NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Abbreviated premeeting briefing

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

This abbreviated premeeting briefing highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

1 Technology

Technology	Aflibercept solution for injection (Eylea, Bayer)
Class of drug	Soluble vascular endothelial growth factor (VEGF) receptor fusion protein
Administration method	Intravitreal injection
List price	40 mg in 0.1 mL vial, £816.00 (BNF)
Patient access scheme (PAS)	A PAS has been available to the NHS since the CRVO indication was appraised; providing a discounted price of £[redacted] per vial.
Annual cost of treatment (including PAS)	0-24 weeks: 2mg aflibercept every 4 weeks (7 doses) = [redacted] 24-48 weeks: 2mg afilbercept every 8 weeks (3 doses) = [redacted] Total annual cost incorporating PAS = [redacted]
Marketing authorisation	Marketing authorisation in the UK received on 25th February 2015, for treating 'visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)'. This is a licence extension to the existing CRVO marketing authorisation in CVRO (August 2013). The CRVO indication has been appraised and is recommended by NICE – see TA305
SmPC	Link to report

EPAR	Link to report
Abbreviations: BNF, British National Formulary; BVRO, branch retinal vein occlusion; CVRO, central retinal vein occlusion; EPAR, European public assessment report; mg, milligram; mL, millilitre ; PAS, patient access scheme; RVO, retinal vein occlusion; SMPC, summary of product characteristics; TA, technology appraisal	

2 Relevant appraisals

NICE has recommended aflibercept in the indication for macular oedema secondary to CRVO (TA305, August 2013) and ranibizumab for macular oedema secondary to BRVO (TA283, May 2013).

TA283 Ranibizumab	TA305 Aflibercept
Indicated for macular oedema secondary to RVO	Indicated for Macular oedema secondary to CRVO
Recommended: • following CRVO • following BRVO only if treatment with laser photocoagulation has not been beneficial or suitable	Recommended for CRVO
Key committee considerations	
Economic model The Committee also considered the manufacturer's revisions to its economic model submitted in response to consultation and broadly accepted the manufacturer's approach to: • reflecting that most patients would be treated in their 'worse-seeing eye' • the use of utilities as applied using the Czoski-Murray equation • applying unpooled transition probabilities although there was a lack of clear data • the inclusion of updated adverse event rates in year 2, albeit cautiously.	**Current treatment** Current standard treatment for macular oedema secondary to central retinal vein occlusion is dexamethasone or antivascular endothelial growth factor (anti-VEGF) drugs, such as ranibizumab. However, clinicians are more likely to use ranibizumab than dexamethasone because it is believed to have fewer side effects.
Clinical effectiveness The Committee accepted that the relative effectiveness of ranibizumab and dexamethasone was uncertain and concluded that it was difficult to quantify any bias.	**Adverse events** The Committee agreed that the evidence suggested the overall frequency of adverse events in the trials was low with aflibercept solution for injection and concluded that aflibercept had a similar adverse event profile to ranibizumab.

Utilities The Committee concluded that although uncertain, the use of utilities as applied using the Czoski-Murray equation was acceptable.	**Clinical effectiveness** The Committee noted that aflibercept was associated with statistically significantly more eyes gaining 15 or more letters at 24 weeks compared with sham injection. The Committee concluded that aflibercept is a clinically effective treatment option for visual impairment caused by macular oedema secondary to central retinal vein occlusion.
WSE utility The ERG exploratory analyses highlighted that the key drivers that increased the manufacturer's base-case ICERs were amending the proportion of patients treated in their 'better-seeing eye' (10% instead of 100%) and the assumption of some benefit associated with treating the 'worse-seeing eye'. The Committee considered that a 0.3 utility gain associated with treating the 'worse-seeing eye' seems high given that utility is driven primarily by the 'better-seeing eye', and therefore lacked face validity.	**Model uncertainty** The Committee considered the following uncertainties in the model: • the assumption that the benefits of treatment at 24 weeks would continue indefinitely • not including the relative risk of losing 15 or more letters • the assumption that the duration of aflibercept treatment was 1 year • the use of EQ-5D data as a source of utility values • not including the cost of adverse events • not including a stopping rule • overestimated administration costs for aflibercept and ranibizumab • underestimated costs of blindness. The Committee concluded that these uncertainties were unlikely to change the dominance of aflibercept over ranibizumab.
Plausible ICER Ranibizumab was associated with an ICER of £26,200 per QALY gained compared with best supportive care in CRVO. The Committee concluded that the most plausible ICER for ranibizumab compared with standard care in treating BRVO was in excess of £44,800 per QALY gained.	**Utilities** The Committee heard from the ERG that using utility values from Czoski-Murray or Brown did not substantially affect the cost-effectiveness estimates of aflibercept compared with ranibizumab.
	Cost effectiveness The Committee noted that the manufacturer's base-case analysis showed that aflibercept dominated ranibizumab (that is, it was more effective and less costly), resulting in more QALYs and lower costs. It also noted that aflibercept continued to dominate ranibizumab despite the changes made by

	the ERG.
	Plausible ICER The Committee noted that the ERG's exploratory analysis, which included the confidential discount applied to the list price for aflibercept, resulted in an incremental cost-effectiveness ratio (ICER) of £12,300 per QALY gained for aflibercept compared with dexamethasone. The Committee also noted that even using the Brown utilities for the 'better-seeing eye', that is to say, the 'worst case scenario', the ICER was below the top end of the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained).

3 Decision problem

Table 1 PICO table from the NICE scope (including indication of adherence/deviations in company submission)

		✓ / ✗
Intervention(s)	Aflibercept solution for injection	✓
Population(s)	Adults with visual impairment caused by macular oedema secondary to branch retinal vein occlusion	✓
Comparators	• Laser photocoagulation • Bevacizumab (not licensed in the UK for this indication) For people for whom laser photocoagulation has not been beneficial or is not suitable: • Ranibizumab • Dexamethasone intravitreal implant • Bevacizumab (not licensed in the UK for this indication)	✓ ✗ ✓ ✓ ✗
Outcomes	• visual acuity (the affected eye) • visual acuity (the whole person) • adverse effects of treatment • health-related quality of life • mortality	✓ ✓ ✓ ✓ ✓

Source: NICE Final Scope

4 Summary of clinical results

The clinical evidence presented by the company comes from 1 phase III, randomised control trial (VIBRANT [n=183]). People were included in the trial if they had BRVO or hemi-retinal vein occlusion (HRVO; a variant of BRVO) causing oedema involving the centre of the macula if the occlusion occurred within 12 months. A further inclusion criteria was that people had a BCVA of 73 to 24 letters Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40 - 20/320 Snellen equivalent).

People in the aflibercept group received aflibercept every 4 weeks until week 24 and every 8 every 8 weeks from week 24 to 48. These people could also receive grid laser photocoagulation (GLP) from week 36. People in the GLP comparator treatment group group received sham injections every 4 weeks and if necessary could receive GLP at weeks weeks 12, 16 and 20. Sham injections were then given from weeks 24 to 52. The primary primary outcome was the proportion of patients gaining at least 15 letters ETDRS at week 24 week 24 from baseline. Results to week 24 and also to week 52 have been published. At published. At week 24 more people in the aflibercept group (52.7%) had gained at least 15 least 15 letters compared with the laser group (26.7%). A summary of the trial results is is presented in

Table 2. Further details on the trial can be found in the company's submission (section 4.3).

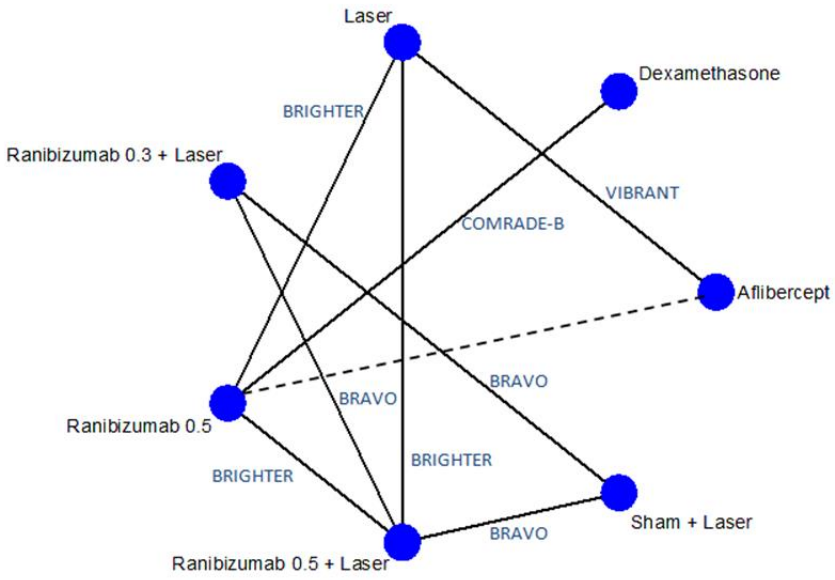
Table 2 Clinical results

	Week 24		**Week 52**	
	Aflibercept (n=91)	Laser (n=90)	Aflibercept (n=91)	Laser (n=90)
Gaining ≥15 letters in BVCA				
Event, n (%)	48 (52.7)	24 (26.7)	52 (57.1)	37 (41.1)
Difference	26.1%		16.0	
Adjusted difference (95% CI)	26.6 (13.0, 40.1)		16.2 (2.0, 30.5)	
p-value	0.0003		0.0296 (nominal)	
Change in BCVA (ETDRS letter score)				
Mean change from baseline (± SD)	17.0 (± 11.88)	6.9 (± 12.91)	17.1 (±13.07)	12.2 (±11.94)
LS mean change in BCVA	13.7	3.2	12.4	7.1
Difference in LS mean vs. Laser [+aflibercept] (95% CI) c	10.5 (7.1, 14.0)		5.2 (1.7 to 8.7)	
p-value c	<0.0001		<0.005	
Received rescue treatment				
N(%) 24 weeks and 36 weeks			9 (10)	67 (74)
Abbreviations: BCVA, best corrected visual acuity; N, number; CI, confidence intervals; SD, standard deviation				

Source: Company submission, tables 20, 22 and 25

Direct efficacy evidence from the trial was limited to a comparison of aflibercept and laser photocoagulation. To explore the efficacy of aflibercept compared with ranibizumab or dexamethasone, the company presented results from a network meta-analysis (NMA). The company did a literature review which identified 9 eligible studies, however, 5 studies were excluded from the NMA due to clinical heterogeneity. Figure 1 shows the network diagram and Table 3 shows the results from the NMA. Further discussion on the NMA can be found in section 4.9 of the company's submission.

Figure 1 Network diagram



Source: Company submission, figure 18

The company states that the results favour aflibercept with median and mean odds ratios (OR) less than 1 when compared with dexamethasone. When comparing aflibercept with ranibizumab the median OR is less than 1, favouring aflibercept, but the mean OR is greater than 1 favouring ranibizumab. The credible intervals were wide and crossed 1.

Table 3 Network meta-analysis results from a fixed effect model

	Mean OR (CrI)	Median OR (CrI)
Gaining ≥15 letters in BVCA		
Ranibizumab vs. Aflibercept	1.04 (0.38, 2.31)	0.93 (0.38, 2.31)
Dexamethasone vs. Aflibercept	0.39 (0.12, 0.96)	0.34 (0.12, 0.96)
Change in BCVA (ETDRS letter score)		
Ranibizumab vs. Aflibercept	-2.68 (-7.43, 2.05)	-2.68 (-7.43, 2.05)
Dexamethasone vs. Aflibercept	-10.59 (-16.08, -5.10)	-10.59 (-16.08, -5.10)

Abbreviations: BCVA, best corrected visual acuity; ETDRS, Early treatment diabetic retinopathy study; CrI, credible interval; OR, odds ratio

Source: Company submission, figure 25, 26, 29, 30

The ERG acknowledged that the VIBRANT trial was a phase III randomised, double masked trial, however, it considered that there were some subgroups missing from the analysis, specifically macular/foveal perfusion. The ERG considered that the company's approach in conducting the systematic review and the NMA was appropriate. The ERG did express some concern in the transparency of the assumptions applied by the company. Notably, the ERG did not agree with the company's decision to exclude five studies from the NMA.

5 Summary of economic model

The company presented a de novo model to assess the cost-effectiveness of aflibercept in people with visual impairment caused by macular oedema secondary to BVRO. The baseline age was 65, and 6.05% of the population had bilateral BRVO. BCVA in the fellow eye was assumed to vary independently of the study eye;

a 5 year incidence rate of 12.3% of fellow eyes, with a 50% treatment rate for BRVO was assumed. Background mortality risk (taken from Office for National Statistics life tables), as well as the mortality risk associated with loss of vision (mortality multiplier of 1.23 for those in health state 5 [blindness in one or both eyes]) was incorporated in the model .25 health states, based on visual acuity (VA), were included in the model in addition to the state of death. Utilities were drawn from the Czoski-Murray study, and it was assumed that any change in the BCVA of the worst seeing eye (WSE) has a 30% of the quality of life impact of the same change in the best seeing eye (BSE).

Transition probability matrices (TPMs) were obtained from VIBRANT for aflibercept and from the NMA for ranibizumab and dexamethasone. Different transition probabilities were calculated for three distinct phases in the model (the efficacy, maintenance and rest of life phases, see below for further detail and discussion). Discontinuation rates for aflibercept and laser were taken from VIBRANT whilst the discontinuation rates for ranibizumab and dexamethasone were assumed to be equivalent to aflibercept in the absence of this data from the NMA.

In the economic model the company based the dosing on the mean number of treatments in the VIBRANT study in the efficacy phase, and on clinical expert opinion during the maintenance phase. Dosing for rescue ranibizumab was assumed to be the same as for rescue aflibercept, and dosing for 2nd line rescue dexamethasone is based upon the SmPC and expert opinion. From year 6 patients are in the 'rest of life' phase and an assumption that patients will no longer be receiving treatment.

Because the marketing authorisation for aflibercept permits its use at various points in the treatment pathway, including as an alternative to laser photocoagulation, the model structure and the results reflect the possibility of laser being used either before or after aflibercept. The submission provides two types of comparisons; one which seeks to address whether aflibercept, ranibizumab or dexamethasone is most cost effective following the failure of laser treatment and second, whether it is most cost effective to give aflibercept before or after laser therapy.

Further details on the model structure are available in the company submission, section 5.2.2.

6 Cost effectiveness

The company presented incremental cost effectiveness results incorporating the existing PAS for aflibercept, however a simple discount confidential PAS also exists for the comparator ranibizumab and this is not incorporated into the company's base case results. The ERG has provided a confidential appendix which provides ICERS when both schemes are taken into account (see below).

