as well as a network meta-analysis to enable indirect comparison between aflibercept 2Q8 and ranibizumab as no head-to-head trials were identified.

The results of the indirect comparison indicated that both aflibercept 2Q8 and ranibizumab were favourable to laser for the main outcomes of mean change in BCVA from baseline to 12 months, gain of ≥10 letters, gain of ≥15 letters, loss of ≥10 and loss of ≥15 letters. The results of the network meta-analysis showed a significant improvement in BCVA mean change from baseline for aflibercept 2Q8 in comparison with ranibizumab. However, no significant differences (random effects) were observed between aflibercept and ranibizumab for other visual acuity outcomes (gain of ≥10 letters, gain of ≥15 letters, loss of ≥10, and loss of ≥15 letters).

For each of the safety outcomes, patients receiving aflibercept experienced fewer adverse events than ranibizumab, but these results are based on small numbers of studies and therefore should be interpreted with caution. Numbers of deaths were found to be greater, but not significantly greater, among participants receiving aflibercept than among those receiving ranibizumab.

5 COST-EFFECTIVENESS

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objectives of the cost-effectiveness review

A systematic review was carried out by the company to identify relevant cost-effectiveness studies.

The company states in the submission that literature searches for cost-effectiveness studies were undertaken in October 2013and s subsequently updated in August 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, EconLIT and NHS EED as well as relevant conference proceedings for the last six years. Full details of the search strategies are included in Appendix 10.10 of the company's submission and are reproducible.

The search strategies followed the same structure as for the clinical effectiveness searches and replace the RCTs filters with appropriate Cost-effectiveness filters. Once again, however, the term 'edema' was not used and this omission had the potential to impact on the sensitivity of the search.

With regard to quality of life data, the company conducted literature searches in February 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, EconLIT and NHS EED. Full details of the search strategies are included in Appendix 10.12 of the company's submission and are reproducible. The search strategies followed the same structure as for previous searches with the inclusion of appropriate quality of life/utilities filters. In addition specific utilities for adverse events and blindness were sought. For all searches, both 'oedema' and 'edema' had been used correctly. These searches were judged by the ERG to be adequate and comprehensive.

5.1.2 Inclusion/exclusion criteria of the cost-effectiveness review

Only full-published economic evaluations were eligible, including studies based on models or performed alongside clinical trials. General cost of illness, economic burden, sot-minimisation and budget impact studies were not considered for inclusion.

5.1.3 Studies included in the cost-effectiveness review

The systematic literature review identified 10 studies[15,47-55] directly related to the decision problem. Table 63 of the company submission provides an overview of these ten studies. The TA274 ranibizumab for DMO is perhaps the most immediately relevant of all identified studies.[15] The submission draws a number of values from this. The Haig et al study, which models the cost-effectiveness of ranibizumab for DMO in the Canadian setting, is also particularly relevant.[54]

5.1.4 Main conclusions of the cost-effectiveness review

The company concludes that most cost-effectiveness studies find ranibizumab to be cost effective compared to laser for treating DMO.

Stein et al[47] found ranibizumab plus laser to have a cost-effectiveness estimate compared to laser of $89,903 per QALY, while bevacizumab plus laser had a cost-effectiveness estimated compared to laser of $11,138 per QALY. Bevacizumab was assumed to have equivalent efficacy and a similar adverse event profile to ranibizumab, and given these assumptions was concluded to provide the greatest value.

Issues around CRT thickness were not addressed within the review, despite the STA of ranibizumab for DMO being reviewed by the company. This found ranibizumab with a PAS to be cost effective for those with a CRT ≥ 400μm but to be not cost effective for those with a CRT < 400μm.

The ERG has also identified Haig et al 2014 sponsored by Novartis,[47,56] which models the cost effectiveness of ranibizumab 0.5mg PRN with aflibercept 2Q8 for DMO in the UK setting, with both being evaluated at their respective list prices of £742 and £816. It is available as an ISPOR poster presentation, the key elements to this being the relative risks, quality of life and the dosing and monitoring assumptions.

Relative risks of gaining 10 letters were drawn from a network meta-analysis by Regnier et al,[27] this also being sponsored by Novartis. Eight RCTs were included: da VINCI, VISTA, VIVID, DCRC.net, READ-2, RESOLVE, RESPOND and RESTORE. Ranibizumab PRN was found to have a significantly better odds ratio of

10 letter improvement than laser: 5.50 (2.73-13.16), and a numerically superior but non-significant odds ratio than aflibercept: 1.59 (0.61-5.37). Limitations noted by the authors were that three of the eight RCTs had not been published.

As with the submission for the TA274 ranibizumab for DMO, the modelling relied upon the quality of life estimates of Czoski-Murray et al.[57] Treatment was assumed to be of three years' duration with the number of treatments for ranibizumab PRN being 7.0 in year one based upon RESTORE and 3.9 and 2.9 in years two and three based upon the RESTORE extension. Monitoring visits for ranibizumab were 12.0 in year one based upon RESTORE and 9.0 and 7.5 in years two and three based upon the DRCR.net. The number of aflibercept treatments was assumed to be 8.5 in year 1 based upon VIVID/VISTA and 5.1 in year 2 based upon VISTA, with 5.1 also being assumed for year three. The number of monitoring visits for aflibercept was assumed to be the same as the number of treatments (Table 20).

Table 20 Haig et al (2014) treatment and monitoring

	Ranibizumab PRN		Aflibercept 2Q8	
	Tx.	Monit.	Tx.	Monit.
Year 1	7.0	12.0	8.5	8.5
Year 2	3.9	9.0	5.1	5.1
Year 3	2.9	7.5	5.1	5.1

Haig et al 2014[56] estimated ranibizumab to provide a lifetime cost saving of £5,841 and to also provide an additional 0.05 QALYs, and so to dominate aflibercept at list prices.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist (Table only)

Table 21 NICE reference case checklist

Attribute	**Reference case and NICE Guide to the Methods of TA**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	The scope specifies: • Laser • Ranibizumab • Fluocinolone • Dexamethasone • Bevacizumab Consideration of bevacizumab is restricted to the subgroup where ranibizumab and fluocinolone are not suitable. The drug treatments may be with or without laser.	The submission mainly considers laser and ranibizumab. Fluocinolone and dexamethasone are also considered. Bevacizumab is not considered.
Patient group	As per NICE scope. "*People with visual impairment because of diabetic macular oedema*"	Yes.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost-utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	A lifetime horizon is adopted.
Synthesis of evidence on outcomes	Systematic review	Yes. For most of the comparators the results of the company NMA are relied upon. For the comparison with fluocinolone due to it not being part of the NMA rates are estimated directly from the reported fluocinolone trial data.

		For the comparisons with dexamethasone and aflibercept where there is no data they are assumed to be clinically equivalent to laser.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	No. The base case uses the quality of life values reported in Czoski-Murray. This as an experimental study using lenses to simulate differing degrees of vision loss. There is an analysis of the VIVID/VISTA EQ-5D data that is used as a sensitivity analysis. Scenario analyses also use quality of life values drawn from Brown 1999 and Brown 2000.
Benefit valuation	Time-trade off or standard gamble	The base case uses Czoski-Murray utility values which are based upon time trade off. The valuations of the EQ-5D data of VIVID/VISTA is based upon the UK social tariff, so is time trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	No. The base case uses Czoski-Murray utility values which are based upon the responses of those taking part in the experiment. The company analysis of the VIVID/VISTA EQ-5D data uses the standard UK social tariff which is based upon a

		representative sample of the UK public.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		Yes. A good range of one way sensitivity analyses are presented, with these only being a subset of the full range of sensitivity analyses undertaken.

5.2.2 Model structure

A de novo Markov model with a monthly cycle was developed by the company. This is a bilateral vision model with each eye being in one of eight possible health states which are in the main 10 ETDRS letters wide. This results in a total of 64 possible vision states plus the additional absorbing health state of death. The health states for each eye are based upon the ETDRS letter ranges (Table 22).

Table 22 Individual eye health states

	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
Letters	86+	76-85	66-75	56-65	46-55	36-45	26-35	0-25

Patients enter the model having at least one eye being treated for DMO. Of these patients 46.5% are assumed to be bilateral at baseline. An additional 10% of the remainder develop fellow eye DMO involvement at the start of years 2, 3, 4 and 5. It is assumed that 50% of the fellow eyes with DMO at baseline will be treated at baseline, and that 50% of incident fellow eye DMO will be treated at incidence. The other 50% of fellow eyes with DMO are assumed not to be treated.

For eyes that are treated there is an initial efficacy phase of one year followed by a maintenance phase of 4 years. Treatments are associated with a treatment specific

discontinuation rate during the first 5 years of treatment. After five years all treatment stops.

The clinical effectiveness estimates for the efficacy phase are based upon applying the relative risks of the NMA to the rates of improving and worsening by at least two health states and by one health state in the pooled VIVID/VISTA laser arm.
During the four year maintenance phase treatment is assumed to continue. Eyes that remain on treatment retain stable vision.

When treatment stops, due to either discontinuation or the end of the maintenance phase, the eye is subject to a monthly 1.15% probability of deteriorating by one health state. This is based upon the 3.5% quarterly rate of deterioration used within the STA of ranibizumab for DMO.

Non-DMO eyes are subject to a monthly 0.17% probability of deteriorating by one health state.

5.2.3 Population

The patient population is that of the VIVID/VISTA trials, though the rate of bilateral involvement at baseline (46.5%) is drawn from expert option rather than the VIVID/VISTA trial data. The starting age of the cohort is 63, with 42.1% being female. The initial distribution between health states for the treated eye and the fellow eye are shown in Table 23.

Table 23 Eyes' baseline distributions between health states

	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
Study eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fellow eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.4 Interventions and comparators

The main comparators for aflibercept are ranibizumab and laser.

Scenario analyses comparing aflibercept with dexamethasone and fluocinolone are also presented.

5.2.5 Perspective, time horizon and discounting

The perspective for outcomes is that of the patient, while the perspective for costs is that of the NHS and the PSS.

A lifetime horizon has been adopted, with costs and benefits discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness

The proportions in the pooled VIVID/VISTA laser arms:

- improving by at least two health states;
- improving by one health state;
- worsening by one health state; and,
- worsening by at least two health states

are calculated based upon patient count data. These are transformed to a monthly proportions according to ((1+p)^(1/12))-1 where p is the annual proportion.

The relative risks of:

- improving by at least 15 letters;
- improving by at least 10 letters;
- worsening by at least 10 letters; and,
- worsening by at least 15 letters

of the NMA are applied to the monthly laser proportions outlined above to derive the monthly proportions:

- improving by at least two health states;
- improving by one health state;
- worsening by one health state; and,
- worsening by at least two health states

for the comparator treatments during the efficacy phase.

Table 24 Relative risks applied within the model during year 1

	+2HS	+1HS	-1HS	-2HS
Aflibercept	3.09	2.07	[redacted]	0.03

Ranibizumab	2.19	1.74	0.37	0.19
Dexamethasone	1.00	1.18	1.00	1.00

The relative risks shown in Table 24 are based upon the NMA. The values derived using the Bucher method are used by the company for a sensitivity analysis. For the comparison with dexamethasone where there is no NMA estimate the effectiveness of dexamethasone is assumed to be the same as laser. For the comparison with fluocinolone, rates of improvement are taken directly from the FAME trial while rates of worsening are assumed to be the same as those of laser. This results in the monthly transition probabilities during the first year of the model shown in Table 25.

Table 25 Monthly transition probabilities applied within the model during year 1

	+2HS	+1HS	-1HS	-2HS
Laser	0.67%	1.70%	1.28%	0.78%
Aflibercept	2.08%	3.51%	[redacted]	0.02%
Ranibizumab	1.48%	2.95%	0.47%	0.15%
Dexamethasone	0.67%	2.00%	1.28%	0.78%
Fluocinolone	1.62%	1.31%	1.28%	0.78%

The submitted model also has the facility to base the transitions for the comparison of aflibercept with laser upon the VIVID/VISTA patient count data, this enabling the population of transition probability matrices (TPMs). Due to the results within the written submission being based exclusively upon the relative risk approach, this has not been examined by the ERG. But given the model validation data it may be something to bear in mind for the future.

Extrapolation

Patients may have their eye treated for up to another four years of maintenance after the first year of treatment. Those eyes remaining on treatment are assumed to have stable vision.

Those coming off treatment are assumed to have a steady decline in their vision, with 1.15% of eyes off treatment being assumed to decline by 10 letters and so to transfer

to the next worst health state. This rates is based upon the three month 3.5% rate used in the STA of ranibizumab for DMO.

Non-DMO eyes are subject to a monthly 0.17% probability of deteriorating by one health state.

Discontinuation and adverse event rates

The rates of discontinuation and adverse events are derived in a similar manner to the main efficacy estimates, with the baseline rate for the laser arm of the VIVID/VISTA trials being conditioned by relative risks derived from the NMA.

Table 26 Monthly rates of discontinuation and adverse events on treatment

	Laser	Aflib.	Ranibiz.	Dexameth.	Fluo.
Discontinuation	0.85%	0.68%	0.63%	0.59%	0.76%
Cataract	0.43%	0.41%	0.11%	0.94%	0.99%
Endophthalmitis	0.03%	0.00%	0.03%	0.03%	0.01%
Ret. Detachment	0.03%	0.03%	0.00%	0.03%	0.03%
Glaucoma	0.31%	0.29%	0.00%	0.00%	0.00%
Vit. Haemorrhage	0.12%	0.11%	0.00%	0.18%	0.02%
Raised IOP	0.29%	0.26%	0.31%	3.63%	1.10%

Mortality multipliers

A relative risk of mortality for patients with diabetes of 1.95 drawn from Preis et al[58] is applied.

An additional relative risk of mortality of 1.23 from Christ et al[59]is applied for those with one or both eyes falling into HS7 or HS8.

The relative risk of mortality for aflibercept versus laser of 2.19 is not applied, due to the small number of deaths that were involved and the wide confidence intervals associated with the estimate.

5.2.7 Health related quality of life

There are four sources of quality of life data available to the model for the main model health states:

- VIVID/VISTA EQ-5D data
- Czoski-Murray et al[57]
- Brown (1999)[60]
- Brown 2000[61]

The trial EQ-5D data is evaluated using the UK social tariff and explicitly accounts for changes in the better seeing eye (BSE) and the worse seeing eye (WSE) while also taking into account age and BMI as covariates. Despite this, the base case uses Czoski-Murray values. The other sources are used as scenario analyses.

Quality of life: VIVID/VISTA EQ-5D data

The submission provides details of an ordinary least squares (OLS) analysis of the pooled VIVID/VISTA EQ-5D data. This regresses quality of life upon the logarithms of the BCVA of the BSE and of the WSE and also upon age and BMI with results shown in Table 27.

Table 27 VIVID/VISTA EQ-5D OLS regression

	OLS	
	Coef	S.E.
Constant	[redacted]	[redacted]
Baseline BMI	[redacted]	[redacted]
Age	[redacted]	[redacted]
Log (BCVA of WSE)	[redacted]	[redacted]
Log (BCVA of BSE)	[redacted]	[redacted]

The coefficients are all statistically significant. Patient visit time was also explored as a variable but was found to be not significant.

Based upon mid points of 90.5, 80.5, 70.5, 60.5, 50.5, 40.5, 30.5 and 20.5 letters for the health states, a BMI of 35 and an age of 63 years the quality of life values shown in Table 28 are produced.

Table 28 Bilateral quality of life: VIVID/VISTA EQ-5D OLS

	BSE

WSE	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	[redacted]							
HS2	[redacted]	[redacted]						
HS3	[redacted]	[redacted]	[redacted]					
HS4	[redacted]	[redacted]	[redacted]	[redacted]				
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
HS7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
HS8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Quality of life: other sources within the literature: changes in overall BCVA

The company provides analyses drawing upon the quality of life estimates within the published literature, using Czoski-Murray, Brown 1999 and Brown 2000[57,60,61]. For ease of comparison, the corresponding values estimated from the VIVID/VISTA EQ-5D OLS regression are presented alongside in Table 29.