The ERG ran exploratory analysis, first correcting the model for a number of factors (full details of model corrections can be found in the ERG report Section 5.4) and then running a range of sensitivity analyses. The sensitivity analysis included the following:

- SA01: Applying the R MSM derived TPMs for the comparison of aflibercept-laser with laser-aflibercept
- SA02: Applying the NMA (derived from 8 studies) median ORs of gaining at least 15 letters of 1.08 for ranibizumab and 0.40 for dexamethasone
- SA03: Revising the quality of life percentage for the WSE to be 15%
- SA04: Revising the quality of life percentage for the WSE to be 43%
- SA05: Revising the quality of life function to have a coefficient of -0.292
- SA06: Revising the quality of life to be the VIBRANT EQ-5D OLS linear model
- SA07: Revising the quality of life to be the VIBRANT EQ-5D random effects linear model
- SA08: Altering anti-VEGF dosing for years 6+ lasting 0, 5 and 10 years, as previously outlined
- SA09: Altering anti-VEGF dosing for years 6+ of an annual 2.0 doses, as previously outlined
- SA10: Altering ranibizumab to have one less administration than aflibercept during year 1, as previously outlined

A comprehensive list of the revisions can be found in section 5.4 of the ERG report.

Incremental cost effectiveness results from the company's base case (including all relevant PAS discounts) and the ERG's revisions and sensitivity analysis can be found in Table 4. Sentitivity results comparing aflibercept-laser compared with laser aflibercept and laser-aflibercept compared with laser-ranibizumab can be found in Table 5 and Table 6 respectively.

Table 4 incremental Cost effectiveness results

Company's base case incremental cost effectiveness					
	Cost	**QALYs**	**Inc. cost**	**Inc. QALYs**	**ICER**
Laser-dexamethasone	[redacted]	[redacted]			
Laser-aflibercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laser- ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept-laser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG's derived central probabilistic cost effectiveness estimates					
	Cost	**QALYs**	**Inc. cost**	**Inc. QALYs**	**ICER**
Laser-dexamethasone	[redacted]	[redacted]			
Laser-aflibercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laser- ranibizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aflibercept-laser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5 Cost effectiveness results of aflibercept in the 1st line

ERG sensitivity analyses: aflibercept-laser compared with laser-aflibercept			
	Inc. cost	**Inc. QALYs**	**ICER**
Base case	[redacted]	[redacted]	£27,259
SA01: R MSM TPMs	[redacted]	[redacted]	£23,847
SA02: 8 study NMA	[redacted]	[redacted]	n.a.
SA03: 15% WSE QoL	[redacted]	[redacted]	£31,581
SA04: 43% WSE QoL	[redacted]	[redacted]	£24,891
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£34,656
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£47,850
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£70,394

SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	£16,801
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	£31,624
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	£23,337
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	n.a.

Table 6 Cost effectiveness results of aflibercept in the 2nd line

ERG sensitivity analyses: laser-2nd line rescue compared with laser-ranibizumab			
	Inc. cost	**Inc. QALYs**	**ICER**
Base case	[redacted]	[redacted]	[redacted]
SA01: R MSM TPMs	[redacted]	[redacted]	[redacted]
SA02: 8 study NMA	[redacted]	[redacted]	[redacted]
SA03: 15% WSE QoL	[redacted]	[redacted]	[redacted]
SA04: 43% WSE QoL	[redacted]	[redacted]	[redacted]
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	[redacted]
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	[redacted]
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	[redacted]
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	[redacted]
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	[redacted]
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	[redacted]
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	[redacted]
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	[redacted]

7 Key issues for consideration

Decision problem

1. Including bevacizumab as a comparator

Clinical effectiveness

2. The clinical pathway

3. Network meta-analysis
4. Last observation carried forward
5. Aflibercept dosing in VIBRANT

Cost effectiveness

6. Model structure
7. Transition probabilities
8. Dosages
9. Preferred quality of life source
10. Quality of life impact on BSE

Other considerations

11. Innovation

Decision problem

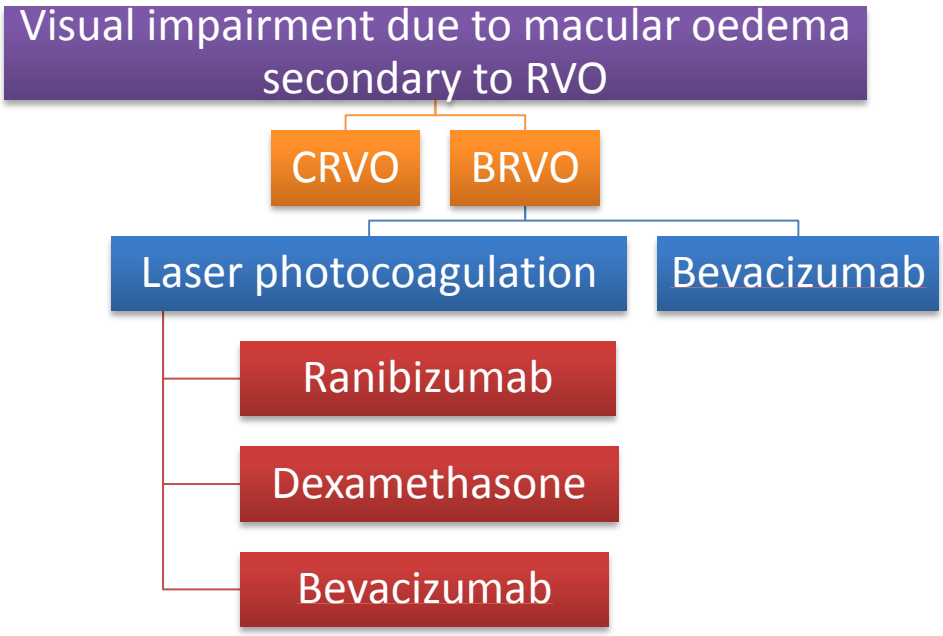
1. Bevacizumab was specified as a relevant comparator in the final scope issued by NICE. However, the company did not consider it a relevant comparator and have not included it in the submission and economic evaluation (company's submission, section 1.1). The company state that since the introduction of several licenced alternative treatments, bevacizumab, an unlicensed treatment in ophthalmology in the UK, is no longer considered best or routine practice. The company further commented that in TA283, bevacizumab was listed in the scope but was not used as a comparator in the cost-effectiveness analysis. This decision was accepted by the committee.
    - Does the committee consider bevacizumab to be a relevant comparator in the treatment of macular oedema secondary to BVRO?

Clinical effectiveness

2. Current NICE guidelines recommend laser photocoagulation as the first-line treatment in BVRO with ranibizumab (TA283) or dexamethasone (TA229) as second line treatment options. However, evidence submitted by the company suggests that clinical practice is changing and that there is a greater use of ranibizumab in the first line. The company commented that this alternative

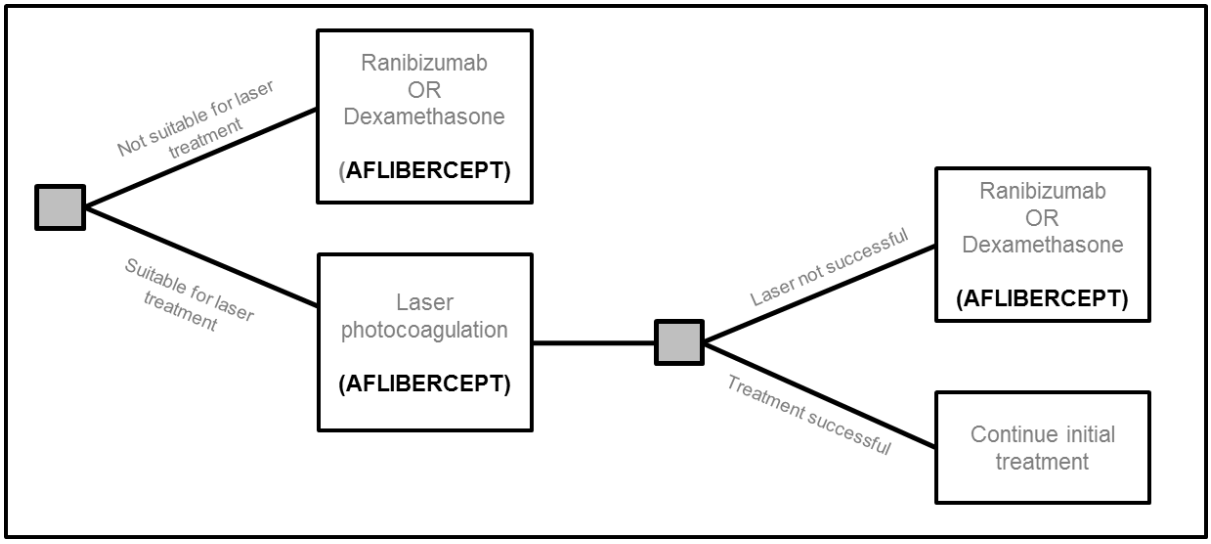
pathway is supported by recent guidance from the Royal College of Ophthalmology (company submission, Section 3.3.3). This view is supported in the submission from clinical experts.

Figure 2 Treatment pathway



The company has placed the proposed use of aflibercept in the first and second line (Figure 3) and commented that clinical practice is changing (company submission, Section 3.3.4). The ERG agrees that the clinical management of BVRO is changing and acknowledges the guidance produced by the Royal College of Ophthalmologists. It further notes that the treatment pathway does not include a periods of observation highlighted by the Royal College.

Figure 3 Company's proposed treatment pathway



Source: Company's submission, figure 3

- What is the appropriate position in the treatment pathway for aflibercept for treating macular oedema secondary to BVRO given current practice and the existing NICE pathway?
- Does the committee consider the health benefit of aflibercept as a first line treatment to be similar to those observed in aflibercept as a second line treatment?

3. The relative clinical effectiveness of aflibercept compared with ranibizumab and dexamethasone is estimated from the results of the NMA. The company commented that they identified 9 eligible studies in their systematic review, however 5 studies were excluded from inclusion in the NMA due to clinical heterogeneity between these studies and the VIBRANT trial (company's submission, table 30 and section 4.10.3).

   The ERG agreed with the company that there was clinical heterogeneity between the excluded studies and the VIBRANT trial, however, it noted that the studies met the inclusion criteria specified in the NICE's final scope could have been included in the primary analyses, or used in the economic model.

   In the NMA the company has presented both mean and median ORs of gaining ≥ 15 letters from fixed and random effect model (company submission, section 4.10.7). However, the company used the median results from the fixed effect

model in the economic model presented (median OR: 0.93 [credible intervals: 0.38, 2.31]). The ERG has commented that they believe that these decisions in isolation are reasonable and justified, but they have resulted in a point estimate favouring aflibercept (ERG report, section 4.4). The ERG noted that if different assumptions were made a point estimate favouring ranibizumab is obtained (mean OR: 1.04 [credible intervals: 0.38, 2.31]).

The ERG did sensitivity analyses that included 8 studies in the NMA. It found that there was a small decrease in the incremental costs, resulting in laser-aflibercept dominating laser-ranibizumab (ERG confidential appendix, table 6).

- What is the committee's view on the exclusion of the 5 studies due to clinical heterogeneity?

- Does the committee consider afilbercept has a greater clinical effectiveness when compared with ranibizumab?

4. The company reported that drop-out rates for the aflibercept-laser arm were 20% in year 1 and for the laser–aflibercept arm 16% for year one. The company used the last observation carried forward (LOCF) approach to impute missing data of those that dropped out of the VIBRANT trial. The ERG noted that the drop-out rates were quite high and that this may be a cause for concern when measuring relative treatment effects. It commented that any tendency for drop-outs to rebound to baseline might worsen the clinical and cost effectiveness estimates for aflibercept-laser compared to laser-aflibercept. The ERG commented on the potential to explore rebound assumptions in sensitivity analyses, however, this is not explored further, and its potential impact on the uncertainty is unclear.

    - What is the committees view on the use of the LOCF approach to impute values for patients who have dropped out of the trial?

5. In the VIBRANT trial the dosing for 1st line aflibercept in the aflibercept-laser arm was more frequent and of longer duration than for 2nd line rescue aflibercept in the laser-aflibercept arm. The ERG noted that the full clinical benefits of rescue aflibercept may not have been realised in the laser-aflibercept arm and may have

lowered the clinical effectiveness estimates in the laser-aflibercept arm to below what might be observed in clinical practice. The ERG did not explore this further and it its potential impact on the uncertainty is unclear.

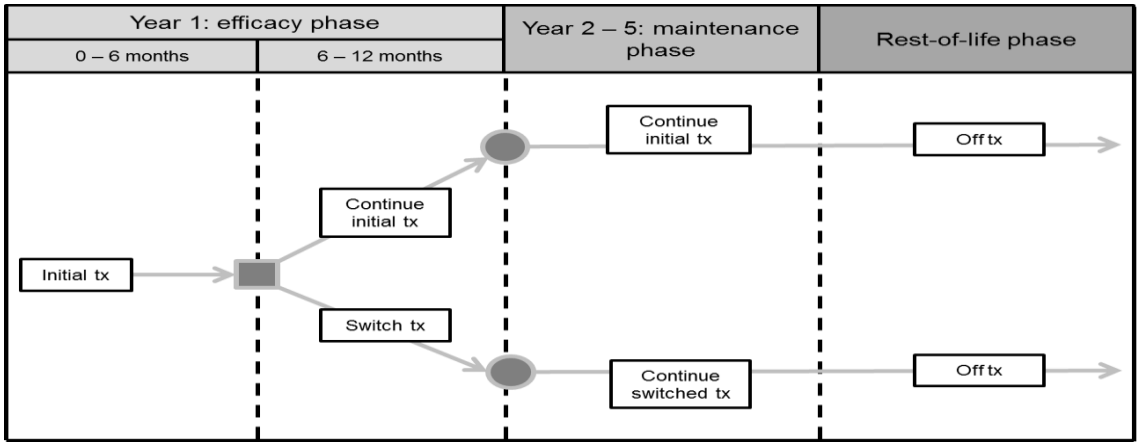
- What is the committees view of the relative dosing of aflibercept in the first and second line?

Cost effectiveness

6. The company presented a de novo Markov model to assess the cost-effectiveness of aflibercept in people with macular oedema secondary to BVRO. The model comprised of 3 phases efficacy phase (0 – 12 months), maintenance phase (year 2 – 5), rest-of-life phase (year 6+). The model has some similarities to other eye models considered by NICE (TA305, TA283), but, the 3 phase aspect of the model differs from previous models as each phase is modelled separately. Figure 4 provides a diagram of the model phases and Table 7 provides some detail on the model structure and assumptions. Further detail on the model structure can be found in the company's submission (section 5.2.2)

- Does the model accurately reflect the clinical pathway of those with macular oedema secondary to BVRO? Is the model structure generalisable to the treatment pathway of those with macular oedema secondary to BVRO?

Figure 4 Model phases



Source: Company's submission, figure 42

Table 7 Model characteristics

Efficacy phase	Maintenance phase	Rest of life phase
- Health states are defined by the visual acuity in both the study eye and the fellow eye - A total of 26 health states in this phase - Starting distribution estimated from the full sample of the VIBRANT study - Patients may transition to improved state, remain stable, or decrease health state (measure by 15 letter BCVA change) - Transition probability matrices (TPM) for afilbercept-laser and laser aflibercept estimated from pooled 4-weekly data from VIBRANT - TPM for laser-dexamethasone, laser-ranibizumab derived by applying the NMA odds ratios of gaining 15 letters - Only phase where visual acuity improves - 4 week cycle length - Patient who fail treatment in the first-line can switch to receive a rescue treatment after 6 months - Rates of rescue treatments applied equally across all arms and all health states - Discontinuation rates taken from VIBRANT trial - Each monitoring visit includes and eye test and optical coherence test - Only 50% of fellow eyes affected by BVRO will receive treatment - Dosing and administrations based about mean number of treatments in the VIBRATN study during the 1st year. - Dosing for rescue ranibizumab is assumed to be the same as for rescue aflibercept , and dosing for rescue dexamethasone based on SmPC - Monitoring base upon SmPC and expert opinion	- Assumed that this phase lasts 4 years - Benefit accrued at the end of the efficacy phase is maintained throughout the phase if on treatment - Those off treatment, it is possible for their health state to decrease - There is a decreasing mean number of injections required to maintain vision - Each monitoring visit includes and eye test and optical coherence test - Visual stability is assumed through this period - Dosing based upon expert opinion - Discontinuation rates from year 1 are still applied	- Patient's vision declines steadily throughout the remainder of their life - Assumed slow visual decline of 2% of eyes losing 15 letters annually

7. In the company base case, the transition probability matrices (TPMs) are calculated directly from the VIBRANT trial using the MSM package in R. However, the company also presented an alternative approach of applying the VIBRANT 4-weekly patient distributions (calculated in 'shift-tables') (further details are available in the company submission, section 5.3.2.3).

   The ERG commented that the MSM derived TPMs are not aligned with the shift-tables approach. The ERG favours the use of the shift-tables for the base case and the MSM approach as sensitivity analysis.

   The ERG revised the model by applying the shift-tables for the comparison of aflibercept-laser with laser-aflibercept and then used the MSM approach in the sensitivity analysis. The results of the sensitivity analysis demonstrate that the use of the MSM approach increases cost effectiveness, reducing the ICER from £27,259 to £23,847 per QALY gained.

   - What is the committee's preferred approach to calculating the TPM for the comparison of aflibercept-laser with laser-aflibercept.

8. The ERG commented on several concerns regarding the dosing assumed in the model. The ERG noted that they were unsure whether aflibercept and ranibizumab have similar dosing requirements, and noted that the company do not report the results of its expert survey for dosing and monitoring for year 6 and beyond. It highlights that the RETAIN trial suggested that there is a requirement for ongoing anti-VEGF dosing, among as many as half the patient population. The ERG also commented that the company's model does not adjust the dosing for cross-over to rescue therapy or for discontinuation.

   The ERG's exploratory analysis makes revisions to the company's model to explore the uncertainty in the dosing. This includes revised dosing to take into account discontinuation and cross-over; and adjusts the dosing levels for year 6 and beyond (sensitivity analysis: SA08 and SA09). The ERG's analysis shows that [redacted] (ERG confidential appendix, table 6). When comparing aflibercept-laser with laser-aflibercept, no anti-VEGF treatment from 6

years increases the cost-effectiveness of aflibercept-laser (£16,901 per QALY gained), and if anti-VEGF treatment was given for 10 years it decreases the cost effectiveness (£31,624 per QALY gained).

- What is the committees view on the dosing requirements aflibercept, ranibizumab and dexamethasone in the treatment of macular oedema secondary to BVRO?

9. The company presented quality of life data drawn from the Czoski-Murray and stated that it has been accepted by appraisal committees as a valid source of quality of life data in previous visual impairment appraisals (TA305). The company further referenced a NICE decision support unit report that states that EQ-5D is likely to be inappropriate for some visual impairment studies. However, the ERG commented that findings from a NIHR report suggest that EQ-5D data could be used in visual impairment appraisals and that it can often be more responsive to the effect of an intervention.

- What is the committee's preferred source of quality of life data?

10. Previous NICE technology appraisals of eye disease have accepted that a change in the BCVA of the WSE has 30% quality of life impact of the same change in the BCVA of the BSE (TA274). However, the ERG commented that it is likely that this was a practical decision based on the evidence available and it questioned whether this assumption still holds. The ERG did sensitivity analysis to account for this (SA03 and SA04) by revising the quality of life percentage for the WSE to 15% and 43%. The results demonstrated that [redacted] (ERG confidential appendix, table 6). When comparing aflibercept-laser with laser-aflibercept an increase to 43% increases the cost-effectiveness of aflibercept-laser (£12,891 per QALY gained), and if decreased to 15% it decreases the cost effectiveness (£31,581 per QALY gained).

- What proportional impact on the quality of life in the BSA does a change in BCVA have on the WSE?

Other considerations

11. The company considered afilbercept to be innovative in the management of macular oedema secondary to BVRO (company submission, section 2.5). The reasons given by the company include aflibercept having higher binding affinity for VEGF-A compared to ranibizumab, which may result in a longer duration of disease control; and, aflibercept addressing a wider range of growth factors. The company that both these factors may lead to patients being seen less often.

- Does the committee consider aflibercept to be an innovative therapy?

8 Equality issues

No equality issues were raised during the scoping process. The company stated in its submission that it had not identified any equality issues related to treatment with trametinib in combination with dabrafenib.

9 Authors

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of aflibercept within its marketing authorisation for treating visual impairment caused by macular oedema secondary to branch retinal vein occlusion.

Background

The macula is the central part of the retina responsible for colour vision and perception of fine detail. Macular oedema is the accumulation of fluid within the retina at the macular area, which can lead to severe visual impairment in the affected eye.

Retinal vein occlusion (RVO) is a common cause of reduced vision. It is classified into central retinal vein occlusion and branch retinal vein occlusion (BRVO). BRVO is caused by a blood clot in the small veins in the retina. Blockages in the retinal veins increase the pressure in the retinal capillaries, which can lead to blood and plasma leaking into the macula. These changes trigger vascular endothelial growth factor (VEGF) to be released, which increases the permeability of the blood vessels and causes new vessels to grow.

The impact of vision loss associated with RVO can have a profound effect on vision-related quality of life. Patients may struggle with daily tasks, lose confidence, and become increasingly dependent on family and carers. RVO is also associated with an increase in the risk of vascular causes of death.

RVO affects 1–2% of people aged over 40 years and macular oedema is the most frequent cause of vision loss in people with RVO. It is estimated that in England around 12,900 people with BRVO and macular oedema have visual impairment. The risk of RVO typically increases with age and there is an equal distribution amongst men and women.

Current treatment options for BRVO aim to improve vision and prevent complications. Where visual loss is not severe and macular oedema is minimal there can be potential for spontaneous resolution and clinical observation is considered, otherwise a grid pattern of laser photocoagulation may be beneficial. Dexamethasone intravitreal implant and ranibizumab are recommended in NICE technology appraisal guidance 229 and 283 respectively only if laser photocoagulation has not been beneficial or is not suitable because of the extent of the macular haemorrhage. Intravitreal

injections of bevacizumab, which does not have a marketing authorisation in the UK for treating any ocular condition, may also be used.

The technology

Aflibercept solution for injection (Eylea, Bayer) is a soluble vascular endothelial growth factor (VEGF) receptor fusion protein which binds to all forms of VEGF-A, VEGF-B, and the placental growth factor. Aflibercept is administered by intravitreal injection.

Aflibercept solution for injection has a marketing authorisation in the UK for treating 'visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)'.

Intervention(s)	Aflibercept solution for injection
Population(s)	Adults with visual impairment caused by macular oedema secondary to branch retinal vein occlusion
Comparators	• Laser photocoagulation • Bevacizumab (not licensed in the UK for this indication) For people for whom laser photocoagulation has not been beneficial or is not suitable: • Ranibizumab • Dexamethasone intravitreal implant • Bevacizumab (not licensed in the UK for this indication)
Outcomes	The outcome measures to be considered include: • visual acuity (the affected eye) • visual acuity (the whole person) • adverse effects of treatment • health-related quality of life • mortality.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The 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.
Other considerations	If the evidence allows, consideration will be given to a subgroup according to baseline visual acuity. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 346, Jul 2015 'Aflibercept for treating diabetic macular oedema'. Review Proposal Date Jul 2018. Technology Appraisal No. 305, Feb 2014, 'Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion.' Review Proposal Date Feb 2017. Technology Appraisal No. 283, May 2013, 'Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion.' Review Proposal Date Mar 2016. Technology Appraisal No. 229, Jul 2011, 'Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion.' Moved to static list. Related Interventional Procedures: Interventional Procedure No. 334, Mar 2010, 'Arteriovenous crossing sheathotomy for branch retinal

	vein occlusion.' Related NICE Pathways: NICE Pathway: Eye Conditions, Pathway last updated: May 2014. http://pathways.nice.org.uk/pathways/eye-conditions
Related National Policy	NHS Standard Contract For Ocular Oncology Service 2013/14 (Adults And Adolescents). "Treatment – Intraocular: steroids for macular oedema (e.g., after radiotherapy)" Ref: D12/S(HSS)/a Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domain 2: Enhancing quality of life for people with long-term conditions. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Matrix of Consultees and Commentators

Consultees	Commentators (no right to submit or appeal)
Company • Bayer (aflibercept) Patient/carer groups • Action for Blind People • Eyecare Trust • Fight for Sight • Macular Society • Muslim Council of Britain • OBAC • Royal National Institute of Blind People (RNIB) • SeeAbility • Sense • South Asian Health Foundation • Specialised Healthcare Alliance • Thomas Pocklington Trust Professional groups • British Geriatrics Society • British Ophthalmic Anaesthesia Society • College of Optometrists • Oxford Eye Foundation • Royal College of General Practitioners • Royal College of Nursing • Royal College of Ophthalmologists • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association Others • Department of Health • NHS England • NHS Merton CCG	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Allergan (dexamethasone intravitreal implant) • Coherent UK (photocoagulation) • Litechnica (photocoagulation) • Liverpool and Broadgreen University Hospitals Pharmacy (bevacizumab) • Lumenis UK (photocoagulation) • Moorfields Pharmaceuticals (bevacizumab) • Novartis Pharmaceuticals (ranibizumab) • Quantel Medical (photocoagulation) • Topcon Great Britain (photocoagulation) Relevant research groups • Cochrane Eyes and Vision Group • Eye Hope

Consultees	**Commentators (no right to submit or appeal)**
• NHS Trafford CCG • Welsh Government	• Institute of Ophthalmology, University College London • MRC Clinical Trials Unit • National Eye Research Centre Charity • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Aflibercept for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion (ID844)

Company evidence submission

01 February 2016

File name	Version	Contains confidential information	Date
EYLEA_ID844_AIC_CIC_Final	Final	Yes	1 February 2016

Contents

List of tables

List of figures

Glossary

2Q4	2 mg every 4 weeks
2Q8	2 mg every 8 weeks
AE	Adverse event
AFL	Aflibercept
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
AST	Aspartate aminotransferase
BCVA	Best corrected visual acuity
BRVO	Branch retinal vein occlusion
BSE	Best Seeing Eye (the eye with the best vision)
CBVOS	Combined Branch Vein Occlusion Study
CI	Confidence interval
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
DEX	Dexamethasone intravitreal implant
DME	Diabetic macular oedema
DR	Diabetic retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
FP	Fundus photography
GLP	Grid Laser Photocoagulation
HRVO	Hemi-retinal vein occlusion
IAI	Intravitreal aflibercept
IOP	Intraocular pressure
IVRS	Interactive voice response system
IVT	Intravitreal

LOCF	Last observation carried forward
LogMar	Logarithm of the Minimum Angle of Resolution
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
NMA	Network Metaanalysis
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
NV	Neovascularisation
OC	Observed case
OCT	Optical coherence tomography
PAS	Patient Access Scheme
PPS	Per protocol set
RAN	Ranibizumab
RCO	Royal College of Ophthalmology
RVO	Retinal vein occlusion
SE	Study eye (the eye treated in the study)
SmPC	Summary of Product Characteristics
FE	Fellow eye (the non-'study' eye)
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
TEAE	Treatment-emergent adverse event
Tx	Treatment
VA	Visual acuity
VEGF Trap-eye	Intravitreal aflibercept injection
VTE	Aflibercept
VEGF	Vascular endothelial growth factor
VIBRANT	VGFTe-RVO-1027
WSE	Worst seeing eye (the eye with the worst vision)

1 Executive summary

Burden of BRVO

Retinal vein occlusion (RVO), particularly in patients with associated chronic macular oedema, is a significant cause of visual impairment. It is the second most common retinal vascular disorder after diabetic retinopathy (1).

There are two main types of RVO – central retinal vein occlusion (CRVO), and branch retinal vein occlusion (BRVO) (2-4). BRVO is approximately three times more common than CRVO (5). In England and Wales it is estimated that there are around 14,488 people with visual impairment due to macular oedema secondary to BRVO (section 6).

Retinal vein occlusion results in a retrograde backup or blockade of retinal blood flow resulting in increased retinal capillary pressure, retinal ischaemia, and hypoxia, which in turn up-regulates release of vascular endothelial growth factor (VEGF). Increased VEGF is associated with neovascularisation, increased capillary permeability and the leakage of blood and plasma into the retina, leading to macular oedema (swelling in the central part of the retina). The degree of vision loss depends on the extent of retinal involvement and on macular perfusion status.

Patients with BRVO typically present with sudden, unilateral, painless loss of vision or ‘blind spots’ (caused by macular oedema). Sudden onset of visual loss, whether unilateral or bilateral, results in significant distress (6). The impact of vision loss associated with BRVO can also have a profound effect on vision-related quality of life. Patients may struggle with daily tasks, lose confidence and become increasingly dependent on family and carers.

Technology - aflibercept

Aflibercept (Eylea) is a potent specific inhibitor of vascular endothelial growth factor (VEGF) and a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2. Aflibercept binds to all known VEGF- A isoforms and also Placental Growth Factor (PlGF). By blocking these factors, aflibercept reduces the growth of the blood vessels and controls the leakage and swelling in macular oedema.

Licence

Marketing approval for aflibercept for the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) was received on 25 February 2015.

Aflibercept is also approved for the treatment of:

- visual impairment due to diabetic macular oedema (DMO) (August 2014);
- visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) (August 2013);
- neovascular (wet) age-related macular degeneration (AMD) (November 2012).
- visual impairment due to myopic choroidal neovascularisation (November 2015)

Management of BRVO

NICE recommends laser photocoagulation as the first-line treatment in BRVO, with ranibizumab (TA283) or dexamethasone intravitreal implant (TA229) being positioned as second-line treatment options where laser has not been beneficial or is not suitable (due to the extent of macular haemorrhage).