Table 29 BCVA quality of life: values from the literature

	Czoski Murray	Brown 1999	Brown 2000	Trial EQ-5D
HS1	0.856	0.839	0.890	[redacted]
HS2	0.764	0.839	0.890	[redacted]
HS3	0.690	0.783	0.810	[redacted]
HS4	0.617	0.783	0.690	[redacted]
HS5	0.543	0.732	0.558	[redacted]
HS6	0.469	0.681	0.545	[redacted]
HS7	0.396	0.630	0.520	[redacted]
HS8	0.263	0.579	0.460	[redacted]

Quality of life: WSE impact as proportion of BSE impact

The utilities from Czoski-Murray, Brown 1999 and Brown 2000 apply to the bilateral BCVA[57,61]. As a consequence, the company has allowed for a proportion of the BSE utility impact for a given change in the BCVA health state of the BSE to apply to the same change in the BCVA health state of the WSE. This adjustment factor is given as 30% and is applied according to the formula 1/[1+(1/30%)], which results in a proportional effect of 23%. For the quality of life values drawn from Czoski-Murray, Brown 1999 and Brown 2000 this results in the bilateral quality of life values shown in Tables 30-32.[57,60,61]

Table 30 Bilateral quality of life: Czoski-Murray[57]

	BSE							
WSE	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	0.8559							
HS2	0.8346	0.7639						
HS3	0.8177	0.7469	0.6903					
HS4	0.8007	0.7299	0.6733	0.6167				
HS5	0.7837	0.7129	0.6563	0.5997	0.5431			
HS6	0.7667	0.6959	0.6393	0.5827	0.5261	0.4695		
HS7	0.7497	0.6790	0.6223	0.5657	0.5091	0.4525	0.3959	
HS8	0.7192	0.6484	0.5918	0.5352	0.4785	0.4219	0.3653	0.2634

Table 31 Bilateral quality of life: Brown 1999[60]

	BSE							
WSE	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	0.8390							
HS2	0.8390	0.8390						
HS3	0.8261	0.8261	0.7830					
HS4	0.8261	0.8261	0.7830	0.7830				
HS5	0.8143	0.8143	0.7712	0.7712	0.7320			
HS6	0.8025	0.8025	0.7595	0.7595	0.7202	0.6810		
HS7	0.7908	0.7908	0.7477	0.7477	0.7085	0.6692	0.6300	
HS8	0.7790	0.7790	0.7359	0.7359	0.6967	0.6575	0.6182	0.5790

Table 32 Bilateral quality of life: Brown 2000[61]

	BSE							
WSE	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	0.8900							
HS2	0.8900	0.8900						
HS3	0.8715	0.8715	0.8100					
HS4	0.8438	0.8438	0.7823	0.6900				
HS5	0.8134	0.8134	0.7518	0.6595	0.5580			
HS6	0.8104	0.8104	0.7488	0.6565	0.5550	0.5450		
HS7	0.8046	0.8046	0.7431	0.6508	0.5492	0.5392	0.5200	
HS8	0.7908	0.7908	0.7292	0.6369	0.5354	0.5254	0.5062	0.4600

Quality of life: adverse events

Quality adjusted life year (QALY) decrements for adverse events are drawn from the literature, with the values presented in Table 33 being applied. These values are described as having been "*normalised*".

Table 33 QALY decrements associated with adverse events

	QALY
Cataract	0.140
Endophthalmitis	0.000
Ret. Detachment	0.130
Glaucoma	0.000
Vit. Haemorrhage	0.020
Raised IOP	0.000

5.2.8 Resources and costs

Direct treatment and administration costs

The £816 list price of aflibercept has a PAS of [redacted] resulting in a with PAS price of [redacted]. Ranibizumab is associated with a list price of £742, dexamethasone with a list price of £870 and fluocinolone with a list price of £5,500, all these being drawn from the BNF.

Administration costs of £194 are applied to aflibercept, ranibizumab and fluocinolone, based upon the TA283 aflibercept for CRVO. Dexamethasone is associated with a higher administration cost of £218, though the source for this is not given. Laser is associated with costs of £117 based upon NHS reference cost BZ23Z Minor vitreous retinal procedures and a £139[a] additional monitoring cost which is apparently based upon the TA283 aflibercept for CRVO, to give a total cost per administration of £256. An initial fluorescein angiography is assumed for all treatments at a cost of £117, based upon NHS reference cost BZ23Z. Thereafter, dedicated monitoring visits are costed at £139, based upon the TA283 aflibercept for CRVO. The number of treatments and monitoring visits for the base case is shown in Table 34.

[a] Note that the written submission suggests £193 with the £139 being taken from the electronic model.

Table 34 Treatment and monitoring visits: base case

	Administrations					Monitoring visits				
	Afli.	Rani.	Dexa.	Fluo.	Laser	Afli.	Rani.	Dexa.	Fluo.	Laser
Year 1	8.00	7.93	3.00	1.00	2.40	8.00	12.00	5.00	4.00	4.00
Year 2	4.00	4.00	2.00	0.00	1.00	6.30	6.30	4.00	4.00	4.00
Year 3	2.30	2.30	2.00	1.00	0.80	4.00	4.00	4.00	4.00	2.60
Year 4	1.20	1.20	0.00	0.00	0.40	4.00	4.00	4.00	4.00	2.20
Year 5	1.00	1.00	0.00	0.00	0.30	2.00	2.00	4.00	4.00	1.90

Note that the electronic copy of the model suggests [redacted] and [redacted] administrations of aflibercept during the first and second years of VIVID/VISTA respectively. It also suggests a mean number of ranibizumab administrations of 7.40 in the first year based upon RESTORE/REVEAL rather than the 7.93 drawn from the publications underlying the network meta-analysis.

The model assumes that all treatment visits can double as monitoring visits (Table 35).

Table 35 Treatment and dedicated monitoring visits: base case

	Administrations					Dedicated monitoring visits				
	Afli.	Rani.	Dexa.	Fluo.	Laser	Afli.	Rani.	Dexa.	Fluo.	Laser
Year 1	8.00	7.93	3.00	1.00	2.40	0.00	4.07	2.00	3.00	1.60
Year 2	4.00	4.00	2.00	0.00	1.00	2.30	2.30	2.00	4.00	3.00
Year 3	2.30	2.30	2.00	1.00	0.80	1.70	1.70	2.00	3.00	1.80
Year 4	1.20	1.20	0.00	0.00	0.40	2.80	2.80	4.00	4.00	1.80
Year 5	1.00	1.00	0.00	0.00	0.30	1.00	1.00	4.00	4.00	1.60

The model also assumes that a fixed percentage of monitoring and eye examination visits will be shared between the study eye and the fellow eye: 88% for the anti-VEGFs and 91% for laser. It is not clear how these percentages have been arrived at. Note that since the study eye is treated from baseline for up to five years while the fellow eye incidence goes out to five years with treatment continuing for up to five years subsequent to this, these percentages seem quite high. This may argue for a sensitivity analysis setting these percentages to zero.

Costs: adverse events

The costs of adverse events are based upon NHS reference costs for procedures, plus some additional outpatient assessment and follow-up visits. The NHS reference cost for the day case BZ02Z of £882 is applied to cataracts. The NHS reference cost for BZ23Z: minor vitreous procedures non-elective long stay of £1,012 is applied to endophthalmitis, though note that only eight of these finished consultant episodes (FCEs) are listed within the reference costs for 2012-13, while the BZ23Z non-elective short stay cost of £1,490 is applied to both retinal detachment and vitreous haemorrhage. Outpatient visits are costed at £88.29[b] based upon consultant led follow-up visits, with cataract requiring three, endophthalmitis requiring six, retinal detachment requiring four and vitreous haemorrhage requiring two. A cost of £1,151 for glaucoma is taken from TA301 fluocinolone, while the £3.57 applied for raised IOP is drawn from the TA283 aflibercept for CRVO. This results in the adverse event costs presented in Table 36.

Table 36 Adverse event costs: company estimates

	Unit cost
Cataract	£1,147
Endophthalmitis	£1,542
Retinal detachment	£1,843
Vitreous haemorrhage	£1,667
Raised IOP	£4
Glaucoma	£1,151

Costs of blindness

An average annual cost of blindness of £6,448 derived from figures within Meads et al (2003) updated for inflation is applied to those with both eyes falling in HS7 or HS8.

5.2.9 Cost-effectiveness results

The base case results for the comparison with laser, including the aflibercept PAS, are presented in Table 37.

[b] The ERG

Table 37 Company base case results aflibercept vs laser: including aflibercept PAS

	Aflibercept	Laser	Net
Tx 1st eye	[redacted]	[redacted]	£7,643
Tx 2nd eye	[redacted]	[redacted]	£3,271
AE 1st eye	[redacted]	[redacted]	-£71
AE 2nd eye	[redacted]	[redacted]	-£22
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£213
Blindness	[redacted]	[redacted]	-£13,046
Total	[redacted]	[redacted]	-£2,438
LYs undisc.	15.626	15.509	0.116
QALYs	7.690	7.300	0.390
ICER			Dominant
Tx: treatment; AE: adverse events; Fl. Angio: fluorescein angiography; LYs undisc: undiscounted life years.			

Aflibercept is estimated to dominate laser, resulting in an additional 0.390 QALYs and a cost saving of £2,438. The cost saving is overwhelmingly due to the savings of £13,046 associated with reductions in the costs of blindness.

The monetised net health benefits, calculated as the willingness to pay per QALY times the net QALYs minus the net costs, are £14,135 at a willingness to pay of £30,000 per QALY and £10,748 at a willingness to pay of £20,000 per QALY.

Based upon figure 74 of the submission probabilistic modelling suggests that for willingness to pay values of £0, £20,000, £30,000 and £50,000 per QALY the probability of aflibercept being cost effective is around 58%, 96%, 99% and 100% respectively.

The base case results for the comparison with ranibizumab, including the aflibercept PAS but not making any allowance for the ranibizumab PAS, are presented in Table 38.

Table 38 Company base case results aflibercept vs ranibizumab: including aflibercept PAS

	Aflibercept	Ranibizumab	Net
Tx 1st eye	[redacted]	[redacted]	-£4,225
Tx 2nd eye	[redacted]	[redacted]	-£1,813
AE 1st eye	[redacted]	[redacted]	£376
AE 2nd eye	[redacted]	[redacted]	£117
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£568
Blindness	[redacted]	[redacted]	-£2,798
Total	[redacted]	[redacted]	-£8,911
LYs undisc.	15.626	15.597	0.028
QALYs	7.690	7.598	0.092
ICER			Dominant

Aflibercept is estimated to dominate ranibizumab, resulting in an additional 0.092 QALYs and a cost saving of £8,911. The cost saving is mainly due to the lower drug costs, but these do not include the ranibizumab PAS. There are also quite large cost savings of £2,798 associated with reductions in the costs of blindness.

The monetised net health benefits are £11,667 at a willingness to pay of £30,000 per QALY and £10,748 at a willingness to pay of £20,000 per QALY.

Based upon figure 74 of the submission probabilistic modelling suggests that at all willingness to pay values the probability of aflibercept being cost effective is around little different from 100%.

Sensitivity analyses that explore the impacts of varying ranibizumab PAS percentages are presented in Table 39.

Table 39 Base case results: aflibercept versus ranibizumab: ranibizumab PAS discounts

Δ QALYs	Rani. PAS	Δ Costs	ICER	Rani. PAS	Δ Costs	ICER
0.0919	5%	-£8,181	Dominant	55%	-£887	Dominant
	10%	-£7,452	Dominant	60%	-£158	Dominant
	15%	-£6,723	Dominant	65%	£572	£6,223
	20%	-£5,993	Dominant	70%	£1,301	£14,163
	25%	-£5,264	Dominant	75%	£2,030	£22,103
	30%	-£4,534	Dominant	80%	£2,760	£30,043
	35%	-£3,805	Dominant	85%	£3,489	£37,983
	40%	-£3,075	Dominant	90%	£4,219	£45,923
	45%	-£2,346	Dominant	95%	£4,948	£53,863
	50%	-£1,617	Dominant	100%	£5,678	£61,803

5.2.10 Sensitivity analyses

Revising the time horizon from the lifetime of the base case to 5 years in cell C15 of the *Executive Summary* worksheet of the model revises the monetised net health benefits from £14,135 to -£5,578. This is not in line with the sensitivity analysis reported in figure 71 of the submission, but is in line with the electronic copy of the model when the subroutine *DetSA()* is run. The values reported in Table 40 are based upon running the subroutine *DetSA()* rather than being taken from the written submission. While the values changes, the broad thrust of the sensitivity analyses is the same.

Note that the one way sensitivity analyses are only reported for the parameters that have the largest impact for the ranges applied. The rate of decline in the non-DMO fellow eye was found to have relatively little impact when tested over the range 1.52% ±20%.

Table 40 One way sensitivity analyses: aflibercept versus laser

	Mean	Low		High	
	Value	Value	NHB	Value	NHB
Base case NHB	-£14,135				
Time horizon 5 years			-£5,578		
Time horizon 10 year			-£1,398		
Starting age of cohort	63	58	£25,053	68	£6,038
Bucher method			£18,048		
DMO eye decline	1.15%	0.92%	£10,573	1.38%	£17,896
Aflibercept gaining 4 lines	2.08%	1.48%	£11,416	2.84%	£17,331
RR of mortality for diabetic patients	1.95	1.64	£17,301	2.33	£11,197
Annual cost of blindness	£6,448	£5,159	£11,526	£7,738	£16,745
Laser losing 4 lines	0.78%	0.51%	£11,539	1.04%	£16,708
Aflibercept gaining 2 lines	3.51%	2.85%	£12,313	4.21%	£16,004
Laser gaining 4 lines	0.67%	0.42%	£15,862	0.92%	£12,501
Aflibercept Injection year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laser losing 2 lines	1.28%	0.96%	£12,659	1.58%	£15,583
Laser gaining 2 lines	1.70%	1.36%	£15,493	2.03%	£12,844
% of bilateral involvement at baseline	46.5%	37.2%	£12,865	55.8%	£15,407
Aflibercept Injection year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept losing 2 lines	0.14%	0.04%	£14,480	0.41%	£13,225
aflibercept 2Q8 administration cost	193.76	155.008	£14,895	232.512	£13,376
Discontinuation laser	0.85%	0.68%	£13,390	1.02%	£14,840
All fellow eyes treated			£14,876		
No fellow eyes treated			£13,395		
Aflibercept losing 4 lines	0.0002	0.0000	£14,303	0.0013	£13,408
VIVID/VISTA injections			£13,595		
% of females	42.1%	33.7%	£13,619	50.5%	£14,674
Discontinuation aflibercept	0.68%	0.54%	£14,529	0.81%	£13,754

As for the sensitivity analyses for aflibercept versus laser, changing the time horizon to 5 years revises the monetised net health benefits from £11,667 to £6,333. This is not in line with figure 70 of the submission, but is in line with the values that result from running the *Det(SA)* subroutine of the electronic model. The values shown in Table 41 are based upon running the *DetSA()* subroutine.

Table 41 One way sensitivity analyses: aflibercept versus ranibizumab

	Mean	Low		High	
	Value	Value	NHB	Value	NHB
Base case NHB	£11,667				
Time horizon 5 years			£6,333		
Time horizon 10 year			£7,918		
Aflibercept gaining 4 lines	2.08%	1.48%	£8,947	2.84%	£14,862
Ranibizumab gaining 4 lines	1.48%	0.99%	£14,126	2.11%	£8,634
Ranibizumab label drug cost	£742	£594	£8,749	£891	£14,585
Bucher method			£8,880		
Starting age of cohort	63	58	£14,438	68	£9,624
Ranibizumab losing 4 lines	0.15%	0.02%	£10,708	0.49%	£14,346
Ranibizumab losing 2 lines	0.47%	0.17%	£10,555	1.17%	£14,265
Ranibizumab Injection year 1	7.93	5.92	£9,131	8.88	£12,865
All fellow eyes treated			£14,010		
No fellow eyes treated			£9,323		
Ranibizumab gaining 2 lines	2.95%	2.31%	£13,621	3.68%	£9,512
Shared visits 0			£13,661		
Aflibercept gaining 2 lines	3.51%	2.85%	£9,844	4.21%	£13,535
Aflibercept Injection year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept Injection year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept losing 2 lines	0.14%	0.04%	£12,011	0.41%	£10,756
DMO eye decline	1.15%	0.92%	£10,845	1.38%	£12,563
RR of mortality for diabetic patients	1.95	1.64	£12,468	2.33	£10,924
Ranibizumab administration cost	£194	£155	£10,905	£233	£12,429
Aflibercept administration cost	£194	£155	£12,426	£233	£10,908
Aflibercept losing 4 lines	0.02%	0.00%	£11,834	0.13%	£10,939
Ranibizumab Injection year 2	4.00	3.20	£10,996	4.80	£12,338

The source of the quality of life estimates is described as scenario analyses within the company submission, the alternative sources being Czoski-Murray as in the base case,[57] the OLS analysis of the VIVID/VISTA EQ-5D data (EQ-5D), Brown (1999) and Brown et al (2000).[60,61] The various sources imply the total QALYs and net QALY gains from aflibercept in Table 42.