However, clinical practice is changing with greater first-line use of ranibizumab. The reasons for the change in practice are evident from the recent Royal College of Ophthalmology Guidelines (6) which recommend prompt treatment with anti-VEGF agents (or dexamethasone implant) for macular oedema due to non-ischaemic BRVO and restrict laser photocoagulation to when these other treatments are unsuccessful. Among the reasons for laser not being recommended as a first-line treatment are:

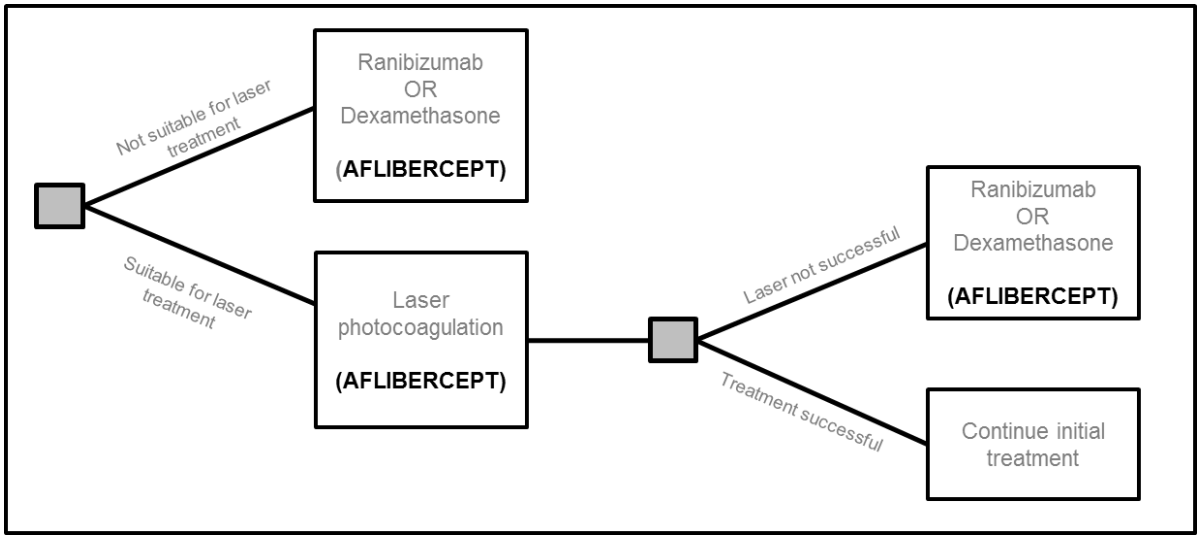
- the poor vision gains with laser
- the potential delay in laser treatment due to the presence of macular haemorrhage, which may compromise visual potential in eyes with persistent MO (7).

- the better outcomes associated with the newer treatments

Aflibercept's place in therapy

The potential positions for aflibercept within NICEs treatment pathway are shown in Figure 1. Existing recommendations are in grey.

Figure 1. Potential positions for aflibercept in the NICE treatment pathway



Evidence base

The evidence for the efficacy and safety of aflibercept in BRVO come from the phase III VIBRANT trial. In this 52-week study, patients were randomised to either aflibercept or laser photocoagulation. The primary endpoint, at week 24, was the proportion of patients gaining ≥15 letters in best corrected visual acuity (BCVA) from baseline. Aflibercept was shown to be superior to laser photocoagulation with 52.7% of patients' achieiving this endpoint compared to 26.7% for laser photocoagulation - between group difference, 26.1% p=0.0003.

Rescue treatment could be given to all patients if required, for the remainder of the study. This resulted in 74% of patients in the laser photocoagulation group receiving rescue aflibercept treatment and nine patients (10%) in the aflibercept group receiving laser treatment.

At week 52, the proportion of patients who had gained at least 15 letters in BCVA was 57.1% (52/91) in the aflibercept group versus 41.1% (37/90) in the laser group (adjusted difference 16%, nominal p=0.0296), demonstrating that early treatment

with the more effective treatment after presentation is important in terms of maximising outcomes.

Economic evaluation

In clinical practice, if patients respond well to initial treatment they will stay on that treatment. However, as per NICEs treatment pathway, if the first treatment is not successful then some patients will switch to a second treatment. The *de novo* economic model developed for this submission differs from other models that have been presented to NICE in that it considers the costs and outcomes for patients who respond to their initial treatment as well as the costs and outcomes of second-line treatment when it is required. The results of the economic analysis are presented in section 1.4 (Table 4). Aflibercept was found to be a cost-effective use of NHS resources regardless of where it is used in the treatment pathway, with the cost per QALY being below £20,000.

1.1 Statement of decision problem

The decision problem is summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)	Adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)	
Intervention	Aflibercept 40mg/ml solution for injection	Aflibercept 40mg/ml solution for injection	
Comparator (s)	Grid laser photocoagulation Ranibizumab Dexamethasone Bevacizumab	Grid laser photocoagulation Ranibizumab Dexamethasone	• Bevacizumab is an unlicensed treatment in ophthalmology and several licensed treatments are available. • There has been no regulatory assessment of bevacizumab in BRVO and it cannot be considered best or routine practice. • Bevacizumab was listed in the scope but was not used as a comparator in the cost-effectiveness analysis referred to in the decision making for ranibizumab (TA283).
Outcomes	Visual acuity (the affected eye) Visual acuity (the whole person) Adverse effects of treatment Health-related quality of life	Visual acuity (the affected eye) Visual acuity (the whole person) Adverse effects of treatment Health-related quality of life	

	Mortality	Mortality	
Economic analysis	Incremental cost per quality-adjusted life year	Incremental cost per quality-adjusted life year	
Subgroups to be considered	According to baseline visual acuity	Subgroup analysis has been conducted for the 24-34 and 35-73 letter BCVA subgroups. This analysis has been conducted based on data from the VIBRANT study.	No subgroup comparisons versus ranibizumab or dexamethasone were possible as a connected evidence network could not be formed.
Special considerations including issues related to equity or equality	None	None	

1.2 Description of the technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	Aflibercept (Eylea)
Marketing authorisation/CE mark status	Approved
Indications and any restriction(s) as described in the summary of product characteristics	Eylea is indicated for adults for the treatment of - neovascular (wet) age-related macular degeneration (AMD), - visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) , - visual impairment due to diabetic macular oedema (DME). - visual impairment due to myopic choroidal neovasclarisation
Method of administration and dosage	The recommended dose for aflibercept is 2 mg aflibercept equivalent to 50 microlitres. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, aflibercept should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

1.3 Summary of the clinical effectiveness analysis

The marketing authorisation for aflibercept in BRVO was based on the phase III VIBRANT study. No randomised, controlled, head-to-head studies comparing aflibercept with ranibizumab or dexamethasone have been conducted and therefore an estimate of relative efficacy was obtained via an indirect treatment comparison.

The outcomes considered were gaining ≥15 letters, losing ≥15 letters, BCVA change from baseline, adverse events and discontinuation. Data availability limited the comparison to two outcomes i.e. proportion of patients gaining 15 or more letters from baseline and change in visual acuity from baseline. The network metaanalysis (NMA) base case and sensitivity analysis results showed no evidence of a statistically significant difference between aflibercept and ranibizumab with the 95% credible intervals crossing zero for both the proportion of patients gaining 15 or more letters and change in letters from baseline. For the comparison with dexamethasone there was evidence that aflibercept was more effective in terms of patients gaining 15 or more letters from baseline (fixed effects model). There was also evidence of a large benefit of aflibercept compared to dexamethasone in terms of change in letters from baseline according to the fixed effects model (10 letters), although, for the random effects model the credible interval was very wide and crossed unity.

The strengths of the indirect comparison are that it was based on systematically sourced data and appropriately accounted for the different treatments received in the trials. The limitations of the analysis are that the number of trials in BRVO is relatively small and the base case analyses were based on four studies. In addition, no safety comparisons were possible as connected networks could not be developed for this outcome.

1.4 Summary of the cost-effectiveness analysis

As described earlier, the *de novo* economic model accounts for the costs and outcomes of first-line and second-line treatment. The treatment pathways considered in the economic analyses were determined by NICE's current recommendations and are presented in Table 3. A summary of the cost-effectiveness results using the PAS price for aflibercept and the list prices for

ranibizumab and dexamethasone is shown in Table 4. Aflibercept was found to be cost-effective when used as a first-line and second-line treatment option.

Table 3. Treatment pathways considered in the economic modelling

First-line treatment	Second-line treatment (if required)
Aflibercept	Laser photocoagulation
Laser photocoagulation	Aflibercept
Laser photocoagulation	Ranibizumab
Laser photocoagulation	Dexamethasone intravitreal implant

No comparisons against bevacizumab have been made (see Table 1).

Table 4. Incremental cost-effectiveness results

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)	Incremental analysis
[A] Laser followed by dexamethasone (for treatment failures)	[redacted]	13.708	[redacted]	-	-	-	-	-
[B] Laser followed by aflibercept (for treatment failures)	[redacted]	13.709	[redacted]	[redacted]	0.001	[redacted]	11,792	11,792
[C] Laser followed by ranibizumab (for treatment failures)	[redacted]	13.709	[redacted]	[redacted]	0.001	[redacted]	28,513	Dominated
[D] Afibercept followed by laser (for treatment failures)	[redacted]	13.717	[redacted]	[redacted]	0.009	[redacted]	14,303	15,365
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

2 The technology

2.1 Description of the technology

Brand name	Eylea®
Approved name	Aflibercept
Therapeutic class	(Intravitreal) vascular endothelial growth factor (VEGF) inhibitor.

2.1.1 Overview of mechanism of action

Aflibercept solution for injection exerts its effect through VEGF inhibition. Increased VEGF is associated with neovascularisation, increased capillary permeability and the leakage of blood and plasma into the retina, which leads to macular oedema (swelling in the central part of the retina). Aflibercept is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2. Aflibercept binds to all known VEGF-A isoforms and also Placental Growth Factor (PlGF). By blocking these factors, aflibercept reduces the growth of the blood vessels and controls the leakage and swelling in macular oedema.

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Approved indications

The marketing authorisation process for the UK was centralised through the EMA. European marketing approval for aflibercept for the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) was received on 25 February 2015.

Aflibercept has been approved for treatment of visual impairment due to myopic choroidal neovascularisation (November 2015); visual impairment due to diabetic macular oedema (DMO) (August 2014); visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) (August 2013); and treatment of neovascular (wet) age-related macular degeneration (AMD) (November 2012).

Regulatory approval outside of the UK

Aflibercept has received marketing approval from the Food and Drug Administration (FDA) in the USA for the same indications as listed above for Europe.

Contraindications

Contraindications to the use of aflibercept are:

- Hypersensitivity to the active substance aflibercept or to any of the excipients.
- Active or suspected ocular or periocular infection.
- Active severe intraocular inflammation.

2.2.2 Summary of product characteristics (SmPC) and European public assessment report (EPAR)

The European Union Marketing Authorisation Application (EU MAA) submission for aflibercept in the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) was based on a review of data from the VIBRANT trial. The SmPC and European public assessment report (EPAR) for this particular therapeutic indication can be found in Appendix **Error! Reference source not found.**. The final EPAR was published on 22nd January 2015 (8).

According to the EPAR, VIBRANT convincingly demonstrated a clinical benefit of aflibercept in treating visual impairment due to macular oedema secondary to BRVO both in terms of functional and anatomical outcomes. One year data confirmed maintenance of the treatment effect in the longer term. Adverse effects observed were generally in line with the known safety profile of aflibercept and mainly related to ocular adverse reactions linked to the intravitreal injection procedure.

However the CHMP considered that the fixed dosing regimen selected for the pivotal trial was not adequately justified and that a similar benefit may be derived with fewer injections. Thus, the final posology recommended for BRVO was a similar regimen as agreed for CRVO, i.e. initial fixed monthly dosing until stabilisation of vision to be followed by a flexible regimen. This was considered by the CHMP to be more appropriate in light of the time course of treatment effects observed in the VIBRANT

study but also taking into account the current knowledge and clinical practice for the class of anti-VEGF inhibitors. The posology recommendations were also aligned with what is recommended for ranibizumab in the same indication.

Other health technology assessments in the UK

On the 7th September 2015 aflibercept was accepted for use by the Scottish Medicines Consortium (SMC) for the treatment of visual impairment due to macular oedema secondary to BRVO.

2.3 Administration and costs of the technology

Table 5: Costs of the technology being appraised

		Source
Pharmaceutical formulation	Eylea 40 mg/ml solution for injection in a vial. 1 ml solution for injection contains 40 mg aflibercept.	SmPC (see (Appendix **Error! Reference source not found.**)
Acquisition cost (excluding VAT) *	£816 per vial A confidential simple patient access scheme is available. The cost after application of the simple discount is [redacted] per vial. The PAS scheme has been previously approved by the Department of Health and the scheme covers all the indications for aflibercept.	List price (British National Formulary)
Method of administration	Intravitreal injection only.	SmPC (Appendix **Error! Reference source not found.**)
Doses **Dosing frequency** **Average length of a course of treatment** **Average cost of a course of treatment** **Anticipated average interval between courses of treatments** **Anticipated number of repeat courses of treatments**	The recommended dose for aflibercept is 2 mg aflibercept (equivalent to 50 microlitres aflibercept solution for injection). After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, aflibercept should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's	SmPC (Appendix **Error! Reference source not found.**)

	response.	
Dose adjustments	Not applicable	
Anticipated care setting	Aflibercept must be given as an intravitreal injection by a qualified physician experienced in administering intravitreal injections. Adequate anaesthesia and asepsis have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are also recommended. If required, sterile equipment for paracentesis should be available.	SmPC (Appendix **Error! Reference source not found.**)
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

Additional tests, investigations: In BRVO the main treatment used in the NHS is ranibizumab and this is the treatment that is most likely to be displaced. The consideration of changes in service provision and management are in this context.

Both aflibercept and ranibizumab are anticipated to be similar in any requirement for tests and investigations and therefore no impact on the NHS is anticipated.

It is not expected that there will be any additional tests or investigations needed for selection of patients for aflibercept solution for injection compared with ranibizumab. Ranibizumab is recommended by NICE and used within the NHS, for the treatment of MO secondary to RVO (Central and Branch) (9).

Resource use: A change in resource use is not anticipated as the treatment most likely to be displaced by aflibercept is ranibizumab - both treatments have similar requirements in terms of monitoring, posology and number of injections needed (Eylea SmPC, ranibizumab SmPC).

In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended. As per current practice for treatment with intravitreal injections for other back of the eye conditions, immediately following the intravitreal injection, patients should be

monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available (Eylea SmPC).

Each vial should only be used for the treatment of a single eye. After injection any unused product must be discarded.

Infrastructure: Introduction of this technology for the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) does not require additional infrastructure to be put in place.

Monitoring: Also, it is not expected that the need for monitoring with aflibercept solution for injection will be over and above that currently required for the treatment of MO secondary to BRVO in the NHS. As with current practice, administration of aflibercept will be via intravitreal injection and monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). The monitoring and treatment schedule is determined by the treating physician based on the individual patient's response.

Concomitant therapies: As with current practice for the treatment of BRVO, aflibercept intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended (Eylea SmPC – appendix **Error! Reference source not found.**)

2.5 Innovation

Aflibercept solution for injection is innovative as it has several differences from other VEGF blockers, such as ranibizumab. It inhibits all isoforms of VEGF-A (10), and has a much higher binding affinity for VEGF-A compared with its native receptors, and also compared with ranibizumab (11). It addresses a wider range of growth factors and includes Placental Growth Factor (PIGF) binding (10-12). The higher binding

affinity may result in a longer duration of disease control in comparison to ranibizumab. This is important as currently many patients, due to resource constraints in the NHS, are unable to be seen as often as is optimal for disease control. The higher binding affinity may also enable patients to be seen less often once disease symptoms have stabilised.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Retinal vein occlusion (RVO), particularly in patients with associated chronic macular oedema, is a significant cause of visual impairment. It is the second most common retinal vascular disorder after diabetic retinopathy (1). There are two main types of RVO – central retinal vein occlusion (CRVO), and branch retinal vein occlusion (BRVO) (2-4). BRVO is approximately three times more common than CRVO (5). In England and Walesit is estimated that there are around 14,488 people with visual impairment due to macular oedema secondary to BRVO (see section 6).