Table 42 Sensitivity analyses around the source of utilities: aflibercept versus laser

	Total QALYs				Net QALY gain from aflibercept			
	CM	EQ-5D	Brown99	Brown00	CM	EQ-5D	Brown99	Brown00
Aflibercept	7.690	9.052	8.941	8.738				
Laser	7.300	8.901	8.745	8.346	0.390	0.150	0.196	0.392
Ranibizumab	7.598	9.035	8.910	8.648	0.092	0.017	0.031	0.089

CM: Czoki-Murray

Czoski-Murray provides the largest net gains.[57] The OLS analysis of the VIVID/VISTA EQ-5D data very much reduces these net gains, particularly for the comparison with ranibizumab.

The above suggests that the main sensitivity of results is to the parameters estimated for:

- the source chosen for the quality of life data;
- the cost of blindness;
- the rate of decline for eyes with DMO that are off treatment;
- the DMO relative risk of mortality;
- the proportion of fellow eyes that are treated;
- the baseline age; and,
- as would be expected, the main effectiveness estimates.

5.2.11 Scenario analyses: other comparators

Due to time constraints the ERG has not cross checked any of the inputs for these comparisons, and only reports the company results.

For the comparison with dexamethasone the relative risk of improving by 10 letters of 0.020 was taken from the NMA, as was the monthly discontinuation rate of 0.0059 and many of the adverse event estimates. For the other main clinical effectiveness estimates of gaining 15 letters, losing 10 letters and losing 15 letters dexamethasone was assumed to be equivalent to laser.

Table 43 Aflibercept vs dexamethasone: no dexamethasone PAS

	Aflibercept	Dexameth.	Net
Total costs	[redacted]	[redacted]	-£9,888
Total QALYs	7.552	7.232	0.320

Table 44 Aflibercept vs dexamethasone: various dexamethasone PAS

Δ QALYs	Dexa. PAS	Δ Costs	ICER	Dexa. PAS	Δ Costs	ICER
0.320	5%	-£9,888	Dominant	55%	-£7,015	Dominant
	10%	-£9,627	Dominant	60%	-£6,754	Dominant
	15%	-£9,366	Dominant	65%	-£6,493	Dominant
	20%	-£9,105	Dominant	70%	-£6,232	Dominant
	25%	-£8,844	Dominant	75%	-£5,970	Dominant
	30%	-£8,582	Dominant	80%	-£5,709	Dominant
	35%	-£8,321	Dominant	85%	-£5,448	Dominant
	40%	-£8,060	Dominant	90%	-£5,187	Dominant
	45%	-£7,799	Dominant	95%	-£4,926	Dominant
	50%	-£7,538	Dominant	100%	-£4,664	Dominant

For the comparison with fluocinolone the probability of gaining 15 letters, discontinuation rates and adverse events rates were taken directly from the FAME trial; i.e. they were not entered into the network meta-analysis. For the other main clinical effectiveness estimates of gaining 10 letters, losing 10 letters and losing 15 letters fluocinolone was assumed to be equivalent to laser.

Table 45 Aflibercept vs fluocinolone: all patients: no fluocinolone PAS

	Aflibercept	Fluocinolone	Net
Total costs	[redacted]	[redacted]	-£12,414
Total QALYs	7.566	7.295	0.271

The comparison with fluocinolone also considered the pseudophakic subgroup. For this the probabilities of gaining 10 and 15 letters for aflibercept were obtained from the pseudophakic subgroup in the VIVD/VISTA trial. The probability of gaining 15 letters for fluocinolone was obtained from the pseudophakic subgroup in the FAME trial, while the probability of gaining 10 letters for fluocinolone was taken from the pseudophakic subgroup of the laser arm of the VIVID/VISTA trial. The probabilities of losing letters was taken from the all patient group of the VIVID/VISTA trial, with it appearing that fluocinolone was assumed to be equivalent to laser, though the submission is slightly ambiguous on this point.

Table 46 Aflibercept vs fluocinolone: pseudophakic patients: no fluocinolone PAS

	Aflibercept	Fluocinolone	Net
Total costs	[redacted]	[redacted]	-£13,662
Total QALYs	7.596	7.278	0.318

Table 47 Aflibercept vs fluocinolone: pseudophakic patients: various fluocinolone PAS

Δ QALYs	Fluo. PAS	Δ Costs	ICER	Fluo. PAS	Δ Costs	ICER
0.318	5%	-£13,662	Dominant	55%	-£8,726	Dominant
	10%	-£13,213	Dominant	60%	-£8,277	Dominant
	15%	-£12,765	Dominant	65%	-£7,828	Dominant
	20%	-£12,316	Dominant	70%	-£7,379	Dominant
	25%	-£11,867	Dominant	75%	-£6,931	Dominant
	30%	-£11,418	Dominant	80%	-£6,482	Dominant
	35%	-£10,969	Dominant	85%	-£6,033	Dominant
	40%	-£10,521	Dominant	90%	-£5,584	Dominant
	45%	-£10,072	Dominant	95%	-£5,136	Dominant
	50%	-£9,623	Dominant	100%	-£4,687	Dominant

5.2.12 Scenario analyses: CRT ≥ 400µm

A scenario analysis labelled as being for the CRT ≥ 400µm subgroup is presented. But this retains the clinical effectiveness estimates for aflibercept versus laser and for ranibizumab versus laser, and by implication for aflibercept versus ranibizumab. All that is changed within the modelling is that the probabilities of gaining and losing letters in the laser arm is made specific to the CRT ≥ 400µm subgroup of the VIVID/VISTA trial data (Table 48).

Table 48 Laser monthly probabilities for all patients and CRT ≥ 400µm subgroup

	All patients	CRT ≥ 400µm
Gain 15 letters	0.0067	[redacted]
Gain 10 letters	0.0170	[redacted]
Lose 10 letters	[redacted]	[redacted]
Lose 15 letters	0.0078	[redacted]

Given the retention of the relative effectiveness data the net impacts are not affected as much as they might have been. The company CRT ≥ 400µm subgroup analyses results, inclusive of the aflibercept PAS but exclusive of any ranibizumab PAS, are in Tables 49 and 50.

Table 49 CRT ≥ 400µm subgroup: aflibercept vs laser

	Aflibercept	Laser	Net
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Aflibercept is estimated to dominate laser among the CRT ≥ 400µm subgroup**.**

Table 50 CRT ≥ 400µm subgroup: aflibercept vs ranibizumab

	Aflibercept	Ranibizumab	Net
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Aflibercept is estimated to dominate ranibizumab among the CRT ≥ 400µm subgroup**.**

5.2.13 Model validation and face validity check

Table 93 of the company submission reports the correspondence between the trial results and the modelled results at 52 weeks in terms of the mean letters change in BCVA (Table 51).

Table 51 52 week model validation data: mean letters change in BCVA

Treatment	Source	Trial results	Model results	Difference
Aflibercept	VIVID/VISTA	[redacted]	[redacted]	2.3
Ranibizumab	RESTORE	5.9	5.9	0.0
Laser	VIVID/VISTA	[redacted]	[redacted]	0.5

The reported discrepancies between the model with the VIVID/VISTA trial results are quite a significant percentage of the gains estimates within the VIVID/VISTA. They also suggest that the model tends to underestimate the net gain from aflibercept over laser at 52 weeks. This is of concern given that the lifetime extrapolation is based upon the modelled distribution at 52 weeks.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has rebuilt the company model structure that is based upon applying the relative risks of improvements to the monthly probabilities of gains and losses in the laser arm. For reasons which are outlined in section 5.3.4 below this cross check rebuild only corresponds with the company model if[c] the annual number of treatments changes between the first, second, third, fourth and fifth years of treatments for FEIs being treated where the DMO is incident in years 2, 3, 4 and 5.

Note that the results in Table 52 have also set the blindness mortality multiplier when only one eye falls into blindness to unity for reasons of simplicity within the cross checking. As a consequence, the impact of applying a blindness mortality multiplier when only one eye falls into blindness has not been formally rebuilt by the ERG.

Table 52 Company deterministic results and ERG cross check rebuild

	Company model			ERG cross check rebuild		
	Aflibercept	Ranibizumab	Laser	Aflibercept	Ranibizumab	Laser
Tx study eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tx fellow eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FAs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs study eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs fellow eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blindness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	7.771	7.663	7.415	7.768	7.660	7.405
AEs decr.	0.030	0.007	0.032	0.036	0.009	0.036
Total QALYs	7.741	7.656	7.383	7.732	7.652	7.369

There is generally a very good correspondence between the submitted company model and the ERG cross check rebuild. The main discrepancies in terms of costs arise in the laser arm with the ERG estimating these to total £343 less than the company model, principally due to £57 lower adverse event costs and £280 lower costs of blindness.

[c] The details of the changes required to align the company model with those of the ERG cross check rebuild are outlined in the footnotes to section 5.4.

The total QALY estimates differ for all three treatments by small amounts: 0.009 QALYs for aflibercept, 0.004 QALYs for ranibizumab and 0.014 QALYs for laser. These QALY discrepancies will to some degree net out within any incremental analysis.

The ERG has not managed to run the probabilistic model. Selected the *Update PSA* option in the *PSA* worksheet causes the model to run through 1,000 iterations. But for the comparison with laser the total costs in the laser arm for each iteration are either #REF! or #VALUE! while for the comparison with ranibizumab the total costs for some iterations within the ranibizumab arm that are variously #REF!, #VALUE! and negative, with some iterations have negative costs in the millions if not billions; e.g. $-2.8*10^{12}$.

5.3.2 Data inputs: correspondence between written submission and sources cited

Rate of worsening off treatment

The submission draws a quarterly rate of worsening for DMO of 3.5% from the TA274 ranibizumab for DMO.[15] The ETDRS letters range of the health states used within this are the same as those currently modelled. This did estimate a 3.5% quarterly rate of worsening, but it also estimated a 2.5% rate of improvement based upon WESDR/ETDRS data. The ERG were not clear about the derivation of these percentages.

Based upon the company method this would suggest a 0.83% monthly rate of improvement and a 1.15% rate of worsening. Given the sensitivity of results to the natural rate of decline associated with DMO, the 0.83% rate of improvement is likely to have a reasonably large impact upon results.

It may be possible that this rate of improvement may be more due to measurement error than the eye actually improving, but this would still seem to argue for netting out the two estimates to arrive at a net quarterly rate of decline of 1.0%.

Due to the construction of the cohort flow within the company model, implementing a rate of increase when off treatment cannot simply be achieved by altering the TPMs.

In the light of this, the simplest means of implementing the 2.5% quarterly improvement and the 3.5% quarterly worsening within the model is to net these out to yield a 1.0% quarterly worsening. But the two methods are not quite the same and will result in different cohort flows.

Diabetes mortality risk

The current submission applies an estimate for the relative risk of mortality for patients with diabetes of 1.95, as drawn from Preis et al.[58] This is based upon the Framingham heart study. Table 3 of Preis et al[58] suggests a hazard ratio of 2.44 in the early period and 1.95 in the later period, the later period relating to data collected from 1976 to 2001.

Blindness mortality multiplier

Christ et al 2008 is a study of a sample of adult respondents to the US National Health Interview Survey (NHIS). The paper is not clear about the number of respondents used in analysis. It notes that the NHIS includes a sample of 135,581 respondents. But it goes on to note that the sample analysed comprised those who provided sufficient data to enable linkage between the NHIS and the National Death Index and who were among the sixth of NHIS respondents selected to complete the visual impairment module.

Severe visual impairment was defined as respondent reported blindness in both eyes. Legal blindness in the US is also defined as a BCVA of 20/200 or less in the better eye; i.e. the BSE being in HS07 or HS08.

Some visual impairment was defined across a range of scenarios, though again the text is slightly ambiguous about this:

- Respondent reported visual impairment in both eyes, with one in blindness and one with visual impairment.
- Respondent reported visual impairment in one eye only, with the other eye having good vision or not being mentioned.

There may be some ambiguity in the definition of visual impairment in the US, but a BCVA of less than 20/60 appears the most reasonable definition for current purposes.

Based upon the midpoint of the health states' BCVAs would seem to require the eye under consideration to be in HS04 or worse.

Two models are fitted by Christ et al:[59] a cox proportional hazards model and a structural equation model (SEM). The SEM not only takes into account the impact of vision, but also respondents' self-reported health and disability, the latter being measured as a latent variable with the indicators of bed days during the past fortnight and reduced activity days during the past fortnight.

Adjusted for covariates, the direct effects modelling gave hazard ratios of 1.28 for severe visual impairment and 1.13 for some visual impairment. Including the indirect effects gave hazard ratios of 1.54 for severe visual impairment and 1.23 for some visual impairment. The company applies the 1.54 and 1.23 from the model that incorporates indirect effects.

The number of non-ocular health comorbidities was included as a covariate within the modelling, defined as none, one or more than one. Whether this is sufficient to take into account the range of comorbidities is a moot point.

For instance, diabetics will tend to have a worse BCVA than the national average and will also tend to have a higher mortality, but it seems likely that for these patients it is mainly the diabetes that is causing the raised mortality rather than any direct vision related mortality effect. The discussion section of Christ et al[59] also notes that running the model for the subset of respondents with data on smoking status reduced the hazard ratio of 1.54 for severe visual impairment to 1.48 and reduced the hazard ration of 1.23 for some visual impairment to 1.16. It is unclear why Christ et al do not prefer these estimates to the estimates that do not control for smoking.

Given the definitions for severe visual impairment and some visual impairment of Christ et al[59] and assuming that the SEM model is the most appropriate, it could be argued that an alternative set of mortality multipliers could be applied (Table 53).

Table 53 Christ et al mortality hazard ratios: model and alternative interpretations[59]

	Model		1st alternative		2nd alternative		3rd alternative	
	BSE	WSE	BSE	WSE	BSE	WSE	BSE	WSE
HS01	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HS02	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HS03	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HS04	1.00	1.00	1.00	1.00	1.00	1.23	1.00	1.00
HS05	1.00	1.00	1.00	1.00	1.00	1.23	1.00	1.00
HS06	1.00	1.00	1.00	1.00	1.00	1.23	1.00	1.00
HS07	1.23	1.23	1.54	1.23	1.54	1.23	1.54	1.00
HS08	1.23	1.23	1.54	1.23	1.54	1.23	1.54	1.00

But as far as the ERG can discern the model structure appears to only really allow for a mortality multiplier to be associated with the study eye, which will typically be the WSE, falling into HS7 or HS8. As a consequence, it seems reasonable to assume no mortality multiplier for the WSE of 1.23 for the base case but to also explore the impact of setting this to unity.

Quality of life: other sources within the literature

The regression coefficients drawn from Czoski-Murray cross check with those of the paper, and the ERG agrees with the company conversion of ETDRS letters to LogMAR equivalents and the company application of the regression coefficients to these. The values drawn from Brown 1999 and Brown 2000[60,61] differ from those derived by the ERG for the TA274 ranibizumab for DMO, which used the same ETDRS health states as the current submission. A fuller account of the papers and values within them is given within the ERG report for the rapid review[d], with the values derived being reported in Table 54.

[d] http://www.nice.org.uk/guidance/TA274/documents/macular-oedema-diabetic-ranibizumab-rapid-review-of-TA237-evidence-review-group-report-for-nice-rapid-review2

Table 54 TTO HRQoL by BSE: Brown 1999 and Brown 2000

	Brown 1999		Brown 2000	
State	Company	ERG	Company	ERG
HS1	0.839	0.920	0.890	0.890
HS2	0.839	0.920	0.890	0.890
HS3	0.783	0.840	0.810	0.810
HS4	0.783	0.770	0.690	0.570
HS5	0.732	0.740	0.558	0.570
HS6	0.681	0.670	0.545	0.570
HS7	0.630	0.660	0.520	0.520
HS8	0.579	0.540	0.460	0.520

The company values suggests a smaller impact from changes in the BCVA when using Brown 1999, but perhaps a larger impact when using the values of Brown 2000.[60,61] It appears that the company values may have in some manner averaged the values reported in the papers over the health states of the model to derive a smoother curve.