While CRVO involves a blockage of the central retinal vein, BRVO is defined as occlusion in any of the four branches of the retinal vein, each of which drains about a quarter of the retina. BRVO is classified into subtypes based on the location of occlusion (13):

- major (first-order) BRVO, when 1 of the major retinal branch veins is occluded, and
- macular (second-order) BRVO, when 1 of the macular venules is occluded

Hemi-retinal vein occlusion (HRVO) may be regarded as a variant of BRVO that involves an obstruction of 2 altitudinal quadrants; therefore, eyes diagnosed with HRVO are often treated in the same way as eyes with BRVO, and HRVO patients may be enrolled in studies enrolling BRVO patients.

Retinal vein occlusion results in a retrograde backup or blockade of retinal blood flow resulting in increased retinal capillary pressure, retinal ischaemia, and hypoxia, which in turn up-regulates release of vascular endothelial growth factor (VEGF). Increased VEGF is associated with neovascularisation, increased capillary permeability and the leakage of blood and plasma into the retina, leading to macular oedema (swelling in the central part of the retina). The degree of vision loss depends on the extent of retinal involvement and on macular perfusion status. BRVO that

does not involve the macula is often asymptomatic and therefore its diagnosis is mostly accidental (13).

Risk factors that have been associated with BRVO include increasing age (it typically affects people over 50 years of age), hypertension, diabetes mellitus, arteriosclerotic vascular disease and thrombophilia (14;15).

Patients with BRVO typically present with sudden, unilateral, painless loss of vision or 'blind spots' (caused by macular oedema). Clinical presentation of BRVO includes flame-shaped, dot and blot haemorrhage and retinal oedema. Often BRVO leads to zones of non-perfusion in the occlusion area and if left untreated, retinal neovascularisation (4).

Fundus fluorescein angiography is commonly performed to assess the severity of retinal vascular leakage and perfusion status. Optical coherence tomography (OCT) is a non-invasive imaging technique used to quantify macular oedema and assess treatment response (13).

3.2 Impact of BRVO

Sudden onset of visual loss, whether unilateral or bilateral, results in significant distress (6). The impact of vision loss associated with RVO can also have a profound effect on vision-related quality of life. Patients may struggle with daily tasks, lose confidence and become increasingly dependent on family and carers.

3.3 Treatment

Aims of treatment of BRVO are to halt, slow or reverse disease progression and improve vision. In some cases spontaneous improvement in vision can occur as the macular oedema (which follows acute occlusion of the vein) resolves, therefore in cases where, at presentation, visual acuity is better than 6/12 or where macular oedema and haemorrhages are not masking fovea or macular ischaemia is not identified or is mild, regular observation for three months may be warranted (6).

3.3.1 Laser photocoagulation

For many years, laser photocoagulation was the treatment of choice for visual impairment due to MO secondary to BRVO. This treatment approach was based on

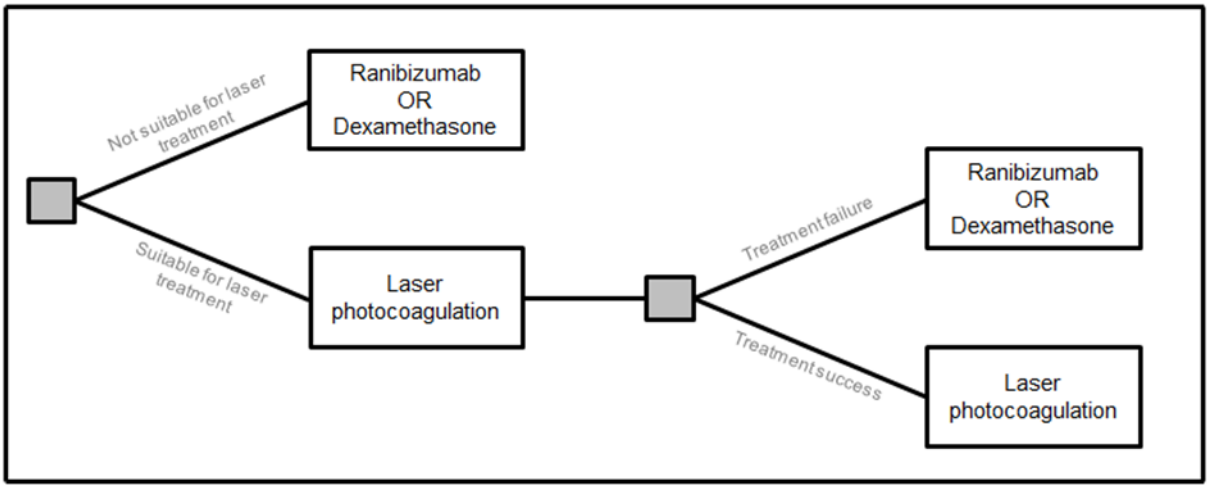
the Branch Vein Occlusion Study (BVOS), a multicentre, prospective, randomised trial designed to study the natural history and effect of laser treatment in BRVO (7). In the BVOS study, the average improvement in VA in the laser arm after three years of follow-up was 1.3 lines; and 40% of patients had a final visual acuity of 6/12 at 36 months despite macular laser treatment.

Over the last few years the treatment options available have increased and now include anti-VEGFs and dexamethasone intravitreal implant.

3.3.2 NICE treatment pathway

The NICE treatment pathway, developed shortly after the introduction of these newer treatments is shown in Figure 2. Ranibizumab (TA283) and dexamethasone intravitreal implant (TA229) are recommended where laser has not been beneficial or is not suitable (due to the extent of macular haemorrhage). Treatment guidelines are discussed in more detail in section 3.6.

Figure 2. NICE treatment pathway for BRVO



3.3.3 Changing clinical practice

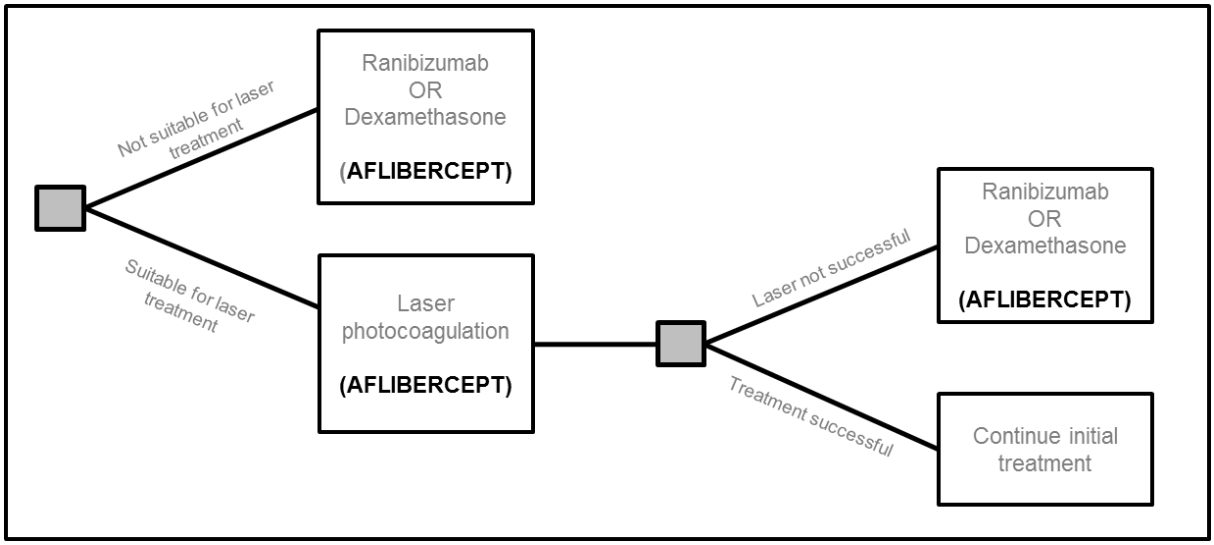
Clinical practice is moving away from the pathway recommended by NICE. In response to evidence from clinical trials, first-line use of laser photocoagulation is declining and there is greater first-line use of ranibizumab, and to a lesser extent dexamethasone. The reasons for the change in practice are evident from the recent Royal College of Ophthalmology Guidelines which are discussed in more detail in section 3.6 and which provide relatively detailed recommendations. These guidelines are almost the reverse of those from NICE in that they recommend prompt treatment with anti-VEGF agents (or dexamethasone implant) for macular oedema due to non-ischaemic BRVO and restrict laser photocoagulation to when these other treatments are unsuccessful. Among the reasons for laser not being recommended as a first line option are:

- the poor vision gains with laser
- the potential delay in laser treatment due to the presence of macular haemorrhage, which may compromise visual potential in eyes with persistent MO (7).
- the better outcomes associated with the newer treatments

3.3.4 Aflibercept's place in the treatment pathway

In relation to the NICE treatment pathway (Figure 2), aflibercept would be an alternative option to first-line treatment with laser photocoagulation or second-line treatment with ranibizumab or dexamethasone intravitreal implant. These potential positions, in the context of the NICE treatment pathway are shown in Figure 3.

Figure 3. Aflibercept's place in the NICE treatment pathway



3.4 Life expectancy and patient numbers

It is not intended for aflibercept, in the indication proposed within this submission, to be considered as a 'life-extending treatment at the end of life'.

3.4.1 Life expectancy of patients with BRVO

A review of the evidence of whether RVO (central or branch) is associated with an increased risk of mortality is available from the recent Royal college Ophthalmologists Retinal Vein Occlusion Guidelines (6). The review found that the evidence was conflicting and unable to establish a clear increased mortality risk of BRVO. Included below is the summary of the evidence taken from the guidelines. The first paragraph relates to CRVO but provides the context for BRVO in the second paragraph.

Reports on this subject are conflicting too. Bertelsen et al (2014) found a higher overall increased mortality compared to controls for CRVO (5.9 deaths/100 person years compared to 4.3 deaths/100 person years (HR, 1.45:95% CI,1.19 – 1.76. However, when the data was adjusted for overall occurrence of cardiovascular disorders including hypertension, peripheral vascular disease, ischaemic heart disease, myocardial infarction, congestive cardiac failure, cerebrovascular disease and diabetes, the mortality rate was comparable to that in the control population (HR 1.19;95% CI,0.96 – 1.46).

Using the same methodology, this finding of no specific increase in mortality was also found for BRVO. Participants with BRVO at baseline did not have an increased 8-year risk of mortality due to ischaemic heart disease in the Beaver Dam study (47). A population based study reported that RVO did not predict acute myocardial infarction. Similarly, other reports show that RVO is not associated with cerebrovascular mortality. However, Cugati et al (2007) found that men with RVO were associated with a non-significant 2.3-fold higher risk of cerebrovascular mortality for all ages in a pooled cohort of two-population based studies. In another population-based study (Beijing Eye Study), RVO was significantly associated with an increased overall mortality rate in subjects aged below 69 years.

Visually impairment and the risk on mortality - Studies on the effects of visual impairment (from a variety of causes) on mortality risk suggest that visual impairment increases the risk of mortality directly and indirectly through its adverse impact on mental well-being (16), disability in walking (17) and increased risk of suicide through its effect on poor health (18).

For the pharmacoeconomic modelling, a literature review was conducted to identify how blindness increases the risk of dying compared with the general population. The most relevant publication, Christ et al (2008) (19), used in a previous HTA submission (9), estimated the effects of vision loss on mortality using a structural equation modelling approach. The paper reports that severe visual impairment, which was coded as blindness, increases the hazard rate by 54% (hazard ratio: 1.54, 95% CI: 1.28 –1.86) and by 23% (hazard ratio: 1.23, 95% CI: 1.16-1.31) when mild visual impairment is observed relative to no visual impairment.

Patients with BRVO in England

In the final scope for aflibercept in BRVO it is stated RVO affects 1–2% of people aged over 40 years and macular oedema is the most frequent cause of vision loss in people with RVO. It is estimated that in England and Wales there are around 14,488 people with BRVO and macular oedema have visual impairment (section 6). The risk of RVO typically increases with age and there is an equal distribution amongst men and women.

As considered in previous NICE appraisals (TA294, TA305 and TA346), aflibercept solution for injection is also indicated for adults for the treatment of neovascular (wet) AMD, Central Retinal Vein Occlusion (CRVO) and Diabetic Macular Oedema (DMO).

DMO: A recent publication highlights the issues with epidemiological estimates for diabetic retinopathy (20). Minassian et al. estimated 64,725 individuals had clinically significant DMO in England based on 2010 diabetes data (21).

Wet AMD: Some estimates suggest that there are an estimated 39 new patients per 100,000 of the population eligible for treatment each year (22). Based on an overall population in England of 54,316,600 (Office of National Statistics – Annual mid-year Population Estimates 2014, released June 2015), this equates to 21,183 in the total population of England.

CRVO: there are an estimated 12 new patients with MO secondary to CRVO eligible for treatment per 100,000 of the population in England (23). Based on an overall population in England of 54,316,600 (Office of National Statistics – Annual mid-year Population Estimates 2014, released June 2015), this equates to 6,517 in the total population of England.

3.5 NICE guidance, pathways or commissioning guides

3.5.1 Related Technology appraisals

TA283 - Ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (May 2013).

Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- following central retinal vein occlusion or
- following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage

- and only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 274

TA229 - Macular oedema secondary to retinal vein occlusion – dexamethasone intravitreal implant (Ozurdex®) (July 2011)

Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion.

Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following branch retinal vein occlusion when:

- treatment with laser photocoagulation has not been beneficial or
- treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage.

Related Interventional Procedures

Interventional Procedure No. 334 - Arteriovenous crossing sheathotomy for branch retinal vein occlusion (March 2010)

Current evidence on the efficacy and safety or arteriovenous crossing sheathotomy for branch retinal vein occlusion (BRVO) is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.

Related NICE Pathways

NICE Pathway: Eye Conditions, Pathway last updated: May 2014.
http://pathways.nice.org.uk/pathways/eye-conditions

This weblink presents the recommendations for the products already covered above.

3.6 Other clinical guidelines

3.6.1.1 Scottish Medicines Consortium

Aflibercept (Eylea®) (September 2015) (1074/15) - accepted for use within NHS Scotland for adults for the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion. Aflibercept has previously been accepted by SMC for macular oedema secondary to central retinal vein occlusion. This advice now extends its use to patients with macular oedema secondary to branch retinal vein occlusion.

Ranibizumab (Lucentis®) (May 2013) (732/11) – accepted for use within NHS Scotland for the treatment of visual impairment due to macular oedema (MO) secondary to retinal vein occlusion (RVO) (branch RVO or central RVO) in adults. SMC has previously accepted ranibizumab for use in macular oedema secondary to central retinal vein occlusion (CRVO) (November 2011).

Dexamethasone (Ozurdex®) (June 2012 – second resubmission) (652/10) – Accepted for restricted use within NHS Scotland for use in adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) who are not clinically suitable for laser treatment including patients with dense macular haemorrhage or patients who have received and failed on previous laser treatment.

3.6.2 Royal College of Ophthalmologists

3.6.2.1 Clinical Guidelines: Retinal Vein Occlusion Guidelines (July 2015)(6)

These guidelines provide separate recommendations for macular oedema (MO) secondary to BRVO and CRVO and also according to whether the condition is ischaemic or non-ischaemic. The guidelines recommend prompt treatment with anti-VEGF agents (or dexamethasone implant) for MO due to non-ischaemic BRVO and restricting grid laser photocoagulation to when these other treatments are unsuccessful or unavailable. In the guidelines the efficacy of the different treatment options is briefly summarised before providing treatment recommendations. The bullet points below are extracts from the guideline which are most relevant to this submission and which provide the context for the recommendations that follow. The

guidelines were also developed in the context of existing NICE recommendations for ranibizumab and dexamethasone.

- The natural history of MO due to BRVO indicates that MO may resolve or reduce over time with an approximate mean gain of 7.3 ETDRS letters at six months (BRAVO sham arm [more details on the BRAVO study are in section 4.10 of this submission]). However, a delay of six months in initiating anti-VEGF therapy in this condition also results in an inferior visual outcome compared to prompt treatment at diagnosis. As BRVO is a predominantly unilateral disease, there is often a delay in the patient being aware of the visual impairment, timely diagnosis of the condition and referral for therapy. Therefore, prolonged delays of six months or more after the diagnosis is established should be avoided unless the patient wishes to delay treatment.

- Macular laser has been the treatment of choice for this condition for the last 20 years. However, with the availability of anti-VEGF agents, the role of laser as first-line treatment should be restricted to patients unsuitable or unwilling to receive anti-VEGF therapy. This recommendation is supported by the BVOS study in which only 40% of patients had a final visual acuity of 6/12 at 36 months despite macular laser treatment.

- Anti-VEGF agents (ranibizumab and aflibercept) have shown significant visual gains in patients with MO due to BRVO.

- Ozurdex [dexamethasone intravitreal implant] was recommended by NICE based on the GENEVA study results. Real-life experience indicates that more frequent dosing (than six-monthly used in GENEVA) is required to produce optimal results. The impact of frequent dosing of Ozurdex is the higher rate of progression of cataract. Ozurdex (700ug) is the only licensed intraocular steroid for this condition. As inflammation likely plays a role in MO due to RVO, Ozurdex is a useful treatment modality.

3.6.2.2 RCO recommendations for non-ischaemic BRVO:

1) At baseline, if VA better than 6/12 - observe progress for three months

2) At baseline, if VA 6/12 or worse with macular oedema and haemorrhages are not masking fovea

    - regularly observe for three months if macular oedema is mild and in opinion of clinician likely to spontaneously improve (30% chance);
    - If mild to moderate macular ischaemia is present consider treatment with ranibizumab or Ozurdex if spontaneous improvement is unlikely;
    - If severe macular ischaemia is present — no treatment is recommended, and regularly observe for neovascular formation.

3) If VA 6/12 or worse and macular oedema and haemorrhages are masking macula

    - monthly ranibizumab or baseline Ozurdex is recommended for three months.
    - If severe macular ischaemia is found to be present at three months, no treatment will likely be beneficial and further therapy should be carefully considered.

4) At three-month follow-up

    - Consider laser photocoagulation if persistent MO, no or minimal macular ischaemia and other treatments unsuccessful or unavailable
    - If VA ≥6/9 or no macular oedema detected, continue to observe (if initially observed). If on anti-VEGF or Ozurdex therapy. In case of recurrence or new macular oedema, consider re-initiating intravitreal ranibizumab or Ozurdex therapy.

3.6.2.3 RCO recommendations for ischaemic BRVO:

1) Watch carefully for neovascularisation; consider laser photocoagulation applied to all ischaemic quadrants if neovascularisation occurs. Intravitreal

bevacizumab (off-license) may also be given in combination with laser. Follow-up at three monthly intervals for up to 24 months.

3.7 Issues relating to current clinical practice and variations or uncertainty about established practice

A key issue for those involved in the treatment of MO secondary to BRVO in England is the disparity between NICE guidance on anti-VEGF therapy in BRVO (i.e. use only where laser photocoagulation has not been beneficial, or is not suitable) and the most recent guidelines developed by the Royal College of Ophthalmologists (i.e. to use ranibizumab or dexamethasone first and consider modified grid laser photocoagulation if persistent macular oedema, no or minimal macular ischaemia and other treatments unsuccessful or unavailable).

3.8 Equality issues

No equality issues have been identified.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic search of the literature was undertaken to identify RCTs investigating the efficacy and safety of aflibercept in the treatment of patients with visual impairment due to macular oedema secondary to BRVO. This search was part of a larger search for RCTs investigating the efficacy and safety of comparator treatments i.e. laser photocoagulation, ranibizumab, dexamethasone intravitreal implant or sham/observation in the same population for the purposes of conducting indirect comparisons (section 4.10 page 88). The search is outlined below. Full details of the literature search strategy including search terms employed are provided in Appendix **Error! Reference source not found.**.

4.1.2 Search strategy

The search was undertaken on the 21st September 2015 using the following databases without a date limit:

- EMBASE (1988 to September 21st 2015);
- MEDLINE (including Medline (R) in process (1946 – September 21st 2015);
- Cochrane Central Register of Controlled Trials (CENTRAL)

In addition, a search was conducted to identify clinical trials from conference abstracts and posters on November 23rd 2015 for the following conferences:

- American Academy of Ophthalmology (AAO) – 2012 to 2014
- Association for Research in Vision and Ophthalmology (ARVO) – 2013 to 2015
- Deutsche Ophthalmology Gesellschaft (DOG) – 2012 to 2015
- European Society of Retina Specialists (Euretina) – 2013 to 2015
- European Association for Vision and Eye Research (EVER) – 2012 to 2015

- Nordic Congress of Ophthalmology (NOK) – 2012, 2014
- World Ophthalmology Congress (WOC) – 2012, 2014

4.1.3 Study selection

The search was performed to locate RCTs that investigated the efficacy and safety of aflibercept and comparator treatments i.e. laser photocoagulation, ranibizumab, dexamethasone intravitreal implant or sham/observation. However, this section focuses on those publications concerning aflibercept and not the comparators (for details of comparator studies see section 4.10). Studies were included if they met the PICOS criteria presented in Table 6.

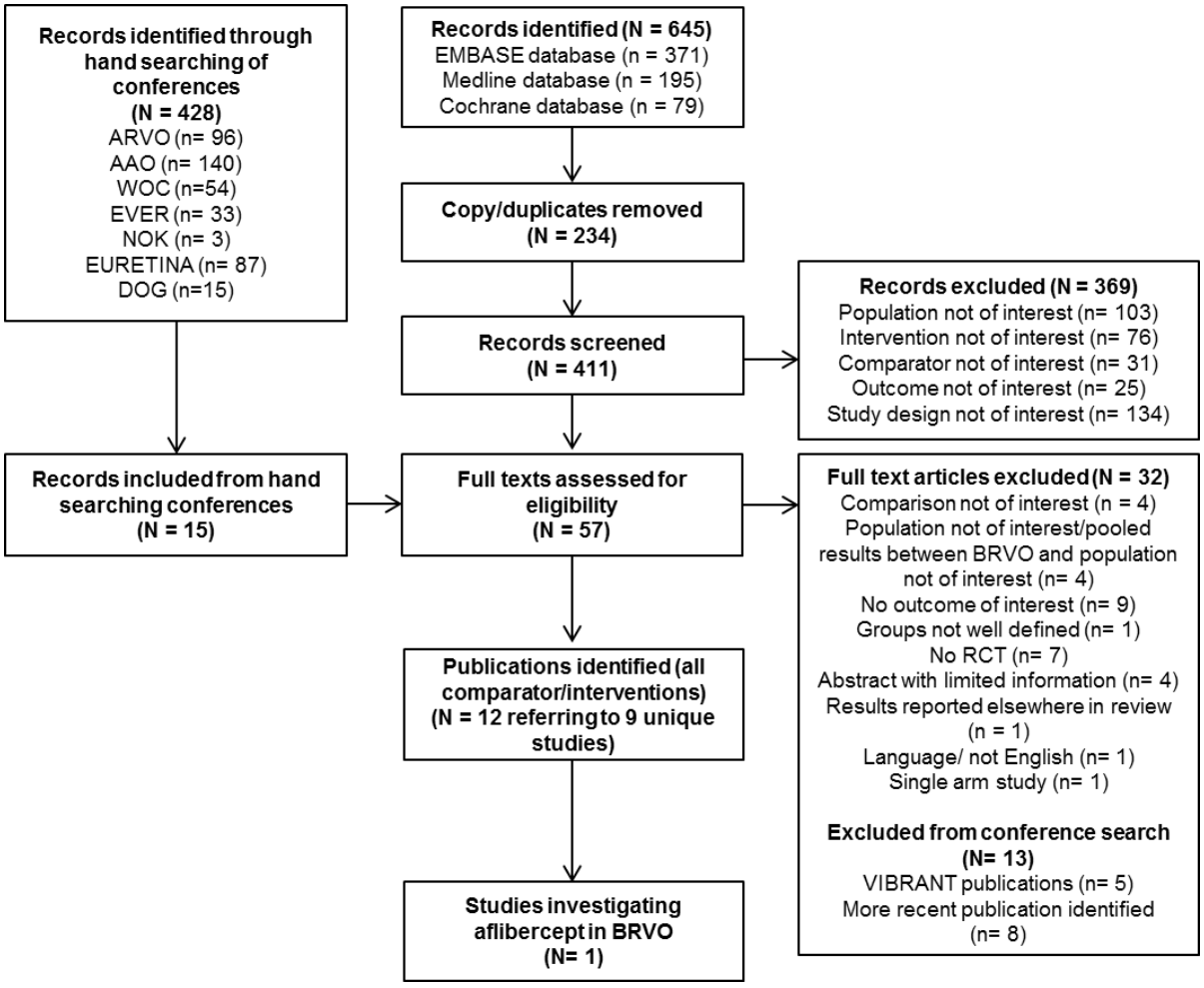
All references identified through searches were exported to Reference Manager 12 databases. The databases were merged and de-duplicated and exported to an Excel spreadsheet. Two reviewers independently screened each reference for relevance and any disagreements were resolved through 'reconciliation' (discussion between the two reviewers) or through 'arbitration' by a third independent reviewer. The 'majority view' determined inclusion or exclusion. Excluded publications were disregarded. Publications that appeared to be potentially relevant were ordered for a full review of the text and assessed for inclusion by two reviewers using the same approach as the initial abstract screening.

A flow diagram of the numbers of records included and excluded at each stage is provided in Figure 4. A list of the publications excluded at full-text stage, along with the reasons for exclusion is provided in Appendix **Error! Reference source not found.** (**Error! Reference source not found.**).

Table 6. Eligibility criteria used in the search strategy

Clinical evidence	Inclusion	Exclusion
Patient population	Adult patients with BRVO (studies reporting results for BRVO patients as "general population" or as a subgroup of RVO)	Patients with RVO only, CRVO, DMO and AMD
Interventions	Aflibercept OR Dexamethasone OR Ranibizumab OR Laser	-
Comparators	Dexamethasone OR Ranibizumab OR Laser OR Placebo/BSC/sham/observation	-
Outcome measures	Efficacy outomes related to visual acuity e.g. percentage of patients gaining/losing 15 letters of BCVA, BCVA mean change from baseline (EDTRS, LogMar), CRT change from baseline Safety outcomes (adverse events) e.g. percentage of patients experiencing intra-ocular pressure HRQoL	-
Study design	RCTs Recent systematic reviews and meta-analyses	Editorials OR Notes OR Comments OR Letters OR Observational studies OR Abstracts not reporting sufficient data for extraction
Restrictions	Language: English	Non-English studies

Figure 4: Prisma Flow diagram of the included clinical studies



In total 12 publications relating to 9 unique studies were located. Only one of these studies was an RCT of aflibercept (the VIBRANT study). Subsequent to this search the 52-week results of the VIBRANT study have also been published (Clark et al 2015 (25). The other 8 studies identified relate to the comparator treatments and are described in section 4.10.

4.2 List of relevant randomised controlled trials

As described in section 4.1, a single randomised, controlled study for aflibercept was located in the systematic literature review. This study is briefly outlined in Table 7.

Table 7: List of relevant RCTs

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref.
VIBRANT (NCT01521559)	Macular oedema secondary to branch retinal vein occlusion (BRVO)	n=91 **Week 0-week 24: Aflibercept** 2 mg given intravitreally every 4 weeks (2q4). Sham laser treatment on day 1. **Week 24-week 48**: aflibercept 2mg intravitreally every 8 weeks. Sham injections administered every 8 weeks from week 28.	n=90 **Week 0-week 24:** Grid laser photocoagulation at day 1. Sham injections every 4 weeks **Week 24-week 52**: sham injections administered every 4 weeks.	6-month data: Campochiaro 2015 (24) Note: since completion of the systematic literature review, the 12 month data has been published (Clark 2015 (25))
		Rescue treatment starting at week 12 (according to specific criteria; see Table 11 and Table 12): Laser rescue treatment at week 36.	Rescue treatment starting at week 12 (according to specific criteria; see Table 11 and Table 12): including laser rescue at from week 12 and aflibercept rescue treatment from week 24	

The VIBRANT study compares aflibercept to laser photocoagulation in patients with visual impairment due to macular oedema secondary to BRVO. This study is therefore applicable to the UK population and the current decision problem in this submission.

4.3 Summary of methodology of the relevant randomised controlled trials

The clinical development programme for aflibercept in BRVO consists of one pivotal phase 3 study:

A double-masked, randomized, active-controlled study of the efficacy, safety, and tolerability of intravitreal administration of VEGF Trap-Eye, intravitreal aflibercept injection [IAI] in patients with macular oedema secondary to Branch Retinal Vein Occlusion (study VGFTe-RVO-1027; the VIBRANT study)

4.3.1 Overview

VIBRANT was designed to assess the efficacy and safety of repeated doses of intravitreal aflibercept in patients with unilateral macular oedema following branch retinal vein occlusion (BRVO) or hemi-retinal vein occlusion with central involvement and a best corrected visual acuity (BCVA) between ≤73 and ≥ 24 (20/40 to 20/320 Snellen equivalent) letters.

The primary objective of VIBRANT was to assess the efficacy of aflibercept in improving best corrected visual acuity (BCVA) compared to laser photocoagulation (the standard of care when the trial was initiated), in patients with macular oedema secondary to BRVO. Secondary objectives included evaluation of the safety and tolerability of aflibercept compared with grid laser photocoagulation (GLP), and assessment of the effects of intravitreal administration of aflibercept on central retinal thickness (CRT) in this patient group.

VIBRANT has completed and results to week 24 (primary endpoint) and also to week 52 have been published (24;25). A European Medicines Agency CHMP assessment report for aflibercept in BRVO (EPAR) has also been published (8). Other data included in this submission (i.e. unpublished) has been drawn from the EMA licence submission dossier and also the Clinical Study Report (26-28).