Dosing

The company estimates 7.93 ranibizumab injections in the first year from the papers underlying the NMA. Mitchell et al[38] report a first year mean of 7.0 ranibizumab injections among the 115 patients in the safety set of the ranibizumab plus sham laser arm of RESTORE. The Ohji et al[40] abstract reports a first year mean of 7.8 ranibizumab injections among the 133 patients of the ranibizumab plus sham laser arm of REVEAL. Elman et al[28] report a median of 9.0 ranibizumab injections among the 188 patients of the ranibizumab plus deferred laser arm of the DCRC.net trial. The weighted average of these is 8.10 ranibizumab injections, while the unweighted average corresponds with the company estimate of 7.93 ranibizumab injections.

But it may not be appropriate to combine the median of the DCRC.net with the means of RESTORE and REVEAL. The European Medicines Agency (EMA) report for aflibercept suggests a higher median than mean for the number of aflibercept injections in the first year pooled across VIVID and VISTA: 9.0 compared to 8.5. Excluding the DCRC.net suggests a weighted average of 7.43 ranibizumab injections. It should also be borne in mind that the TA274 ranibizumab for DMO[15] was mainly

based upon the RESTORE trial, due to REVEAL being conducted at site in the Far East. To the ERG this suggests a central estimate of 7.43 ranibizumab injections in the first year, and sensitivity analyses that assume 8.10 and 7.00.

The company estimates 4.00 and 2.30 ranibizumab injections in the second and third years from its survey of 30 UK ophthalmologists. Schmidt-Erfurth et al[62] report the results of the RESTORE extension study, which suggests means of 7.4, 3.9 and 2.9 injections in years one, two and three among those in the ranibizumab plus sham laser in the core RESTORE study. The reason for the difference in the first year figure from that reported by Mitchell et al[38] may be due to Schmidt-Erfurth et al[62] reporting the value for only the 83 patients who initially received ranibizumab who continued into the extension trial rather than the 116 initially randomised to ranibizumab within RESTORE. The value for year two is in line with the survey of ophthalmologists, while the value for year three is a little higher at 2.9 compared to the survey estimate of 2.3.

The company estimates 8.00 aflibercept injections in the first year. But the SmPC dosing regimen suggests to the ERG an average of 8.5 injections since the final injection in the first year will be at the start of the twelfth month. This is also in line with the value of the EMA report. Korobelnik et al[36] reports a mean of 8.4 injections among the 152 2Q8 patients of VISTA and 8.7 among the 135 2Q8 patients of VIVID, which suggests a weighted mean of 8.54 aflibercept injections in the first year. In the opinion of the ERG this suggests a base case estimate of 8.5 aflibercept injections in the first year.

For the second year the company assumes that the number of aflibercept injections will be the same as the number of ranibizumab injections. Data supplied at clarification reports that between week 52 and week 100 the mean number within VISTA was [redacted] aflibercept injections among the 144 patients remaining at week 52 within the 2Q8 arm and within VIVID was [redacted] aflibercept injections among the 120 patients remaining at week 52 within the 2Q8 arm. This suggests an average of [redacted] aflibercept injections in the second year, though since this is only to week 100 it may slightly underestimate the actual number of aflibercept injections in the second year.

The number of laser administrations in the first year is in line with pooled VIVID/VISTA data supplied at clarification.

To the ERG this suggests revising the number of doses in the first, second and third years to the those presented in Table 55.

Table 55 ERG base case dosing

	Aflibercept	Ranibizumab	Laser
Year 1	8.50	7.43	2.40
Year 2	[redacted]	4.00	1.00
Year 3	3.00	3.00	0.80

Sensitivity analyses:

- of 8.10 doses in the first year for ranibizumab;
- of 4.00 doses in the second year for aflibercept;
- of 2.30 doses in the third year for aflibercept and ranibizumab;

are also warranted.

Monitoring

Aflibercept is only associated with 8 monitoring visits in the first year, but since treatment visits can double as monitoring visits in the first year there are no dedicated monitoring visits for aflibercept. It is assumed that in the first year ranibizumab will be associated with 12 monitoring visits in the first year, so there are around 4 additional dedicated monitoring visits. This increased monitoring used to arise from the ranibizumab SmPC specifying monthly monitoring, but this has changed.

Aflibercept SmPC:

- *Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. The schedule for monitoring should be determined by the treating physician.*

Ranibizumab SmPC:

- *30 Oct 2014 current: Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.*
- *23 Sep 2014: Amend monitoring frequency for wAMD, DME, RVO from "monthly" to "as needed" (exact treatment recommendations still to be clarified); Include morphologic retreatment criteria (e.g. OCT, FA) in addition to visual acuity across indications.*

In the light of this it seems that aflibercept monitoring in year 1 is the same as the number of treatments. The revised SmPC suggests something similar for ranibizumab, though it is a bit less explicit and could argue for more monitoring visits than treatment visits. This suggests a sensitivity analysis that equalises the number of monitoring visits between aflibercept and ranibizumab to 8 in the first year. It can be argued that this should be used for the base case, if this better reflects how practice is likely to evolve in the short to medium term.

Costs: adverse events

Within the NHS 2012-13 reference costs the ERG cannot source the £88.29, but the consultant non-admitted face to face follow-up is costed at £80.04, which is sufficiently close as to have no practical impact upon results. It is possible that the £88.29 is a weighted average across consultant led visits.

The ERG has not been able to source the cited reference cost for BZ02Z day cases cost of cataract of £882, but there is a day case cost of £882 for BZ02A phacoemulsification cataract extraction for ophthalmology for those with a complications and comorbidity score of 5+. Only 1,017 of these procedures were performed in ophthalmology, with complications and comorbidity scores of 2-4 being more common with 41,158 and of 0-1 of 225,730. But the day-case costs for these of

£888 and £866 are similar to the £882 that is used and a weighted average would only reduce this to £869.

Note that the £1,021 for BZ23Z non-elective long stay is a weighted average across specialities, with the ophthalmology specific cost being £1.393. The ERG cannot source the BZ23Z £1,490 non-elective short stay cost, with the weighted average across specialities being £885 and the average for ophthalmology being £837 for those specific to ophthalmology. Note that the BZ23Z day case cost is £356, and the BZ23Z outpatient procedure cost is £117. Not all procedures may require an inpatient stay.

Applying the £776 weighted average for cataract extraction, £1,393 for BZ23Z non-elective long stay, £837 non-elective short stay and £80 per outpatient visit and retaining the company assumptions suggests average costs as present in Table 56.

Table 56 Adverse event costs: revised NHS reference costs

	Unit cost
Cataract	£1,016
Endophthalmitis	£1,873
Retinal detachment	£1,157
Vitreous haemorrhage	£997

Cost of blindness

The company applies an annual cost of blindness of £6,448. The STA of ranibizumab for CNV from pathological myopia identified a recent Kings Fund report, McCrone et al[63] that provides a better estimate of the costs of depression than that used in Meads et al.[64] This results in a first year cost for blindness of £7,510 and a subsequent annual cost of blindness of £7,429.

Note that the costing of Meads et al was intended for an AMD patient group and as such is possibly older than the baseline age assumed in the model of 63 years. The submission for the STA of aflibercept for AMD assumed a baseline age of 74 years. The vast majority of the estimated costs relate to residential care. This may argue for a sensitivity analysis that reduces the proportion requiring residential care. Meads et al[64]

applied an estimate of 30%. Arbitrarily reducing this by a third to 20% reduces the annual costs of blindness to £5,620. But it should be borne in mind that the starting age within the model is 63 and the average survival is around a little over 15 years which may tend to increase the likelihood of blindness requiring residential care as the model progresses.

5.3.3 Data inputs: correspondence between written submission and electronic model

Adverse event rates

The ERG has been unable to reconcile the relative risks of adverse events of the written submission with those used in the electronic model (Table 57).

Table 57 Relative risks of adverse events applied within the electronic model

	Aflibercept.	Ranibizumab.	Dexamethasone.
Cataract	[redacted]	[redacted]	[redacted]
Endophthalmitis	[redacted]	[redacted]	[redacted]
Retinal detachment	[redacted]	[redacted]	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]
Vitreous haemorrhage	[redacted]	[redacted]	[redacted]
Raised IOP	[redacted]	[redacted]	[redacted]

Treatment while in HS7 and HS8

The written submission states that during the maintenance phase eyes in HS7 and HS8 are not treated. The model has the facility for this, but it appears to not have been used for the base case analyses. This has relatively little impact upon results.

Drug administration and monitoring visits

The drug administration and monitoring visits of table 76 of the written submission correspond with those of the base case of the electronic model. The electronic copy of the model also suggests that the company has sought figures from Medical Radar (Table 58).

Table 58 Treatment and monitoring visits: medical radar

	Administrations					Monitoring visits				
	Afli.	Rani.	Dexa.	Fluo.	Laser	Afli.	Rani.	Dexa.	Fluo.	Laser
Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 6+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG is not familiar with Medical Radar but it appears to be the source of the number of administrations in year three and onwards for ranibizumab, with these also being carried over as an assumption to aflibercept. The Medical Radar number of administration and monitoring visits for ranibizumab in year one are somewhat below the 7.93 and 12.0 of the base case.

5.3.4 ERG commentary on model structure, assumptions and data inputs

Modelling approach

There are some general methodological problems with the approach adopted:

- The proportions transferring between health states within the laser arm are assumed to be constant and not related to the eye's BCVA. In other words, the likelihood of a 2 health state improvement for an eye in HS3 is assumed to be the same as that for an eye in HS5.
- The monthly proportions transferring between health states within the laser arm are calculated based upon the annual proportion changing according to ((1+p)^(1/12))-1. While this is correct for deriving a monthly rate such as an interest rate, which will over 12 monthly compound up to the annual rate, the situation of probabilities within TPMs is not exactly analogous to this. This also assumes that a constant proportion change each month. The clinical evidence suggests that the changes occur mainly during the first month with a tailing off after that to six months, and broad stability for the six months thereafter.
- The relative risks apply to the 12-month period. The approach adopted assumes that these are constant through time and that it is correct to apply these annual relative risks to monthly quantities.

- It appears that the relative risks of gaining (losing) 10 or more letters are applied within the model to the probability of improving (worsening) by one health state in the laser arm. But the relative risks of 10 or more letters in some sense encompass the relative risks of gaining 15 or more letters, the latter being applied to the probability of improving by a minimum of two health states within the laser arm.

These concerns may be part of the reason for the relatively poor correspondence between the modelled health state distributions and those observed in VIVID/VISTA.

The model assumes that a patient has the same probability of improving or worsening by a given number of health states regardless of the health state that patient is in. While the patient numbers for some of the rows of the TPMs are quite small, even those for patients in the centre of the distribution appear to have quite dissimilar probabilities of gaining and losing health states. The percentages implied for all patients based upon the TPM given above are shown in Table 59.

Table 59 Pooled laser arm probabilities between baseline and week 52: all patients

	+2HS	+1HS	0HS	-1HS	-2HS	N
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
HS7						
HS8						
Pooled						

As an example, it appears that those in HS3 and HS4 have a smaller probability of improving by two health states than those in HS5 and HS6. While these differences may not be statistically significant between the subgroups, applying the pooled rates to the subgroup will cause the modelled distribution at 52 weeks to be differ from that observed in the laser arm of VIVID/VISTA.

The model estimates monthly transitions and applies these 12 times to the baseline distribution to arrive at the one year distribution between health states, and the distributions for the intervening 11 months. It may have been preferable to estimate 12 monthly transitions and apply these to the baseline distribution to arrive at the one year distribution between health states, with the distributions for the intervening 11 months then being inferred by some method. It seems likely that this method would, if only for the comparison of aflibercept with laser, have resulted in a more accurate distribution at 12 months. Since the remainder of the modelling extrapolates from the 12 month distribution, it seems particularly important to get this distribution as close to being correct as possible. In the opinion of the ERG this could also be the more natural method for modelling aflibercept versus ranibizumab, given that the relative risks relate to the 12 month period.

For the comparison of aflibercept with laser, there remains the possibility of populating the model with the monthly TPMs derived directly from the patient counts for the all patients analysis and for the CRT ≥ 400μm subgroup. But it seems doubtful if there are sufficient numbers for this for the CRT < 400μm subgroup.

Model structure dosing

The model estimates the mean monthly number of injections and applies this to the proportion remaining on treatment each month. But there are discontinuations each month, amounting to an annual discontinuation rate of around 10%. This will artificially reduce the mean number of administrations to be below that observed during the trials. This could argue for increasing the number of administrations within the model by around 5% in order to cause the modelled mean number of administrations in the first year to be in line with that observed.

Treatments in the fellow eye being qualified by death

Within the cohort flow, death is associated with the study eye rather than the fellow eye. When calculating the distribution across the bilateral health states for the main QALY calculations the proportion of study eyes in one health state is multiplied by the proportion of fellow eyes in another health state to give the proportion of patients whose eyes fall into that particular bilateral health state. Since the study eye cohort flow takes death into account this is correct.

But the number of injections required for the fellow eye within the cohort flow is based solely upon the fellow eye cohort flow. As far as the ERG can see this means that death is not taken into account and as a consequence the number of treatments for the fellow eye will be overestimated.

Number of fellow eye treatments

For fellow eyes that are incident in years 2, 3, 4 and 5 it appears that these are assumed to have the efficacy phase number of treatments applied to both the first year efficacy phase and the subsequent four year maintenance phase. These should differ between the years of treatment[e].

Treatment of eyes falling into HS7 or HS8

The submission states that for the maintenance period "*blind patients are not treated during this phase*". While eyes falling into HS7 may be treated, it may be questionable to assume that those falling into blindness or eyes falling from higher health states such as HS4 into either of HS7 or HS8 will be treated during the maintenance phase as this would seem to constitute a lack of efficacy. It appears that the company base cases have assumed that eyes in HS7 or HS8 are treated during the maintenance phase. This has little impact upon results.

Discounting

Discounting within the model is of the form $(1-r)^t$ rather than $1/(1+r)^t$. This will have discounted future amounts by slightly too high a discount factor, which may have worsened the cost-effectiveness of the more effective treatment. But the effects of this are slight, with $(1-r)^t$ giving surprisingly similar values to $1/(1+r)^t$.

Scenario analysis of CRT ≥ 400μm subgroup

The company scenario analysis for the CRT ≥ 400μm subgroup retains the relative risks of the NMA. All that is changed are the probabilities of gaining and losing letters in the laser arm. As would be expected, this has only limited impact upon the cost-effectiveness results. But the main elements of interest are the relative risks, and

[e] This is most easily seen within the *Markov*- worksheets by scanning down columns HG through to HK. Column HG has step changes between e.g. cell HG100 and HG101 as would be expected. But columns HH through to HK evolve smoothly through time.

for instance whether the gain from aflibercept over laser is greater in the CRT ≥ 400µm subgroup than in the CRT < 400µm subgroup.

It is possible that there may be insufficient data to inform a comparison between aflibercept and ranibizumab, but the company has access to the VIVID/VISTA trial data for the comparison of aflibercept with laser. A problem may arise due to the relatively small number of patients in the CRT < 400µm subgroup. But the point estimates of the submission for the integrated analysis report 52 weeks estimates net effect of 2Q8 dosing compared to the laser arm of:

- Letters change in BCVA of [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 10 letters [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 15 letters [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 2 step ETDRS [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm

While the above are point estimates, there is a consistent pattern across them of the gain from aflibercept over laser being less among those with a CRT < 400µm compared to those with a CRT ≥ 400µm.

This is a similar pattern to that observed during the STA of ranibizumab for DMO. Ranibizumab was found to be cost effective compared to laser for those with a CRT ≥ 400µm, and was found to be not cost effective compared to laser for those with a CRT < 400µm.

In response to the ERG clarification question B6 the estimates for VISTA and VIVID were presented separately. This was partly requested in the light of VISTA having a higher proportion of patients with previous anti-VEGF treatment with this also possibly being linked to a larger net effect from aflibercept over laser. For VIVID the point estimates are as follows:

- Letters change in BCVA of [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 10 letters [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm

- Proportion ≥ 15 letters [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 2 step ETDRS [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm[f]

For VISTA the point estimates are as follows:

- Letters change in BCVA of [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 10 letters [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 15 letters [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm
- Proportion ≥ 2 step ETDRS [redacted] for CRT < 400µm versus [redacted] for CRT ≥ 400µm

Laser transition probabilities

For the analysis based upon applying the relative risks of the NMA to the transition probabilities for laser, it appears that the transition probabilities for laser between baseline and week 52 are based upon the FAS patient population pooled across VIVID and VISTA (LOCF). The patient numbers transitioning in the pooled laser arms as provided by the company in response to the ERG clarification question B10 are presented in Tables 60-62.

Table 60 Pooled laser arm transitions between baseline and week 52: all patients

	Week 52 VA							
Baseline VA	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[f] From table 1.4 / 7: VIVID on page 204 of the company response to the ERG clarification questions.

Table 61 Pooled laser arm transitions between baseline and week 52: CRT ≥ 400µm

	Week 52 VA							
Baseline VA	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
HS7								
HS8								

Table 62 Pooled laser arm transitions between baseline and week 52: CRT < 400µm

	Week 52 VA							
Baseline VA	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
HS7								
HS8								

For each TPM, the sum of the principal diagonal corresponds to the number of patients the study eye of whom is in the same health state at week 52 as it was at baseline. The diagonal below the principal diagonal would seem to correspond with the number of patients improving by one health state, while the diagonal above it would seem to correspond with the number of patients worsening by one health state. The remaining triangular elements would seem to be the number of patients improving by two or more health states and worsening by two or more health states.

Table 63 Patient numbers changing by a given number of health states

	+2HS	+1HS	0HS	-1HS	-2HS	Total
All patients						
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT ≥ 400µm						
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT < 400µm						
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64 Patient proportions changing by a given number of health states

	+2HS	+1HS	0HS	-1HS	-2HS	Total
All patients						
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT ≥ 400µm						
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT < 400µm						
Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For reasons that are unclear, the patient numbers across all patients do not correspond between the model and the data supplied at clarification but they do correspond for the subgroup with a baseline CRT ≥ 400µm. If the numbers implied by the TPM supplied by the company at clarification are the correct interpretation there should be a somewhat higher proportion of patients improving by one health state within the laser arm. This would boost the clinical effectiveness of laser, and given the relative risks that are applied would also boost the clinical effectiveness of aflibercept and ranibizumab.

The patient numbers for the subgroup with a baseline CRT < 400µm suggest a higher proportion of patients improving, but fewer improving by two health states or more.

However, patient numbers within this group are quite small and it may be quite difficult to make reliable estimates for the transition probabilities for this subgroup.

Baseline bilateral involvement and patient distributions

Data supplied in response to ERG clarification question B10 suggests the following patient numbers pooled over VIVID/VISTA for patients with and without fellow eye involvement at baseline (Table 65and 66).

Table 65 Bilateral distribution for those with DMO FEI at baseline: patient numbers

		Non-study eye								
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	Total
Study eye	HS1									
	HS2									
	HS3									
	HS4									
	HS5									
	HS6									
	HS7									
	HS8									
	Total									

Table 66 Bilateral distribution for those without DMO FEI at baseline: patient numbers

		Non-study eye								
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	Total
Study eye	HS1									
	HS2									
	HS3									
	HS4									
	HS5									
	HS6									
	HS7									
	HS8									
	Total									

The immediately striking element of this is that within VIVID/VISTA there was a bilateral DMO involvement at baseline of [redacted], which is considerably higher than the base case estimate of 46% that the company derived from expert opinion.

Using the patient numbers to derive the fellow eye distribution between the health states by study eye health state and across all study eyes yields the values in Table 67 and 68.

Table 67 Bilateral distribution for those with DMO FEI at baseline: percentages

		Non-study eye								
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	Total
Study eye	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 68 Bilateral distribution for those without DMO FEI at baseline: percentages

		Non-study eye								
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	Total
Study eye	HS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	HS8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The above may suggest that there tends to be a positive correlation between the study eye and the non-study eye. This is perhaps more evident among the patients with

bilateral DMO at baseline. Not taking this into account may mean that the model tends to underestimate the proportions of patients that fall into blindness, which may in turn underestimate the quality of life impacts and cost offsets that may accrue to the more effective treatment from avoiding blindness.

Taking this into account might argue for modelling the study eye health states individually and then recombining the results of this modelling as weighted averages; i.e. modelling 100% of patients as having a study eye in HS3 and weighting the results of this by 36%, 100% as having a study eye in HS4 and weighting the results of this by 35%, 100% as having a study eye in HS5 and weighting the results of this by 18%, etc. For this modelling, the fellow eye percentage involvement percentage at baseline, the distribution of the fellow eyes without bilateral involvement at baseline and the distribution of the fellow eyes with bilateral involvement at baseline would be specific to the study eye being modelled.

Unfortunately, given the model structure, differentiating the distribution of fellow eyes between those with and without DMO involvement at baseline is difficult to achieve. However, it is feasible to make the fellow eye percentage involvement at baseline specific to the study eye, and to use the corresponding pooled fellow eye distribution.

Table 69 Pooled bilateral distribution and percentage FEI at baseline

		Non-study eye									
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	FEI	Wght
Study eye	HS1										
	HS2										
	HS3										
	HS4										
	HS5										
	HS6										
	HS7										
	HS8										
	All										

Given the similar proportions with fellow eye involvement at baseline and the low patient numbers with a study eye in HS2 and HS8 at baseline, it seems reasonable to apply a common [redacted] fellow eye involvement at baseline and only to make the fellow eye distribution specific to the study eye (Table 69).

DMO mortality relative risk

There will be an increased mortality hazard for patients with type 2 diabetes without DMO compared to members of the general public. The current submission applies an estimate for the relative risk of mortality for patients with diabetes of 1.95, as drawn from Preis et al. [58]This is based upon the Framingham heart study.

Mulnier et al[65] estimate a mortality hazard ratio of 1.93 (1.89-1.97) among male patients with type 2 diabetes compared to men in the general population without diabetes, and 1.77 (1.72-1.83) for women. These figures are further stratified by age groups:

- 65-74 years 1.84 (1.75-1.93) for men and 2.44 (2.30-2.60) for women
- 75-84 years 1.58 (1.51-1.66) for men and 1.97 (1.88-2.07) for women
- 85-89 years 1.44 (1.30-1.60) for men and 1.65 (1.52-1.78) for women

Mulnier et al[65] was the source for the mortality relative risk for diabetics compared to the general population during the TA274 ranibizumab for DMO. Their estimates are very much in line with that of Preis et al.[58]

But there will be an additional mortality multiplier for patients with diabetes who have DMO compared to patients with diabetes who do not have DMO. Hirai et al[66] analysed the US Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) data grouped by type 1 and type 2 diabetes. Among patients with type 2 diabetes the average age was around 65 years. Adjusting for other variables, DMO was associated with a survival hazard ratio of 1.27 (1.01–1.61, P=0.04).

These estimates can be linked to provide an estimate of the mortality relative risk for a patient with DMO compared to the general public, and this is the source of the estimate of 2.45 that was used within the TA274 ranibizumab for DMO.[15] This will

cause some slight bias in that the survival hazard for a patient with type 2 diabetes compared to a member of the general public without diabetes will incorporate some additional survival risk since a subgroup of the patients with type 2 diabetes within this will have DMO. Also, the general population survival curves for England and Wales will incorporate a proportion of diabetes related deaths. It may be possible to adjust for these two factors.

Caveats are necessary when applying mortality rates from older studies to present day modelling. The cohort in the Mulnier study was recruited on 1st January 1992. [65]No details on duration of diabetes are given in the paper, but most would have had diabetes for some time. Mortality was based on deaths in the years 1992 to 1998. The reported prevalence of diabetes then was only 1.5% which is very much less than now. It is possible that diabetes care may have improved since then, for example with more use of the statins in diabetes, and better control of blood pressure. As a consequence, overall mortality among patients with type 2 diabetes may now be lower which could argue for a lower relative risk being applied than that estimated by Mulnier et al.[65]

There is also the concern that even if the model is restricted to only apply the blindness mortality multiplier when both eyes fall into either HS7 or HS8, some of this additional mortality will be contributing to the mortality multiplier of 1.27 drawn from Hirai et al.[66]

Within the TA274 ranibizumab for DMO the company revised the mortality relative risk for patients with DMO relative to the general public to be 2.45 over the course of the assessment. This might have caused some overestimation of the mortality relative risks. Nonetheless, this estimate appeared preferable to the others used. In the light of this, the overall relative risk of 2.45 appears the most reasonable to use for the base case, with sensitivity analyses being undertaken around this value.

Quality of life: additional VIVD/VISTA EQ-5D models

In response to the ERG clarification question C5, the company has outlined two models for utility: a random effects model and a general estimating equation (GEE) model (Table 70).

Table 70 Additional VIVD/VISTA EQ-5D models

	OLS		Random effects		GEE	
	Coef	S.E.	Coef	S.E.	Coef	S.E.
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline BMI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log (BCVA of WSE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log (BCVA of BSE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The random effects and GEE models suggest a higher sensitivity to changes in the BCVA of the BSE compared to the OLS model and a lower sensitivity to changes in the BCVA of the WSE.

For the OLS regression, the overall R^2 was [redacted]. Perhaps surprisingly, the coefficient for the BCVA of the BSE is only just significant with a p-value of [redacted] while the coefficient for the BCVA of the WSE has a p-value of [redacted].

For the random effects model, the overall R^2 was [redacted], while the p-values for the coefficients on the BCVAs of the BSE and the WSE are [redacted] and [redacted] respectively. For the GEE model the Wald X^2 of [redacted] suggested a p-value of less than [redacted]. The p-values for coefficients on the BCVAs of the BSE and the WSE are [redacted] and [redacted] respectively.

The random effects model and the GEE model suggest slightly different quality of life values from those of the OLS regression (Tables 71 and 72).

Table 71 Bilateral quality of life: VIVID/VISTA EQ-5D random effects

	BSE							
WSE	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	[redacted]							
HS2	[redacted]	[redacted]						
HS3	[redacted]	[redacted]	[redacted]					
HS4	[redacted]	[redacted]	[redacted]	[redacted]				
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
HS7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
HS8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 72 Bilateral quality of life: VIVID/VISTA EQ-5D GEE

	BSE							
WSE	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
HS1	[redacted]							
HS2	[redacted]	[redacted]						
HS3	[redacted]	[redacted]	[redacted]					
HS4	[redacted]	[redacted]	[redacted]	[redacted]				
HS5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
HS6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
HS7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
HS8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In response to the ERG clarification question C5 the company has confirmed that the OLS, the random effect and the GEE analyses each use a data set of [redacted] observations. Given the pooled VIVD/VISTA number of patients of 865 across the three arms, this suggests around 3 observations per patient, which would correspond with baseline, 24 weeks and 52 weeks.

If this is the case and around three observations per patient are being treated as independent observations within the OLS analysis, the opinion of the ERG is that this is not valid. In these circumstances, the GEE analysis should be preferred.

Quality of life: mean BCVA within health states

The company utility calculations that are based upon the VIVD/VISTA EQ-5D regression apply a mean BCVA of 90.5 letters for HS1 and of 20.5 letters for HS8.

The company utility calculations that are based upon the Czoski-Murray regression apply a mean BCVA of 93 letters for HS1 and of 12.5 letters for HS8. While the best and worst health states are wider than the other health states, it may be more reasonable to apply the same mean step change in BCVA when going from HS1 to HS2 and from HS7 to HS8 as for going from, say, HS3 to HS4. In the opinion of the ERG the descent to only 12.5 letters for eyes entering and remaining in HS8 is particularly questionable.

Quality of life: WSE impact as proportion of BSE impact

The calculated proportionate effects of the impact of the WSE means that as the BCVA of the WSE worsens the impact of changes in the BCVA of the BSE upon quality of life is also reduced. For instance, the formula of Czoski-Murray suggests that a reduction in bilateral BCVA from the mean 70.5 letters of HS3 to the mean 60.5 letters of HS4 results in quality of life falling from 0.690 to 0.617: a reduction of 0.074. Within the company method, for those with a WSE in HS4, if the BSE falls from HS3 to HS4 the quality of life falls now only falls from 0.673 to 0.617: a reduction of 0.057.

Due to the linear nature of the Czoski-Murray regression, provided that the WSE is at least one health state worse than the BSE, for a given WSE health state a one health state change in the BCVA of the BSE results in a quality of life change of only 0.057 compared to the 0.074 quality of life change that would result from the same step in bilateral BCVA.

Drug administration and monitoring visit costs

The £194 administration cost per intravitreal injection and £139 cost per dedicated monitoring visit are broadly in line with the £180 and £130 applied by the ERG within the TA283 aflibercept for CRVO once inflation has been taken into account.

The TA274 ranibizumab for DMO applied a laser administration cost of £150 based upon BZ23Z - Vitreous Retinal Procedures Category 1: outpatient procedures. The 2012-13 reference costs list BZ23Z: Minor intravitreal procedure and BZ22B Intermediate intravitreal procedure, which within ophthalmology saw:

- 801,444 outpatient BZ23Zs at a mean cost of £117

- 78,836 outpatient BZ22Bs at a mean cost of £131
- 94,821 day case BZ23Zs at a mean cost of £356
- 3,919 day case BZ22Bs at a mean cost of £989

ERG expert opinion suggests that laser treatment is less involved than intravitreal injections and as a consequence a lower cost per laser administration seems reasonable. This suggests the outpatient costs, with the choice as to BZ23Z or BZ22B having little practical impact. It is also questionable whether laser administrations should have the additional £139 monitoring cost added to them. This appears to assume that no laser administrations double as monitoring visits while all intravitreal injection administration visits double as monitoring visits. It seems more reasonable to apply the £131 to retain some consistency with the TA274 ranibizumab for DMO, but to remove the £139 monitoring cost from laser administrations. The impact of not all administration visits doubling as monitoring visits can then be consistently explored across treatments through sensitivity analyses.

Costs of blindness

The submission for TA294 aflibercept for AMD was criticised by the ERG for treating an annual cost of blindness as a monthly amount[g]. It appears that the current submission also treats the annual cost of blindness as a monthly amount[h]. It also appears that the costs of blindness are not discounted[i]. If this was the case, the costs of blindness and the cost offsets associated with this might have been greatly exaggerated within the modelling. This may hugely affect the comparison of aflibercept with laser and also the comparison with ranibizumab.

[g]http://www.nice.org.uk/guidance/TA294/documents/macular-degeneration-wet-agerelated-aflibercept-1st-line-evaluation-report2

[h] For instance, within the *Markov-Laser* worksheet cell KO71 is the product of cell KN71 and from the worksheet *PH* cell G44. Cell KN71 is the sum of the proportion of patients with both eyes in either HS7 or HS8, summed across the monthly cycles. The worksheet *PH* cell G44 is the annual cost of blindness £6,448.

[i] Within the Markov-Laser worksheet the elements contributing to cell KN71 do not appear to have any discounting applied. Revising the cost discount rate in cell C16 of the *Executive_Summary* worksheet changes the costs within the modelling with the exception of the costs of blindness.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

For the revised base case the ERG has:

- Revised the number of aflibercept injections to 8.50, [redacted] and 3.00 in years 1, 2 and 3[j].
- Revised the number of ranibizumab injections to 7.43, 4.00 and 3.00 in years 1, 2 and 3[k].
- Revised the cost per laser administration to £139[l].
- Revised the adverse event costs to be as per those tabulated in section 5.3.2 above[m].
- Revised the WSE quality of life adjustment factor from 30% to 42.85% so as to result in a final adjustment factor of 30%[n].
- Revised discounting to be of the form $1/(1+r)^t$ rather than $(1-r)^t$ [o].
- Netted out the quarterly rates of increase and of decrease for those off treatment to yield a quarterly rate of decrease of 1% in order to better reflect the estimates used within the cited reference[p].
- Revised the DMO mortality multiplier to be 2.45[q].
- Revised the cohort flows so as to evolve the number of treatments between the years for fellow eyes incident in years 2, 3, 4 and 5[r].
- Conditioned the number of fellow eyes by the proportion remaining alive[s].
- Revised the mid health state values so as to retain a 10 letter step between these[t].

---

[j] Implemented within the *Tx_Input* worksheet by inputting the relevant values to cells C77:C78.

[k] Implemented within the *Tx_Input* worksheet by inputting the relevant values to cells C97:C99.

[l] Implemented within the *Cost_Input* worksheet by setting G24=0 and C24=139.

[m] Implemented within the *Cost_Input* worksheet by setting cells C39:C42 to the relevant values.

[n] Implemented in the *Utility_regression_models* worksheet by setting cells D62, D87 and D112 equal to 42.85%

[o] Implemented by amending the formulae in cells GU88:GV484 of the *Markov-Aflibercept* worksheet to be of the appropriate functional form, and setting the corresponding values in the other markov worksheets equal to these values.