4.3.2 Trial design

VIBRANT was an international, multicentre, randomised, double-masked, active-controlled, 52-week phase 3 study. Enrolment started for VIBRANT in April 2012 and

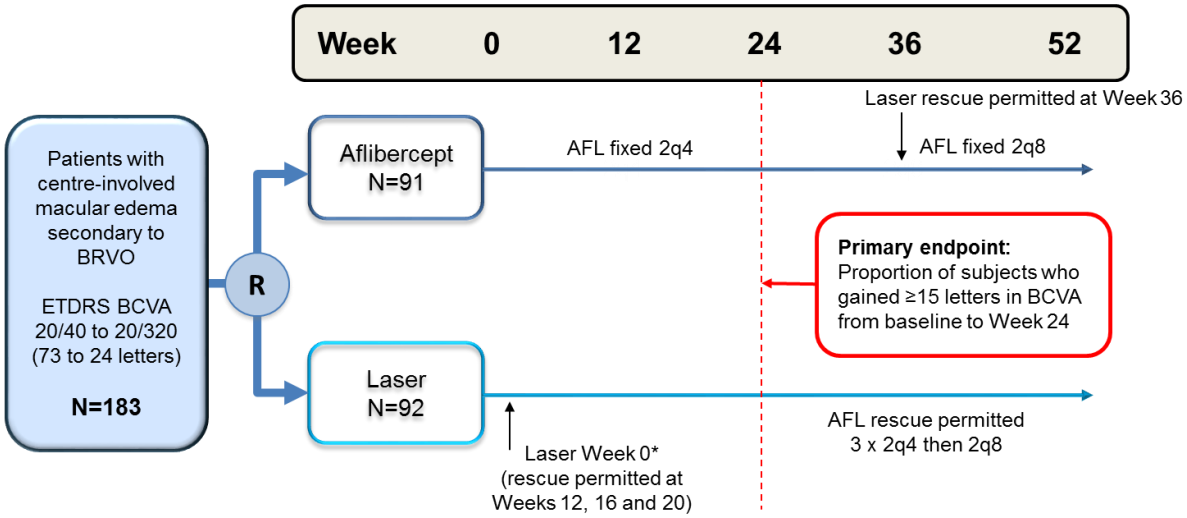
the date of the last patient visit for the primary endpoint (at 24-weeks) was August 2013. Data for the 52-week results were collected to March 2014 (last patient visit).

Patients were randomised on a 1:1 basis to one of two treatment groups (see Table 8 and Figure 5). Only one eye per patient was designated the 'study eye' and received treatment under the study protocol.

Table 8: Summary of VIBRANT treatment groups

Treatment Group 1 ***Aflibercept*** ***[n=91]***	***Treatment Group 2*** ***Macular (grid) laser photocoagulation (GLP)*** ***[n=92]***
• Day 1 to week 24: aflibercept 2mg every 4 weeks (2Q4); Sham grid laser photocoagulation (GLP) treatment on day 1; • *Week 24 to week 52*: aflibercept 2mg every 8 weeks (2Q8) through week 48; Sham injections 2Q8 starting week 28. Aflibercept patients could receive rescue GLP at week 36.	• Day 1 to week 24: GLP on day 1; Sham aflibercept injections every 4 weeks. If necessary, patients could receive one more GLP at weeks 12, 16 or 20 • Week 24 to week 52: sham injections every 4 weeks Patients in the GLP group could receive rescue aflibercept from 6-months

Figure 5: VIBRANT study treatment schedule



AFL = aflibercept; R = randomisation; 2q4 = 2mg every 4 weeks; 2q8 = 2mg every 8 weeks
*There was a 21 day screening period prior to Week 0; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

At any time during the study all study eyes were eligible to receive scatter laser photocoagulation if they developed clinically significant ocular neovascularisation. Note - Scatter laser photocoagulation differs from grid-laser photocoagulation and does not impact visual acuity.

Premature Withdrawal from the Study

A patient could discontinue treatment due to an intercurrent illness, adverse event (AE), treatment failure, protocol violation, administrative and other reasons or by patient, investigator or sponsor request. Patients who withdrew from the study were asked to complete study assessments.

4.3.3 Method of randomisation

Patients were randomised according to a predetermined central randomisation scheme provided by an interactive voice/web response system. They were randomised into the 2 treatment groups in a 1:1 ratio. Randomisation was stratified according to region (Japan and North America) and baseline BCVA (>20/200 and ≤20/200).

4.3.3.1 Masking

Study drug was received, tracked, and prepared by unmasked individuals and all study injections and GLP were performed by an unmasked physician. All other site personnel were masked to treatment assignment, including the physician assessing adverse events, supervising the assessment of efficacy and deciding on the need for rescue treatment (see Table 9). Masked and unmasked roles were assumed for the entire study and switching from an unmasked to a masked role after the first patient was randomised at a site was not permitted. NEI VFQ-25 was administered by masked, certified site personnel and optical coherence tomography, fundus and angiographic images were sent to an independent reading centre and read by masked readers.

In order to maintain masking in the study, sham injections and sham laser were performed throughout the duration of the study. Sham injections were performed with no active drug and without intraocular penetration – in all other aspects the procedures were identical to an intravitreal injection of study drug. The sham laser photocoagulation procedure involved positioning the patient at the laser slit lamp with a contact lens, and following the same process including operating the equipment as for active laser therapy, but with the power on the laser turned ‘off’.

Table 9: Responsibilities of the Masked and Unmasked Personnel

Masked personnel
– Assesses rescue treatment criteria (physician only) – Assesses all AEs, including severity and relationship – Assesses efficacy – Performs ophthalmic examinations at all study visits (except post injection examinations immediately after treatment) – Evaluates all safety, including review of images for safety concerns at the site (except those immediately after intravitreal injection) – Evaluates vital signs; performs physical examinations – Tests refraction and BCVA (no exceptions will be granted) – Checks intraocular pressure pre-dose (bilateral) – Indirect ophthalmoscopy pre-dose (bilateral) – Assesses OCT, FP, and FA – Administers NEI VFQ-25 and EQ-5D questionnaires
Unmasked personnel
– Coordinates randomisation with masked and unmasked physicians – Receipt and accountability of study drug – Prepares sham and study drug – Performs study drug (aflibercept) or sham injection – Performs grid laser photocoagulation or sham laser treatment – Observes safety at the end of the observation period (approximately 30 minutes following study treatment) – Checks intraocular pressure post-dose (study eye) before the end of the approximately 30 minute observation period – Checks indirect ophthalmoscopy post-dose (study eye)

BCVA= best corrected visual acuity; EQ-5D= EuroQoL 5 Dimensions FA= fluorescein angiography; FP= Fundus photography; NEI VFQ-25= National Eye Institute Visual Functioning Questionnaire-25; OCT=optical coherence tomography

4.3.3.2 Inclusion and exclusion criteria

VIBRANT took place between April 2012 and March 2014 in 58 sites from North America (United States [US] and Canada) and Japan. A total of 183 patients were randomised.

The inclusion/exclusion criteria were designed to select patients with baseline characteristics representative of the disease state. Study eligibility criteria are summarised in Table 10. A complete list of all inclusion and exclusion criteria is given in Appendix **Error! Reference source not found.**.

Table 10: Main eligibility criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years old • BRVO or HRVO causing oedema involving the centre of the macula if the occlusion occurred within 12 months. BRVO was defined by the presence of retinal haemorrhages or other biomicroscopic evidence of RVO and a dilated venous system in <2 quadrants of the retina drained by the same vein. HRVO was as an RVO that involved 2 retinal quadrants. [Overall, 1 eye (1.1%) in the aflibercept group and 3 eyes (3.3%) in the laser group had macular oedema after HRVO at baseline.] • BCVA of 73 to 24 letters Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40 - 20/320 Snellen equivalent).	• History of vitreo-retinal surgery or anticipation of such within 12 months or any intraocular surgery within the last 3 months • Reductions in visual acuity from causes other than BRVO • Presence of diabetic macular oedema or retinopathy (>1 microaneurysm outside the area of the vein occlusion), ocular inflammation, or uncontrolled glaucoma (intraocular pressure ≥ 25 mmHg or previous filtration surgery); • Periocular corticosteroid use within the last 3 months • Prior treatment with intraocular corticosteroids or antiangiogenic drugs, scatter or panretinal laser, macular grid laser, or sector laser.

4.3.3.3 Interventions

- Intervention (n=91) :
    - aflibercept 2mg every 4 weeks (2Q4) (day 1 to week 24); Sham grid laser photocoagulation (GLP) treatment on day 1; then,
    - aflibercept 2mg every 8 weeks (2Q8) through week 48 (week 24 to week 52) with sham injections 2Q8 starting week 28.

Aflibercept was supplied in a single use 1mL, glass pre-filled syringe with a snap-off syringe cap. The injection volume was 50µL (0.05ml), administered by intravitreal injection.

The sham kits did not contain drug product or needles. In all other respects, including the same labelling and storage information, they resembled the treatment kit.

The rationale for the choice of dose and regimen for aflibercept was based primarily upon the favourable safety and efficacy profile achieved using the 2Q4 regimen in the pivotal phase 3 studies for wet age-related macular degeneration (wet AMD)

(VIEW 1 and VIEW 2) (29) as well as the pivotal phase 3 studies for central retinal vein occlusion (CRVO)(COPERNICUS and GALILEO) (30-33).

- Comparator (n=92): Macular (grid) laser photocoagulation (GLP) treatment was administered based on the Combined Branch Vein Occlusion Study (CBVOS) protocol (7).

- Laser treatment / sham laser treatment was administered before the aflibercept injection / sham injection.

At any time during the study, patients could receive scatter laser photocoagulation if they developed clinically significant ocular neovascularisation in the study eye. Note that scatter laser photocoagulation does not affect visual acuity.

Dose modification

No dose modification was permitted.

4.3.3.4 Rescue treatment

Rescue treatment could be given, and the treatment schedule adjusted accordingly for any patient meeting at least one rescue treatment criterion (see Table 11 and Table 12). Essentially this meant that patients in the aflibercept group could be given rescue laser treatment at week 36, and patients from the laser group could receive laser rescue at weeks 12, 16 or 20 and aflibercept rescue from week 24.

Table 11: VIBRANT study rescue treatment criteria

1. a >50µm increase in central retinal thickness (CRT) compared with the lowest previous measurement; 2. presence of new or persistent cystic retinal changes, sub-retinal fluid, or persistent diffuse oedema in the central optical coherence tomography subfield; or 3. loss of ≥5 letters compared with the best previous measurement because of BRVO in conjunction with any increase in CRT.

Table 12: VIBRANT study rescue treatment

Laser group rescue treatment	If a patient in the laser group met at least 1 rescue treatment criterion shown in Table 11 at the weeks specified in each bullet point below, the listed action(s) were taken: • Weeks 12, 16, 20: Active laser was given (12 weeks must have passed since last active laser). • Weeks 24 to 48: patients begin aflibercept (a single 2 mg dose 2Q4 for 3 doses, followed by 2Q8 dosing. The final opportunity for dosing was week 48. All patients complete the study at week 52). • Week 36: In addition to aflibercept, sham laser was given.
Aflibercept group rescue treatment	If a patient in the aflibercept treatment group met at least 1 rescue treatment criterion shown in Table 11 at the weeks specified in each bullet point below, the listed action/s were taken: • Weeks 12, 16, 20: Sham laser was given (12 weeks must have passed since last sham laser). • Weeks 24, 28, 32, 40, 44, and 48: No action taken. • Week 36: In addition to aflibercept, active laser was given.

4.3.3.5 Permitted and disallowed concomitant medications

Patients could not receive any medication for BRVO in the study eye, other than study treatment, until they had completed the end of study or early study termination visit.

If a pre-treatment concomitant medication was administered in the study eye e.g. antibiotic, anaesthetic, it was required to be administered for both active and sham treatments.

Any other medication that was considered necessary for the patient's welfare and that was not expected to interfere with the evaluation of the study drug could be given at the investigator's discretion.

Patients could not receive any systemic medications with the intent of treating the study and/or fellow eye during study participation. Systemic anti-angiogenic agents were not permitted during the study.

Fellow eye (non-study eye) - Standard of care treatment could be administered, if necessary, to the fellow eye for diabetic macular oedema (DMO), AMD, CRVO or BRVO involving or threatening the centre of the macula. Bevacizumab was not permitted.

4.3.4 Efficacy outcome measures

Table 13 summarises VIBRANT study endpoints, and when / how each were measured. The primary efficacy outcome measure was the proportion of eyes that gained at least 15 ETDRS letters in BCVA at week 24 from baseline.

Table 13: **VIBRANT trial – primary and key secondary endpoints (24;25)**

Endpoint	**Measure – definition & assessment**	
Primary Endpoint		
Proportion of patients gaining ≥ 15 ETDRS letters at week 24 from baseline	Assessments performed at day 1, week 4 and every 4 weeks thereafter.	The ETDRS 4m protocol (34).
Secondary Endpoints		
Change from baseline in BCVA score at week 24	Assessments performed at day 1, week 4 and every 4 weeks thereafter.	The ETDRS 4m protocol (34).
Change from baseline in central retinal thickness (CRT) at week 24.	Assessments performed at day 1, week 4 and every 4 weeks thereafter.	Assessed by spectral domain optical coherence tomography (OCT) scans, evaluated by an independent central reading centre (Duke Reading Center, Durham, NC).
Vision-related quality of life (QoL): Change from baseline in the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) total score at week 24.	NEI VFQ-25 was administered at baseline, week 12 and 24.	Assessed by masked interviewer before each intravitreal injection. Three of the subscales were measured as additional efficacy endpoints: Near Activities (reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf); Distance Activities (reading street signs or names on stores, and going down stairs, steps, or curbs); and Vision Dependency (the need to stay at home, reliance on others, and the need for help).
Safety: Ocular and non-ocular adverse events (AEs), and serious adverse events (SAEs), vital signs, laboratory measures.	AEs, vital signs and concomitant medications were recorded at each visit i.e. every 4 weeks. Laboratory assessments were performed at baseline, week 12, 24, 36 and 52.	Adverse events were summarised using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0

Additional efficacy variables included:

- Proportion of patients who gained ≥ 15 ETDRS letters in BCVA from baseline to week 52
- Change from baseline in BCVA score at week 52
- Change in CRT from baseline to week 52
- Change from baseline in the NEI VFQ-25 total score at week 52
- Proportion of patients with a decrease in retinal ischaemia and post-baseline retinal perfusion status through week 24 and week 52, as assessed by the reduction in the area of non-perfused retina on fluorescein angiography (FA). Perfused retinas were defined as retinas with <10 disc areas of retinal capillary non-perfusion. Non-perfused retinas were defined as retinas with ≥10 disc areas of retinal capillary non-perfusion.
- Time to first gain of ≥15 letters from baseline, defined as the time of first treatment (active or sham) until the date when a gain of at least 15 letters compared to baseline was reached through week 24 and end of study. Patients who did not have a gain of ≥15 ETDRS letters were censored at the visit date of their last BCVA.
- Time to first confirmed (sustained) gain of ≥15 letters from baseline; a patient was considered to have a confirmed gain at the time the patient first had a gain of ≥ 15 ETDRS letters, which was confirmed by the next scheduled ETDRS measurement through week 24 and end of study. Patients who did not have a confirmed gain of ≥ 15 ETDRS letters were censored at the visit of their second-to-last BCVA measurement.
- Retinal fluid status as assessed by OCT through week 24 and end of study. The status was “dry” if neither intra-retinal fluid nor sub-retinal fluid was present. The status was “not dry” if either intra-retinal fluid or sub-retinal fluid was present. Otherwise, the status was “indeterminate.”
- Change from baseline in the EQ-5D (EuroQoL 5 Dimensions) Questionnaire at week 24 (assessed at baseline, week 12, 24 and 52).
- Change from baseline in scores for NEI VFQ-25 subscales (distance activities, near activities, and visual dependency) at week 24.

Fundus photography (FP) and fluorescein angiography (FA) were performed at baseline and weeks 12, 24, 36 (FP only) and 52. Telephone safety checks also took place ~3 days post-injection (28).

Reliability/ validity/ current use in clinical practice - All efficacy and safety parameters assessed in VIBRANT, and the methods to measure them are standard variables and methods in clinical studies for RVO, and in ophthalmic practice. They are widely used and generally recognised as valid, reliable, accurate and relevant. In addition, all evaluations were in accordance with Good Clinical Practice (GCP) to ensure safety of patients participating in research.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Analysis sets

Efficacy outcome measures were analysed in the full analysis set (Table 14). A per protocol analysis was performed as a supportive analysis at 24 weeks.

Table 14: Definition of all data analysis sets (24;28)

Analysis set	Definition	Number of valid patients in treatment group	
		Aflibercept	**Laser**
Full analysis set (FAS)	All randomised patients who received study treatment and had a baseline and at least 1 post-baseline BCVA assessment. Based on treatment allocated (as randomised).	91 (100%)	90 (97.8%)*
Per protocol set (PPS)	All patients in the FAS except those excluded due to major protocol violations (24 week evaluation only).	90 (98.9%)	85 (92.4%)
Safety analysis set (SAF)	All randomised patients who had received any study medication.	91 (100%)	92 (100%)

* Two patients did not have post-baseline best-corrected visual acuity assessment

Table 15: **Summary of statistical analyses in VIBRANT**

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
VIBRANT	The null hypothesis was that there was no difference between treatment groups in the proportion of BRVO patients at week 24 who gained at least 15 letters in BCVA compared to baseline. The alternative hypothesis was that there was a difference between treatment groups in the proportion of BRVO patients at week 24 who gained at least 15 letters in BCVA compared to baseline. When testing for superiority, H_0 was to be rejected in favour of superiority (H_1), if the two-sided significance level was less than or equal to 0.05.	**Primary efficacy analysis** Primary efficacy variable: proportion of patients gaining ≥ 15 ETDRS letters at week 24 from baseline. The primary analysis was conducted on the FAS. With respect to the primary efficacy endpoint, the 2 groups (aflibercept and laser) were compared using the Cochran-Mantel-Haenszel test with stratification adjustment for geographic region (Japan and North America) and baseline BCVA (letter score of 35 to 73 and 24 to 34 [>20/200 and ≤20/200]) at a 2-sided test level of 5%. A 2-sided 95% Mantel-Haenszel confidence interval (CI) for the difference of proportion adjusted for region and baseline BCVA was calculated using normal approximation. To assess the robustness of the results of the primary analysis, a per-protocol analysis and several sensitivity analyses were performed (see 'Data Management, patient withdrawals column of this table and Table 21). **Secondary efficacy analyses** The main analysis of the secondary	Based on prior studies with anti-VEGF agents and grid laser photocoagulation, the proportion of eyes gaining ≥3 lines (≥15 letters) was estimated to be 55% for the aflibercept group and 30% for the laser group in this study (35;36). Hence, a sample size of 81 eyes per study group was required to ensure 90% power at a 2-sided 5% significance level. Assuming a 10% dropout rate, 90 eyes were needed per treatment group.	Missing data were imputed using the last-observation-carried-forward method. Baseline values were not carried forward (28). **Sensitivity analyses** were performed to address the impact of missing data due to drop-outs: 1) Observed case (OC) analysis: Observed values without any imputation. Performed for all efficacy endpoints. 2) Multiple imputation analysis (primary endpoint only): 1. Imputation - Missing BCVA data were imputed using multiple imputation procedure based on the OC data, that is, the observed BCVA measurements without imputation. First, missing data were imputed to achieve a monotone missing pattern using the Markov Chain Monte Carlo method with number of imputations = 100. Subsequently missing data was imputed by a regression model with number of imputation = 1. 2. Analysis - The responder variable which is the gain of at least 15 letters at week 24 and week 52 from baseline was determined from the complete BCVA data sets. The proportion of responders was analysed using Cochran-Mantel-

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		variables was performed in the FAS. If statistical significance was attained for the primary outcome measure, the secondary efficacy variables were tested with the use of a hierarchical testing procedure to control for multiplicity in the following order: mean change from baseline in (a) BCVA, (b) CRT, and (c) NEI VFQ-25 questionnaire total scores. Between-group differences in the secondary efficacy variables were analysed using 2-way analysis of covariance. The differences in proportions of eyes that gained ≥0, ≥5, ≥10, and ≥30 ETDRS letters (post hoc analysis), lost >0, ≥5, ≥10, and ≥15 ETDRS letters (post hoc analysis), or had retinal perfusion were analysed with the Cochran-Mantel-Haenszel test. All additional efficacy endpoints were analysed descriptively at week 24 and week 52. Safety was analysed descriptively.		Haenszel test with stratification adjustment for region and baseline BCVA category. 3. Pooling - Cochran-Mantel-Haenszel statistic from step 2, under the null hypothesis, has an asymptotic chi-square distribution. This was transformed to standard normal distribution by Wilson-Hilferty transformation. After normalisation, the analysis results from multiple imputed data sets were combined into 1 overall result based on Rubin's rules using the Statistical Analysis Software (SAS) MIANALYZE procedure.

4.4.1 Subgroup analyses

Subgroup analyses were performed on the FAS population using descriptive statistics for primary and secondary efficacy endpoints with LOCF and OC methods based on the following efficacy subgroup variables:

- Gender
- Age: <40y; ≥40 to <65y; ≥65y to <75y; ≥75y
- Race: Asian, or Non-Asian (White, Black or African American, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other)
- Ethnicity: Hispanic or Latino (no/yes)
- Smoking history (Never, Former, Current)
- Anti-drug antibody (ADA) response (positive or negative)
- Geographic region: Japan or North America
- Baseline visual acuity (VA) category > 20/200 (35 to 73 letters) or ≤ 20/200 (24 to 34 letters)
- Baseline retinal perfusion status (perfused or non-perfused).

Subgroups considered for safety analyses only:

- Medical history of hypertension
- Medical history of cerebrovascular disease
- Medical history of ischaemic heart disease
- Renal impairment (normal / mild: >50 to 80 mL/min / Moderate: >30 to 50 mL/min / Severe: ≤30 mL/min or requiring dialysis)
- Hepatic impairment

4.5 Participant flow in VIBRANT

4.5.1 Disposition of study patients

The patient disposition for the VIBRANT study is shown in Figure 6.

Figure 6: Patient Disposition in VIBRANT

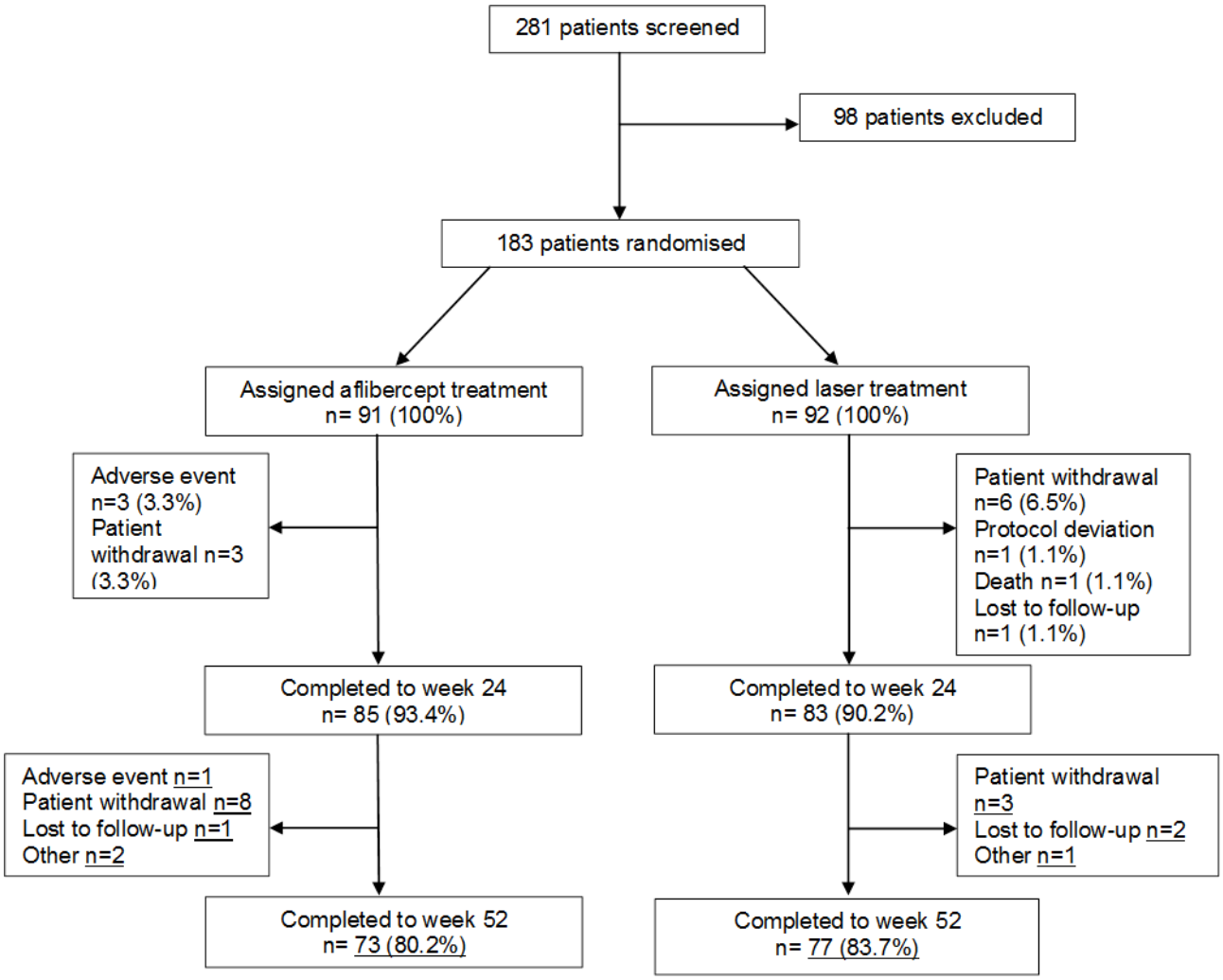


Table 16 summarises the reasons for discontinuation of treatment during the study.

One hundred and sixty eight patients (91.8%) of the 183 randomised patients completed the study up to 24 weeks (primary endpoint analysis) and 150 patients (82%) completed the entire 52 weeks of study. The primary reason for premature discontinuation from the study in the laser group was 'withdrawal by patient'. From week 24, 67 patients in the laser group received aflibercept rescue therapy. There were no premature discontinuations from the study due to adverse events in the laser group even when many patients were initiated

on aflibercept rescue therapy. The primary reasons in the aflibercept group were 'withdrawal by patient' and 'adverse events'.

Of the 4 patients in the aflibercept group with adverse events (AEs) leading to premature discontinuation of study participation, 2 patients had ocular events in the study eye (IOP increased, traumatic cataract), and one patient had metastatic breast cancer. The fourth patient had two AEs (central pelvic abscess and small bowel obstruction).

Table 16: **Primary reasons for premature discontinuation in the VIBRANT study (24;25;27)**

	Aflibercept N=91	**Laser N=92**
Completed week 24, n (%)	**85 (93.4%)**	**83 (90.2%)**
Discontinuations before week 24, n (%)	6 (6.6%)	9 (9.8%)
Adverse event	3 (3.3%)	0
Withdrawal by patient	3 (3.3%)	6 (6.5%)
Protocol deviation	0	1 (1.1%)
Death	0	1 (1.1%)
Lost to follow-up	0	1 (1.1%)
Other	0	0
	Aflibercept [a] N=91	**Laser (+aflibercept) [b] N=92**
Completed week 52, n (%)	**73 (80.2%)**	**77 (83.7%)**
Discontinuations during entire study, n (%)	18 (19.8%)	15 (16.3%)
Adverse event	4 (4.4%)	0
Withdrawal by patient	11 (12.1%)	9 (9.8%)
Protocol deviation	0	1 (1.1%)
Death	0	1 (1.1%)
Lost to follow-up	1 (1.1%)	3 (3.3%)
Other	2 (2.2%)	1 (1.1%)

[a] 9 patients in the aflibercept group received laser rescue treatment at week 36
[b] 67 patients received aflibercept rescue treatment from week 24

4.5.2 Patient baseline characteristics

Demographics and baseline characteristics of patients were similar in both treatment groups (Table 17).

More than half of patients were male (98/181, 54%). The total population ranged in age from 42 to 94 years, with a mean age of 65.5 years. Most patients were white (132/181, 72.9%).

Baseline BCVA in the study eye was >20/200 in the majority (92.8%) of patients. Retinal perfusion status was considered "perfused" in 64.6% of patients. The mean number of days since BRVO diagnosis for the study population was 42.8 days. At baseline, 4 patients had HRVO: 3 in the GLP group and 1 in the aflibercept group.

Table 17: Patient baseline demographic and disease characteristics (FAS) (24)

	Aflibercept n=91	Laser N=90
Mean age, years (SD)	67.0 (10.4)	63.9 (11.4)
Women, n (%)	47 (51.6)	36.0 (40.0)
Race, n (%)		
White	70 (76.9)	62 (68.9)
Black or African American	8 (8.8)	11 (12.2)
Asian	12 (13.2)	11 (12.2)
Other*	1 (1.1)	6 (6.7)
Geographic region, n (%)		
North America	80 (87.9)	81 (90.0)
Japan	11 (12.1)	9 (10.0)
BCVA		
Mean, letters (SD)	58.6 (11.4)	57.7 (11.3)
>20/200 (35-73 letters), n (%)	85 (93.4)	83 (92.2)
<20/200 (24-34 letters), n (%)	6 (6.6)	7 (7.8)
Retinal perfusion status, n (%)		
Perfused†	55 (60.4)	62 (68.9)
Nonperfused‡	20 (22.0)	16 (17.8)
Cannot grade	16 (17.6)	10 (11.1)
Missing	0	2 (2.2)
Mean central retinal thickness, µm (SD)	558.9 (185.9)	553.5 (188.1)
Mean intraocular pressure, mmHg (SD)	14.6 (3.1)	14.9 (3.0)
Time since BRVO diagnosis		
Mean, days (SD)