[p] Implemented in the *PH* worksheet by setting cell I84 equal to [(1+1.0%)^(1/3)]-1

[q] Implemented in the *PH* worksheet by setting G18=2.35

[r] Implemented in the *Markov-* worksheets by amending the formulae in columns HH through to HK so that the indexing is conditioned by the cells in HH84:HK84, just as the indexing in column HG refers to HE88 and is conditioned by HG84; e.g. HG88= IF($HE88<HH$84,0,IF($HE88-HH$84<6, INDEX($HF$76:$HF$81,
$HE88+1-HH$84)/12,0)*GM88)

[s] Implemented in the Markov- worksheets by conditioning cells GL88, GM88, GN88, GO88 and GP88 by (1-W88), not conditioning cell GQ88 by (1-W88) and setting GR88=1-GQ88-W88, and copying these formulae into the cells below.

- Assumed that eyes in HS7 and HS8 are not treated during the maintenance phase, as per the stated company base case[u].
- Revised the annual costs of blindness to be £7,429[v].
- Revised the costs of blindness to be monthly[w].
- Revised the costs of blindness to be discounted[x].
- Revised the proportion of treatment visits that double as monitoring visits within the aflibercept cohort flow to no longer be hard coded[y].

Note that the ERG base case retains the quality of life values derived from Czoski-Murray.[57] This can be objected to on the grounds that the VIVID/VISTA EQ-5D values are in line with the NICE guide to the methods of technology appraisal and so are more appropriate.

Sensitivity analysis undertaken by the ERG:

- Apply the ERG calculated relative risks based upon the four main trials, based upon excluding VISTA from the analysis, based upon excluding REVEAL from the analysis and based upon excluding both VISTA and REVEAL from the analysis[z].
- Explore the VIVID/VISTA EQ-5D utilities being based upon the OLS, random effects and GEE models[aa].
- Applying the ERG derived quality of life values from Brown 1999 and Brown 2000[bb].[60,61]
- Revert to the company mid letters of 93.0 for HS1 and 12.5 letters for HS8[cc].

---

[t] Implemented in the *Utility_regression_models* worksheet by setting U13=90.5 and U20=20.5 and by setting cells E109:E116 of the *Utilities_Input* worksheet equal to cells U13:U20 of the *Utility_regression_models* worksheet.
[u] Implemented in the *Executive_Summary* worksheet by setting cell C28 to *No.*
[v] Implemented in the *PH* worksheet by setting cell *I44* equal to £7,429.
[w] Implemented in the *PH* worksheet by qualifying cell *I44* by 1/12.
[x] Implemented in the all the *Markov-…* worksheets by revising cell KN71 to be of the form SUMPRODUCT(GV$88:OFFSET(GV$88,$KM71-1,0),KM$88:OFFSET(KM$88,$KM71-1,0))
[y] Implemented in the *Markov-Aflibercept* worksheet by setting HQ73 = PH!G21
[z] Implemented in the *Tx_Inputs* worksheet by copying the appropriate values into cells C22:C25, C35:C38, C609 and C628.
[aa] Implemented in the *Utility_regression_models* worksheet by copying the relevant values into D53:D57
[bb] Implemented in the *Utility_regression_models* worksheet by setting cells D24:D31 and D37:D44 to the relevant values.

- Explore the impact of reducing the proportion of those blind that require residential care from 30% to 20%, due to the 30% being an estimate for an older patient group with AMD. This causes the annual average cost of blindness to fall from £7,429 to £5,640[dd].
- Revise the proportion of fellow eyes with DMO that are treated from 50% to 0% and 100%[ee].
- Revise the proportion of treatment visits that double as monitoring visits from 100% to 50%[ff].
- Revise the proportion of visits that can be shared between the study eye and the fellow eye to 0%[gg].
- Revise the blindness mortality multiplier so as not to apply to those blind in only one eye[hh].
- Assume 8.1 treatments for ranibizumab in year 1[ii].
- Assume 4.0 treatments for aflibercept in year 2[jj].
- Assume 2.3 treatment visits for aflibercept and ranibizumab in year 3[kk].
- Assume 8.0 monitoring visits for ranibizumab in year 1[ll].

[cc] Implemented in the *Utility_regression_models* worksheet by setting U13=93.0 and U20=12.5.
[dd] Implemented in the *PH* worksheet by setting cell *I44* equal to £5,620 with this also being qualified by 1/12.
[ee] Implemented in the *PH* worksheet by setting cell I15 equal to the appropriate percentage.
[ff] Implemented in the *PH* worksheet by setting cells I21:I22 to the 50%.
[gg] Implemented in the *PH* worksheet by setting cells I16:I17 equal to the 50%.
[hh] Implemented in the *PH* worksheet by setting G19=1
[ii] Implemented in the *Tx_Inputs* worksheet by setting cell C97=8.1.
[jj] Implemented in the *Tx_Inputs* worksheet by setting cell C78=4.0.
[kk] Implemented in the *Tx_Inputs* worksheet by setting cell C79=C99=2.3.
[ll] Implemented in the *Tx_Inputs* worksheet by setting cell C177=8.0.

Table 73 ERG base case results aflibercept vs laser: including aflibercept PAS

	Aflibercept	Laser	Net
Tx 1st eye	[redacted]	[redacted]	£9,327
Tx 2nd eye	[redacted]	[redacted]	£4,179
AE 1st eye	[redacted]	[redacted]	-£5
AE 2nd eye	[redacted]	[redacted]	-£5
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£355
Blindness	[redacted]	[redacted]	-£211
Total	[redacted]	[redacted]	£12,931
LYs undisc.	14.239	14.174	0.065
QALYs	7.424	7.043	0.381
ICER			£33,921

Compared to the company estimates, the costs of blindness are very much reduced due to the division by 12 and the application of discounting. The direct treatment costs are also increased, resulting in a net total cost of £12,931. The 0.381 QALY gain yields a cost-effectiveness estimate for aflibercept versus laser of £33,921 per QALY gained (Table 73).

Table 74 ERG base case results aflibercept vs ranibizumab: including aflibercept PAS

	Aflibercept	Ranibizumab	Net
Tx 1st eye	[redacted]	[redacted]	-£2,797
Tx 2nd eye	[redacted]	[redacted]	-£1,263
AE 1st eye	[redacted]	[redacted]	£307
AE 2nd eye	[redacted]	[redacted]	£138
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£739
Blindness	[redacted]	[redacted]	-£35
Total	[redacted]	[redacted]	-£4,390
LYs undisc.	14.239	14.225	0.015
QALYs	7.424	7.333	0.091
ICER			Dominant

With no ranibizumab PAS it is estimated that aflibercept results in cost savings of £4,390 and a 0.091 QALY gain, so dominates ranibizumab (Table 74). Sensitivity

analyses that explore the impacts of varying ranibizumab PAS percentages are presented in Table 75.

Table 75 ERG base case results: aflibercept versus ranibizumab: ranibizumab PAS discounts

Δ QALYs	Rani. PAS	Δ Costs	ICER	Rani. PAS	Δ Costs	ICER
0.091	5%	-£3,473	Dominant	55%	£5,696	£62,403
	10%	-£2,556	Dominant	60%	£6,613	£72,448
	15%	-£1,639	Dominant	65%	£7,530	£82,492
	20%	-£722	Dominant	70%	£8,447	£92,537
	25%	£195	£2,134	75%	£9,364	£102,582
	30%	£1,112	£12,179	80%	£10,281	£112,626
	35%	£2,029	£22,224	85%	£11,198	£122,671
	40%	£2,946	£32,269	90%	£12,115	£132,716
	45%	£3,863	£42,313	95%	£13,032	£142,761
	50%	£4,780	£52,358	100%	£13,949	£152,805

SUPERSEDED BY ERRATUM

The sensitivity analyses for the comparison of aflibercept with laser yield the values presented in Table 76.

Table 76 ERG sensitivity analyses: aflibercept vs laser - including aflibercept PAS

	Δ QALY	Δ Cost	ICER
Base case	0.381	£12,931	£33,921
ERG RR			
All trials	0.382	£12,910	£33,810
Excl. VISTA	0.358	£13,035	£36,363
Excl. REVEAL	0.376	£12,909	£34,356
Excl. VISTA & REVEAL	0.358	£12,971	£36,242
EQ-5D QoL			
OLS	0.128	£12,931	£101,198
Random Effects	0.111	£12,931	£116,800
GEE	0.110	£12,931	£117,222
Brown 1999 QoL	0.287	£12,931	£45,024
Brown 2000 QoL	0.432	£12,931	£29,915
46% FEI baseline	0.346	£11,660	£33,657
Company mid letters	0.403	£12,931	£32,121
Blind res. care 20%	0.381	£12,982	£34,056
FEI DMO Tx 0%	0.277	£8,804	£31,757
FEI DMO Tx 100%	0.485	£17,058	£35,158
Tx share monit. 50%	0.381	£13,768	£36,117
SE share NSE 0%	0.381	£12,770	£33,500
No one eye blind mort.	0.358	£12,908	£36,063
4.0 Afli Tx yr2	0.381	[redacted]	[redacted]
2.3 Rani. Afli. Tx yr3	0.381	[redacted]	[redacted]

The main sensitivities are to the quality of life values which are applied. All the VISTA/VIVID EQ-5D analyses seriously worsen the cost-effectiveness estimate, with the ERG preferred GEE analysis worsening the cost-effectiveness estimate to £117,222 per QALY. Using the Brown 1999 quality of life values also worsens the ICER to £45,024 per QALY, but perhaps surprisingly the Brown 2000 values improve it to £29,915 per QALY.[60,61]

Reducing the proportion of treatment visits that double as monitoring visits to 50% worsens the cost-effectiveness estimate to £36,117 per QALY. Removing the blindness mortality multiplier when one eye falls into blindness has a similar effect, revising the cost-effectiveness estimate to £36,063 per QALY.

Note that a scenario analysis that assumes 100% of the study eyes are in a given health state and then makes the distribution of fellow eyes specific to that study eye, and then weights the results of these analyses by the study eye proportions yields a gain of 0.381 QALYs and an incremental cost of £12,700, The resulting cost-effectiveness estimate of £33,360 per QALY gained is little different from the base case analysis.

The sensitivity analyses for the comparison with ranibizumab are presented in Tables 77-81. Due to the number of PAS percentages explored by the company, these sensitivity analyses are divided into five tables examining the ranibizumab PAS percentages:

- 5% to 20%;
- 25% to 40%;
- 45% to 60%;
- 65% to 80%; and,
- 85% to 100%.

For reasons of space the sensitivity analyses of the ERG relative risks from all trials and the random effects EQ-5D quality of life values have not been presented. They are very similar to the base case.

The pattern of sensitivities is similar to those for the comparison of aflibercept with laser, but for the comparison with ranibizumab the inclusion and exclusion of studies from the NMA has a more noticeable effect. Excluding the VISTA trial somewhat worsens the cost-effectiveness estimates, while excluding the REVEAL trial improves the cost-effectiveness estimates.

Applying the VIVID/VISTA EQ-5D quality of life estimates greatly reduces the anticipated gains, with the ERG preferred GEE analysis almost eliminating them.

The proportion of fellow eyes that are treated appears to be more important than in the comparison of aflibercept with laser.

Results show a reasonable sensitivity to the number of ranibizumab treatments that are assumed for the first year and the number of aflibercept treatments that are assumed for the second year. If the number of monitoring visits for ranibizumab in the first year falls to that of aflibercept due to the recent changes in the ranibizumab SmPC this worsens the cost-effectiveness estimates by a reasonable amount.

Table 77 ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 5% to 20%

Ranibizumab PAS		5%		10%		15%		20%	
	Δ QALYs	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER
Base case	0.091	-£3,473	Dominant	-£2,556	Dominant	-£1,639	Dominant	-£722	Dominant
RR excl. VISTA	0.073	-£3,368	Dominant	-£2,452	Dominant	-£1,535	Dominant	-£618	Dominant
RR excl. REVEAL	0.152	-£2,514	Dominant	-£1,645	Dominant	-£775	Dominant	£94	£623
RR excl. VISTA & REVEAL	0.072	-£2,507	Dominant	-£1,634	Dominant	-£761	Dominant	£112	£1,554
EQ-5D QoL OLS	0.012	-£3,473	Dominant	-£2,556	Dominant	-£1,639	Dominant	-£722	Dominant
EQ-5D QoL GEE	0.008	-£3,473	Dominant	-£2,556	Dominant	-£1,639	Dominant	-£722	Dominant
Brown 1999 QoL	0.061	-£3,473	Dominant	-£2,556	Dominant	-£1,639	Dominant	-£722	Dominant
Brown 2000 QoL	0.106	-£3,473	Dominant	-£2,556	Dominant	-£1,639	Dominant	-£722	Dominant
46% FEI baseline	0.082	-£3,197	Dominant	-£2,368	Dominant	-£1,539	Dominant	-£711	Dominant
Company mid letters	0.098	-£3,473	Dominant	-£2,556	Dominant	-£1,639	Dominant	-£722	Dominant
Blind res. care 20%	0.091	-£3,464	Dominant	-£2,547	Dominant	-£1,630	Dominant	-£713	Dominant
FEI DMO Tx 0%	0.064	-£2,591	Dominant	-£1,958	Dominant	-£1,325	Dominant	-£692	Dominant
FEI DMO Tx 100%	0.118	-£4,355	Dominant	-£3,154	Dominant	-£1,953	Dominant	-£752	Dominant
Tx share monit. 50%	0.091	-£3,353	Dominant	-£2,436	Dominant	-£1,519	Dominant	-£602	Dominant
SE share NSE 0%	0.091	-£3,750	Dominant	-£2,833	Dominant	-£1,916	Dominant	-£999	Dominant
No one eye blind mort.	0.087	-£3,478	Dominant	-£2,561	Dominant	-£1,644	Dominant	-£726	Dominant
8.1 Rani. Tx yr1	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 Afli Tx yr2	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3 Rani. Afli. Tx yr3	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 Rani. Monit. Yr1	0.091	-£2,919	Dominant	-£2,003	Dominant	-£1,086	Dominant	-£169	Dominant

SUPERSEDED BY ERRATUM

Table 78 ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 25% to 40%

Ranibizumab PAS		25%		30%		35%		40%	
	Δ QALYs	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER
Base case	0.091	£195	£2,134	£1,112	£12,179	£2,029	£22,224	£2,946	£32,269
RR excl. VISTA	0.073	£299	£4,096	£1,216	£16,651	£2,133	£29,205	£3,050	£41,760
RR excl. REVEAL	0.152	£964	£6,362	£1,834	£12,102	£2,703	£17,841	£3,573	£23,580
RR excl. VISTA & REVEAL	0.072	£985	£13,660	£1,858	£25,766	£2,731	£37,872	£3,603	£49,978
EQ-5D QoL OLS	0.012	£195	£15,701	£1,112	£89,591	£2,029	£163,481	£2,946	£237,371
EQ-5D QoL GEE	0.008	£195	£24,195	£1,112	£138,058	£2,029	£251,922	£2,946	£365,785
Brown 1999 QoL	0.061	£195	£3,215	£1,112	£18,344	£2,029	£33,473	£2,946	£48,602
Brown 2000 QoL	0.106	£195	£1,836	£1,112	£10,478	£2,029	£19,120	£2,946	£27,762
46% FEI baseline	0.082	£118	£1,439	£947	£11,522	£1,776	£21,605	£2,605	£31,688
Company mid letters	0.098	£195	£1,979	£1,112	£11,295	£2,029	£20,610	£2,946	£29,925
Blind res. care 20%	0.091	£203	£2,229	£1,120	£12,273	£2,037	£22,318	£2,954	£32,363
FEI DMO Tx 0%	0.064	-£60	Dominant	£573	£8,898	£1,206	£18,721	£1,839	£28,544
FEI DMO Tx 100%	0.118	£449	£3,803	£1,650	£13,968	£2,851	£24,134	£4,053	£34,299
Tx share monit. 50%	0.091	£315	£3,453	£1,232	£13,498	£2,149	£23,542	£3,066	£33,587
SE share NSE 0%	0.091	-£82	Dominant	£835	£9,143	£1,752	£19,188	£2,669	£29,233
No one eye blind mort.	0.087	£191	£2,201	£1,108	£12,790	£2,025	£23,379	£2,942	£33,969
8.1 Rani. Tx yr1	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 Afli Tx yr2	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3 Rani. Afli. Tx yr3	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 Rani. Monit. Yr1	0.091	£748	£8,197	£1,665	£18,242	£2,582	£28,286	£3,499	£38,331

SUPERSEDED BY ERRATUM

Table 79 ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 45% to 60%

Ranibizumab PAS		45%		50%		55%		60%	
	Δ QALYs	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER
Base case	0.091	£3,863	£42,313	£4,780	£52,358	£5,696	£62,403	£6,613	£72,448
RR excl. VISTA	0.073	£3,967	£54,315	£4,884	£66,869	£5,801	£79,424	£6,717	£91,979
RR excl. REVEAL	0.152	£4,442	£29,320	£5,312	£35,059	£6,182	£40,798	£7,051	£46,537
RR excl. VISTA & REVEAL	0.072	£4,476	£62,084	£5,349	£74,190	£6,222	£86,296	£7,095	£98,402
EQ-5D QoL OLS	0.012	£3,863	£311,261	£4,780	£385,150	£5,696	£459,040	£6,613	£532,930
EQ-5D QoL GEE	0.008	£3,863	£479,648	£4,780	£593,511	£5,696	£707,374	£6,613	£821,238
Brown 1999 QoL	0.061	£3,863	£63,731	£4,780	£78,860	£5,696	£93,990	£6,613	£109,119
Brown 2000 QoL	0.106	£3,863	£36,404	£4,780	£45,046	£5,696	£53,688	£6,613	£62,330
46% FEI baseline	0.082	£3,434	£41,771	£4,262	£51,854	£5,091	£61,937	£5,920	£72,020
Company mid letters	0.098	£3,863	£39,240	£4,780	£48,555	£5,696	£57,870	£6,613	£67,185
Blind res. care 20%	0.091	£3,871	£42,408	£4,788	£52,452	£5,705	£62,497	£6,622	£72,542
FEI DMO Tx 0%	0.064	£2,472	£38,367	£3,104	£48,190	£3,737	£58,014	£4,370	£67,837
FEI DMO Tx 100%	0.118	£5,254	£44,465	£6,455	£54,630	£7,656	£64,796	£8,857	£74,961
Tx share monit. 50%	0.091	£3,983	£43,632	£4,900	£53,677	£5,817	£63,721	£6,734	£73,766
SE share NSE 0%	0.091	£3,585	£39,278	£4,502	£49,322	£5,419	£59,367	£6,336	£69,412
No one eye blind mort.	0.087	£3,859	£44,558	£4,776	£55,147	£5,693	£65,737	£6,610	£76,326
8.1 Rani. Tx yr1	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 Afli Tx yr2	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3 Rani. Afli. Tx yr3	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 Rani. Monit. Yr1	0.091	£4,416	£48,376	£5,333	£58,421	£6,250	£68,465	£7,167	£78,510

SUPERSEDED BY ERRATUM

Table 80 ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 65% to 80%

Ranibizumab PAS		65%		70%		75%		80%	
	Δ QALYs	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER
Base case	0.091	£7,530	£82,492	£8,447	£92,537	£9,364	£102,582	£10,281	£112,626
RR excl. VISTA	0.073	£7,634	£104,533	£8,551	£117,088	£9,468	£129,642	£10,385	£142,197
RR excl. REVEAL	0.152	£7,921	£52,277	£8,790	£58,016	£9,660	£63,755	£10,530	£69,494
RR excl. VISTA & REVEAL	0.072	£7,968	£110,509	£8,841	£122,615	£9,713	£134,721	£10,586	£146,827
EQ-5D QoL OLS	0.012	£7,530	£606,820	£8,447	£680,710	£9,364	£754,600	£10,281	£828,489
EQ-5D QoL GEE	0.008	£7,530	£935,101	£8,447	£1,048,964	£9,364	£1,162,827	£10,281	£1,276,690
Brown 1999 QoL	0.061	£7,530	£124,248	£8,447	£139,377	£9,364	£154,506	£10,281	£169,635
Brown 2000 QoL	0.106	£7,530	£70,972	£8,447	£79,614	£9,364	£88,256	£10,281	£96,898
46% FEI baseline	0.082	£6,749	£82,103	£7,578	£92,186	£8,406	£102,269	£9,235	£112,352
Company mid letters	0.098	£7,530	£76,501	£8,447	£85,816	£9,364	£95,131	£10,281	£104,446
Blind res. care 20%	0.091	£7,539	£82,586	£8,456	£92,631	£9,373	£102,676	£10,290	£112,721
FEI DMO Tx 0%	0.064	£5,003	£77,660	£5,636	£87,483	£6,269	£97,306	£6,901	£107,130
FEI DMO Tx 100%	0.118	£10,058	£85,127	£11,259	£95,292	£12,460	£105,458	£13,661	£115,623
Tx share monit. 50%	0.091	£7,651	£83,811	£8,568	£93,855	£9,485	£103,900	£10,402	£113,945
SE share NSE 0%	0.091	£7,253	£79,457	£8,170	£89,501	£9,087	£99,546	£10,004	£109,591
No one eye blind mort.	0.087	£7,527	£86,915	£8,444	£97,505	£9,361	£108,094	£10,278	£118,683
8.1 Rani. Tx yr1	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 Afli Tx yr2	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3 Rani. Afli. Tx yr3	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 Rani. Monit. Yr1	0.091	£8,084	£88,555	£9,001	£98,599	£9,918	£108,644	£10,835	£118,689

SUPERSEDED BY ERRATUM

Table 81 ERG sensitivity analyses: aflibercept vs ranibizumab: with aflibercept PAS and ranibizumab PAS 85% to 100%

Ranibizumab PAS		85%		90%		95%		100%	
	Δ QALYs	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER	Δ Costs	ICER
Base case	0.091	£11,198	£122,671	£12,115	£132,716	£13,032	£142,761	£13,949	£152,805
RR excl. VISTA	0.073	£11,302	£154,752	£12,219	£167,306	£13,136	£179,861	£14,053	£192,415
RR excl. REVEAL	0.152	£11,399	£75,234	£12,269	£80,973	£13,138	£86,712	£14,008	£92,451
RR excl. VISTA & REVEAL	0.072	£11,459	£158,933	£12,332	£171,039	£13,205	£183,145	£14,078	£195,251
EQ-5D QoL OLS	0.012	£11,198	£902,379	£12,115	£976,269	£13,032	£1,050,159	£13,949	£1,124,049
EQ-5D QoL GEE	0.008	£11,198	£1,390,554	£12,115	£1,504,417	£13,032	£1,618,280	£13,949	£1,732,143
Brown 1999 QoL	0.061	£11,198	£184,764	£12,115	£199,894	£13,032	£215,023	£13,949	£230,152
Brown 2000 QoL	0.106	£11,198	£105,539	£12,115	£114,181	£13,032	£122,823	£13,949	£131,465
46% FEI baseline	0.082	£10,064	£122,435	£10,893	£132,518	£11,722	£142,601	£12,551	£152,684
Company mid letters	0.098	£11,198	£113,761	£12,115	£123,076	£13,032	£132,391	£13,949	£141,707
Blind res. care 20%	0.091	£11,207	£122,765	£12,124	£132,810	£13,041	£142,855	£13,958	£152,900
FEI DMO Tx 0%	0.064	£7,534	£116,953	£8,167	£126,776	£8,800	£136,599	£9,433	£146,423
FEI DMO Tx 100%	0.118	£14,862	£125,789	£16,063	£135,954	£17,264	£146,120	£18,465	£156,285
Tx share monit. 50%	0.091	£11,318	£123,990	£12,235	£134,034	£13,152	£144,079	£14,069	£154,124
SE share NSE 0%	0.091	£10,921	£119,635	£11,838	£129,680	£12,755	£139,725	£13,672	£149,770
No one eye blind mort.	0.087	£11,195	£129,273	£12,112	£139,862	£13,029	£150,451	£13,947	£161,041
8.1 Rani. Tx yr1	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 Afli Tx yr2	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3 Rani. Afli. Tx yr3	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 Rani. Monit. Yr1	0.091	£11,752	£128,734	£12,668	£138,778	£13,585	£148,823	£14,502	£158,868

SUPERSEDED BY ERRATUM

5.5 Conclusions of the cost-effectiveness section

There is always uncertainty as to how well trials' results transfer to clinical practice. One concern is that often patients seen in clinical practice have worse control of their HbA1c than the average participants enrolled in clinical trials.

There are general concerns with the modelling approach that has been adopted. The model developed by the company makes a number of implicit assumptions that are not necessarily justified:

- The likelihood of a letters gain (loss) is the same regardless of the health state the treated eye is in.
- It is appropriate to infer monthly probabilities from annual probabilities in a manner analogous to compounding interest rates.
- The monthly rates of gain (loss) are constant over the first year.
- It is appropriate to apply 12 month relative risks to monthly quantities.
- It is appropriate to apply the relative risks of improving by 10 or more letters to the probability of improving by 10 letters.

These concerns may be part of the reason that the modelled results after one year show a relatively poor correspondence with the pooled VIVID/VISTA trial results. This suggests that the model underestimates the benefit from aflibercept over laser.

The ERG has a number of concerns about the model structure and possible errors within it. The ERG revisions to the model to address these concerns are outlined in more detail in the footnotes to section 5.4.

The company submission assumptions around dosing for both aflibercept and ranibizumab are not in line with those suggested by the trials' data, and the aflibercept dosing in year one also appears to be slightly out of line with the SmPC. The trials also appear to suggest a higher dosing rate for aflibercept than for ranibizumab in the second year. It is possible that this is more a reflection of the differences between the trials than any difference that will apply in the real world.

The model structure does not take into account the impact of discontinuations upon the mean number of doses each year. This suggests that the model may underestimate the costs of treatment by around 5%.

The ranibizumab SmPC has been recently revised to permit a monitoring schedule in the first year that is more flexible and is more in line with that of aflibercept. In the short to medium term the number of ranibizumab monitoring visits in the first year may tend to converge with that of aflibercept.

The company submission applies the 3-monthly 3.5% rate of worsening of the STA of ranibizumab for DMO that is off treatment but does not apply the corresponding 3-monthly 2.5% rate of improvement.

The mortality multiplier for DMO remains uncertain, but the most appropriate value for the base case would seem to be that used in of the TA274 ranibizumab for DMO.

Results are sensitive to the source of quality of life values. The NICE guide to the methods of technology appraisal suggests that the EQ-5D values should be preferred for the base case. These greatly reduce the anticipated QALY gains from aflibercept. However, previous assessments of treatments for eye diseases have frequently relied upon the values of Czoski-Murray and Brown. There may be an argument for using these for the base case if comparability of results with those of previous assessments is required.

The company submission also appears to produce biased estimates due to its calculation of the costs of blindness. These estimates appear to be too large and are the main source of difference between the company submitted model and the ERG revisions to it, which see aflibercept change from being estimated to dominate laser to having a cost-effectiveness estimate of £33,921 per QALY.

The analysis for the CRT ≥ 400µm subgroup only changes the probabilities of improving and worsening within the laser arm. The relative risks of the NMA are retained. But the point estimates of the pooled VIVID/VISTA trial may suggest a smaller gain for those with a CRT < 400µm than for those with a CRT ≥ 400µm. This

is hampered by the relatively small number of patients with a CRT < 400µm. It may not be possible to perform an NMA for the CRT ≥ 400µm subgroup. The company, however, has the VIVID/VISTA trial data for the comparison of aflibercept with laser for the CRT ≥ 400µm subgroup. It may be difficult to make formal estimates of the cost-effectiveness of aflibercept versus laser for the CRT < 400µm, but some inference might be possible from the all patient analysis if combined with a CRT ≥ 400µm subgroup analysis.

The model has the facility to base the analysis upon the four weekly TPMs of the VIVID/VISTA trial. This modelling may be a sounder basis for the comparison of aflibercept with laser, and at a minimum it would seem sensible to present this as structural sensitivity analysis. The ERG has not examined this aspect of the model.

The ERG has not been able to run the company model probabilistically.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

A fuller account of the ERG analyses is given in section 5.4.

For the comparison of aflibercept with laser the base case suggests a gain of 0.381 QALYs, a net cost inclusive of the aflibercept PAS of £12,931 and a cost-effectiveness estimate of £33,921 per QALY gained.

Results are sensitive to the source of the quality of life estimates. Using the VIVID/VISTA EQ-5D data worsens the cost-effectiveness estimate to £117,222 for the ERG preferred GEE analysis. The Brown 1999 quality of life values worsen the cost-effectiveness estimate to £45,024 per QALY gained, while those of Brown 2000 improve it to £29,915 per QALY gained.

For the comparison of aflibercept with ranibizumab, the base case suggests a gain of 0.091 QALYs and cost savings inclusive of the aflibercept PAS but exclusive of any ranibizumab PAS of £4,390. As a consequence, aflibercept is estimated to dominate ranibizumab. Cost savings turn to additional costs of £195 with a ranibizumab PAS of 25%. A ranibizumab PAS of 35% yields a cost-effectiveness estimate for aflibercept compared to ranibizumab of £22,224 per QALY gained, while a ranibizumab PAS of 40% yields a cost-effectiveness estimate of £32,296 per QALY gained.

Excluding VISTA from the NMA causes the gain from aflibercept to fall to 0.073 QALYs. A ranibizumab PAS of 35% results in a cost-effectiveness estimate of £29,205 per QALY gained.

Excluding the REVEAL trial from the NMA causes the gain from aflibercept to rise to 0.152 QALYs. A ranibizumab PAS of 45% results in a cost-effectiveness estimate of £29,320 per QALY gained.

Using the VIVID/VISTA EQ-5D data and the GEE analysis causes the gain from aflibercept to fall to only 0.008 QALYs. A ranibizumab PAS of 25% results in a cost-

effectiveness estimate of £24,195 per QALY gained, while a ranibizumab PAS of 30% results in a cost-effectiveness estimate of £138,058 per QALY gained.

Costs effectiveness estimates also show some sensitivity to the number of ranibizumab treatments in year 1, the number of aflibercept administrations in year 2 and the number of monitoring visits for ranibizumab in year 1.

7 OVERALL CONCLUSIONS

In the two main, multicenter, RCTs, VIVID and VISTA, aflibercept treatment (2Q4 and 2Q8) showed more favourable visual outcomes at 52 weeks than laser photocoagulation therapy and a similar safety profile. Benefits were maintained at longer assessments (week 100). More deaths were observed among participants treated with aflibercept than among those who received laser photocoagulation therapy, but the difference did not reach statistical significance. Results of the network meta-analysis indicated that, compared with ranibizumab, aflibercept 2Q8 showed a significant improvement at 12 months in the BCVA mean change from baseline but no significant differences were observed for other visual outcomes. Aflibercept was also significantly more effective than dexamethasone for the outcome 'gain of ≥10 letters'. A comparison of aflibercept with fluocinolone was not possible due to lack of a common comparator to allow indirect analysis.

With regard to the economic model, one difference between the company and the ERG's assumptions relates to the number of treatment administrations. The ERG has applied those that appear to be implied by the available estimates of trial means. The DCRC.net trial only reports medians for the first year dosing and so has not been included in the ERG base case. Including it increases the number of ranibizumab treatments in the first year from 7.43 to 8.10. The VIVID/VISTA data for week 52 to week 100 appears to suggest a mean dose of [redacted] while the data for ranibizumab appears to suggest a mean dose of 3.90. Whether it is sensible to differentiate between the treatments to this degree is questionable.

There is uncertainty about how quickly the revised ranibizumab SmPC will lead to a different monitoring schedule during the first year. The company assumes that no changes will take place and that the old fixed monthly monitoring schedule for the first year will be maintained.

Results are quite sensitive to the source of quality of life estimates. The base cases uses those derived from the experimental lens study of Czoski-Murray 2009. It can be argued that the base case should use the values derived from the VIVID/VISTA EQ-

5D data. The ERG prefers the GEE estimates from this, while the company uses the OLS estimates.

Results for the comparison of aflibercept with laser are not particularly sensitive to the exclusion of VISTA or REVEAL from the NMA. Results for the comparison with ranibizumab are more sensitive to this. VISTA may be seen as less applicable due to the extent of previous treatment with anti-VEGF, while REVEAL may be seen as less relevant due to it being a Far Eastern study. The TA274 ranibizumab for DMO was mainly based upon the RESTORE study.

Results are also sensitive to the rate of worsening in eyes with DMO when they are off treatment. The company applies the 3-month 3.5% rate of worsening of the STA of ranibizumab for DMO, but not the corresponding 3-month 2.5% rate of improvement. The ERG nets these out to yield a 3-month 1.0% rate of improvement. The ERG also prefers the 2.45 DMO mortality multiplier that was arrived at over the course of the STA of ranibizumab for DMO, but recognises that it may be too high.

7.1 Implications for research

Head-to-head trials of aflibercept versus ranibizumab with respect to efficacy and safety outcomes would contribute to reduce the uncertainty surrounding any differences between treatments in clinical effectiveness and would inform cost-effectiveness.

There is current an ongoing trial sponsored by the Diabetic Retinopathy Clinical Research Network (DRCR.net) that aims at assessing the comparative effectiveness of aflibercept, bevacizumab, and ranibizumab for DMO (NCT01627249).

Future trials should also attempt to identify people who are more likely to respond to treatment.

Given the burden of current treatments (requiring close monitoring and frequent therapy, likely long-term) research into new, less demanding, therapeutic strategies should be sought. Currently, newly introduced treatments for DMO, including anti-VEGFs and steroids, require intravitreal administration by an injection into the eye.

The disutility associated with this form of administration has not been evaluated and, thus, research into this area would be beneficial. Furthermore, new, more comfortable and accessible routes of administration should be sought. As current treatments for DMO are successful in only a proportion of patients (at best 50-60%), research that aim at identifying new potential treatment strategies is much needed.

8 REFERENCES

1 Jampol LM, Bressler NM, Glassman AR. Revolution to a new standard treatment of diabetic macular edema. *JAMA* 2014;**311**:2269-70.

2 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabet Res Clin Pract* 2010;**87**:4-14.

3 *Diabetes: facts and figures [webpage on the Internet]*. International Diabetes Federation; 2014 [accessed November 2014]. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0111322.

4 Stewart MW. Anti-VEGF therapy for diabetic macular edema. *Current Diabetes Reports* 2014;**14**:510.

5 Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;**376**:124-36.

6 *Eye health data summary for England.* UK Vision Strategy; 2014 [accessed]. http://www.vision2020uk.org.uk/ukvisionstrategy/page.asp?section=359&sectionTitle=Eye+Health+Data+Summary+for+England.

7 Chen E, Looman M, Laouri M, Gallagher M, Van NK, Lakdawalla D et al. Burden of illness of diabetic macular edema: literature review. *Curr Med Res Opinion* 2010;**26**:1587-97.

8 Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Curr Diabet Report* 2012;**12**:346-54.

9 Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;**35**:556-65.

10 Diep TM, Tsui I. Risk factors associated with diabetic macular edema. *Diabet Res Clin Pract* 2013;**100**:298-305.

11 Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. *Br J Ophthalmol* 2012;**96**:345-9.

12 Bresnick GH. Diabetic maculopathy. A critical review highlighting diffuse macular edema. *Ophthalmology* 1983;**90**:1301-17.

13 Browning DJ, Altaweel MM, Bressler NM, Bressler SB, Scott IU, Diabetic Retinopathy Clinical Research Network. Diabetic macular edema: what is focal and what is diffuse?. *Am J Ophthalmol* 2008;**146**:649-55.

14 Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985;**103**:1796-806.

15 *Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237)NICE Technolgy Appraisal TA274 [document on the Internet]*. London: National Institute for Health and Care Excellence; 2013 [accessed November 2014]. http://www.nice.org.uk/guidance/TA274.

16 Benarous R, Sasongko MB, Qureshi S, Fenwick E, Dirani M, Wong TY et al. Differential association of serum lipids with diabetic retinopathy and diabetic macular edema. *Invest Ophthalmol Vis Sci* 2011;**52**:7464-9.

17 Dolz-Marco R, Abreu-Gonzalez R, Alonso-Plasencia M, Gallego-Pinazo R. Treatment decisions in diabetic macular edema based on optical coherence tomography retinal thickness map: LET classification. *Graefes Arch Clin Experiment Ophthalmol* 2014;**252**:1687-8.

18 Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med* 2012;**366**:1227-39.

19 Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema. Long-term visual results. *Ophthalmology* 1991;**98**:1594-602.

20 Mitchell P, Wong TY, Diabetic Macular Edema Treatment Guideline Working Group. Management paradigms for diabetic macular edema. *Am J Ophthalmol* 2014;**157**:505-13.

21 Pearce E, Sivaprasad S, Chong NV. Factors affecting reading speed in patients with diabetic macular edema treated with laser photocoagulation. *PLoS ONE [Electronic Resource]* 2014;**9**:e105696.

22 Lavinsky D, Cardillo JA, Melo LA, Jr., Dare A, Farah ME, Belfort R, Jr. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2011;**52**:4314-23.

23 Vujosevic S, Bottega E, Casciano M, Pilotto E, Convento E, Midena E. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. *Retina* 2010;**30**:908-16.

24 Ford JA, Lois N, Royle P, Clar C, Shyangdan D, Waugh N. Current treatments in diabetic macular oedema: systematic review and meta-analysis. *BMJ Open* 2013;**3**:

25 Bandello F, Casalino G, Loewenstein A, Goldstein M, Pelayes D, Battaglia PM. Pharmacological approach to diabetic macular edema. *Ophthalmic Res* 2014;**51**:88-95.

26 Romero-Aroca P. Targeting the pathophysiology of diabetic macular edema. *Diabetes Care* 2010;**33**:2484-5.

27 Regnier S, Malcolm W, Allen F, Wright J, Bezlyak V. EFficacy of anti-VEGF and laser photocoagulation in the treatment of visual impairment due to diabetic

macular edema: A systematic review and network meta-analysis. *PLoS ONE* 2014;**9**:e102309.

28 Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR et al. Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema. *Ophthalmology* 2010;**117**:1064-77.

29 *Eyelea (Aflibercept) European public assessment report (EPAR) [document on the Internet]*. European Medicines Agency; 2014 [accessed November 2014]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002392/WC500135745.pdf.

30 *Ranibizumab and pegaptanib for the treatment of age-related macular degeneration NICE Technology Appraisal TA155*. London: Niational Institute for Health and Care Excellence; 2008 [accessed November 2014]. http://www.nice.org.uk/guidance/TA155.

31 *Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271)NIICE Technology Appraisal 301*. London: National Institute for Health and Care Excellence; 2013 [accessed November 2014]. http://www.nice.org.uk/guidance/TA301.

32 Ohr M, Kaiser PK. Intravitreal aflibercept injection for neovascular (wet) age-related macular degeneration. *Expert Opin Pharmacotherapy* 2012;**13**:585-91.

33 Mansourian M, Kazemnejad A, Kazemi I, Zayeri F, Soheilian M. Using mixed models with flexible random effects for determining the best diabetic macular edema treatment. *J Isfahan Med School* 2011;**29**:

34 Zhang L-W, Su K-X, Ma J, Qiu H, Wei X-H. Investigation on effects of intravitreal injection of bevacizumab and triarncinolone acetonide for diabetes macular edema. *Int Eye Sci* 2013;**13**:798-800.

35 Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, Beck RW, Bressler NM, Chan CK et al. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;**114**:1860-7.

36 Korobelnik J-F, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology* 2014;**121**:2247-54.

37 Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;**117**:1064-77.

38 Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO et al. The RESTORE study: ranibizumab monotherapy or combined with

laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;**118**:615-25.

39 Soheilian M, Ramezani A, Yaseri M, Mirdehghan SA, Obudi A, Bijanzadeh B. Initial macular thickness and response to treatment in diabetic macular edema. *Retina* 2011;31:1564-73.

40 Ohji M, ishibashi TRSG. Efficacy And Safety Of Ranibizumab 0.5 Mg As Monotherapy Or Adjunctive To Laser Versus Laser Monotherapy In Asian Patients With Visual Impairment Due To Diabetic Macular Edema: 12-month Results Of The REVEAL Study. *Invest Ophthalmol Vis Sci* 2012;53:4664.

41 Almeida FP, Katayama B, Messias A, Paccola ML. Macular laser photocoagulation combined with intravitreal bevacizumab or triamcinolone for diabetic macular edema. *Invest Ophthalmol Vis Sci* 2011;52:1300.

42 Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W et al. A randomized trial to assess functional and structural effects of ranibizumab versus laser in diabetic macular edema (the LUCIDATE study). *Am J Ophthalmol* 2014;**157**:960-70.

43 Diabetic Retinopathy Clinical Research Network, Googe J, Brucker AJ, Bressler NM, Qin H, Aiello LP et al. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina* 2011;**31**:1009-27.

44 Maia OO, Jr., Takahashi BS, Costa RA, Scott IU, Takahashi WY. Combined laser and intravitreal triamcinolone for proliferative diabetic retinopathy and macular edema: one-year results of a randomized clinical trial. *Am J Ophthalmol* 2009;**147**:291-7.

45 Ristau T, Voegler J, Lang J. Relevance of inner versus outer retinal thickness in diabetic macular efema in the RELATION study. *Invest Ophthalmol Vis Sci* 2013;**54**:2376.

46 Callanan DG, Gupta S, Boyer DS, Ciulla TA, Singer MA, Kuppermann BD et al. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology* 2013;**120**:1843-51.

47 Stein JD, Newman-Casey PA, Kim DD, Nwanyanwu KH, Johnson MW, Hutton DW. Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema. *Ophthalmology* 2013;**120**:1835-42.

48 Smiddy WE. Clinical applications of cost analysis of diabetic macular edema treatments. *Ophthalmology* 2012;**119**:2558-62.

49 Dewan V, Lambert D, Edler J, Kymes S, Apte RS. Cost-effectiveness analysis of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2012;**119**:1679-84.

50 Mitchell P, Annemans L, Gallagher M, Hasan R, Thomas S, Gairy K et al. Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial. *Br J Ophthalmol* 2012;**96**:688-93.

51 Smiddy WE. Economic considerations of macular edema therapies. *Ophthalmology* 2011;**118**:1827-33.

52 Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis. *Curr Opin Ophthalmol* 2000;**11**:175-9.

53 Haig J, Lawrence D, Barbeau M, Blouin J. Economic evaluation of tanizumab for the treatment of diabetic macular edema in Canada. *Value in Health* 2011;**14**:A96-A97.

54 Haig J, Barbeau M, Ferreira A, Pickering M. Quebec economic evaluation for 36 months of ranizumab in the treatment of diabetic macular edema. *Value in Health* 2013;**16**:A507.

55 Brennig C, Schollbauer V, Walter E, Gallagher M, Knudsen MS. Economic ebvaluation of ranizumab in the treatment of visual impairment dur to diabetic macular edema in Austria. *Value in Health* 2011;14:A478.

56 Haig J, Regnier S, Malcolm W, Weigunag W. Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular oedema: analysis from a UK healthcare perspective. *ISPOR 17th Annual European Congress, 8-12 November 2014, Amsterdam, Netherlands* 2014. PSS34.

57 Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. *Value in Health* 2009;**12**:793-9.

58 Preis SR, Hwang S-J, Coady S, Pencina MJ, D'Agostino RB, Savage PJ et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the framingham heart study, 1950 to 2005. *Circulation***119**:07.

59 Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: Structural equation modeling. *Invest Ophthalmol Vis Sci* 2008;**49**:3318-23.

60 Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. *Am J Ophthalmol* 1999;**128**:204-9.

61 Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;118:47-51.

62 Schmidt-Erfuth U. Efficacy and Safety of Intravitreal aflibercept in DME: Results of two phase III studies (VIVID-DME and VISTA-DME) . *13th EURETINA Congress, Hamburg, Germany, September 2013* 2014.

63 McCrone P, Dhanasiri S, Patel A, Knapp M. *Paying the price; the cost of mental illness in England to 2026.* London: King's Fund; 2008.

64 Meads C, Hyde C. What is the cost of blindness?. *Br J Ophthalmol* 2003;**87**:1201-4.

65 Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA. Mortality in people with Type 2 diabetes in the UK. *Diabet Med* 2006;**23**:65-8.

66 Hirai FE, Moss SE, Klein BEK, Klein R. Relationship of glycemic control, exogenous insulin, and C-peptide levels to ischemic heart disease mortality over a 16-year period in people with older-onset diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). *Diabetes Care* 2008;**31**:114-8.

67 Soheilian M, Ramezani A, Bijanzadeh B, Yaseri M, Ahmadieh H, Dehghan MH et al. Intravitreal bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina* 2007;**27**:1187-95.

68 Soheilian M, Ramezani A, Obudi A, Bijanzadeh B, Salehipour M, Yaseri M et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology* 2009;**116**:1142-50.

69 Soheilian M, Garfami KH, Ramezani A, Yaseri M, Peyman GA. Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. *Retina* 2012;32:314-21.

70 Faghihi H, Esfahani M, Hirandi Z, Madani S. Intravitreal Bevacizumab vs. Combination of Intravitreal Bevacizumab plus Macular Photocoagulation in Clinically Significant Diabetic Macular Edema: 6 months Results of a Randomized Clinical Trial. *Iranian J Ophthalmol* 2010;22:21-6.

71 Cho WB, Oh SB, Moon JW, Kim HC. Panretinal photocoagulation combined with intravitreal bevacizumab in high-risk proliferative diabetic retinopathy. *Retina* 2009;**29**:516-22.

72 Cho WB, Moon JW, Kim HC. Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy. *Br J Ophthalmol* 2010;**94**:858-63.

73 Solaiman KA, Diab MM, Abo-Elenin M. Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. *Retina* 2010;**30**:1638-45.

74 Zhao Q-L, Zhang C-X. Intravitreal injection of Bevacizumab combined retinal photocoagulation for diabetic macular edema. *Int Eye Sci* 2013;**13**:1651-3.

75 Michaelides M, Fraser-Bell S, Hamilton R, Kaines A, Egan C, Bunce C et al. Macular perfusion determined by fundus fluorescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (Bolt Study): Report 1. *Retina* 2010;**30**:781-6.

76 Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology* 2010;**117**:1078-86.

77 Fraser-Bell S, Rajendram R, Kaines A, Michaelides M, Hamilton RD, Peto T et al. Intravitreal bevacizumab is superior to laser for diabetic macular oedema. Two-year results from the bolt study. *Clin Exp Ophthalmol* 2011;**39**:26.

78 Rajendram R, Fraser-Bell S, Kaines A, Michaelides M, Hamilton RD, Esposti SD et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol* 2012;**130**:972-9.

79 Sivaprasad S, Crosby-Nwaobi R, Heng LZ, Peto T, Michaelides M, Hykin P. Injection frequency and response to bevacizumab monotherapy for diabetic macular oedema (BOLT Report 5). *Br J Ophthalmol* 2013;**97**:1177-80.

80 Sivaprasad S, Crosby-Nwaobi R, Esposti SD, Peto T, Rajendram R, Michaelides M et al. Structural and functional measures of efficacy in response to bevacizumab monotherapy in diabetic macular oedema: exploratory analyses of the BOLT study (report 4). *PLoS ONE [Electronic Resource]* 2013;**8**:e72755.

9 APPENDICES

Appendix 1 Published studies involving bevacizumab and laser photocoagulation therapy for DMO

Study	Population	Intervention(s)	Study design
DRCR.net 2007[35]	Patients with type 1 or type 2 diabetes and DMO	bevacizumab vs bevacizumab + laser vs bevacizumab + sham injection vs laser	RCT (Phase 2)
Soheilian 2007[67]	Patients meeting ETDRS criteria for CSMO	bevacizumab vs bevacizumab + triamcinolone vs laser	RCT
Soheilian 2009[68] Soheilian 2011[39] Soheilian 2012[69]	Patients meeting ETDRS criteria for CSMO	bevacizumab vs bevacizumab + triamcinolone vs laser	RCT
Faghihi 2008[70]	Patients with type 2 diabetes with DMO	bevacizumab vs bevacizumab + triamcinolone vs laser	RCT
Cho 2009[71]	Patients with high risk PDR with CSMO	bevacizumab + laser vs laser	RCT
Cho 2010[72]	Patients with very severe NPDR and CSMO	bevacizumab + laser vs triamcinolone + laser vs laser	Non-randomised comparative
Solaiman 2010[73]	Patients with diffuse DMO	bevacizumab vs bevacizumab + laser vs laser	RCT
Mansourian 2011[33]	Patients with DMO	bevacizumab vs bevacizumab + triamcinolone vs laser	NR
Zhang 2013[34]	People with DMO	bevacizumab + triamcinolone vs	RCT

		triamcinolone vs laser	
Zhao 2013[74]	Patients with diffuse DMO	bevacizumab + laser vs bevacizumab	RCT
BOLT study Michaelides 2010[75] Michaelides 2010a[76] Fraser-Bell 2011[77] Rajendram 2012[78] Sivaprasad 2013[79] Sivaprasad 2013a[80]	Patients with centre-involving CSMO and at least 1 prior laser treatment	bevacizumab vs laser	RCT

CSMO: clinically significant macular oedema; DMO: diabetic macular oedema; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy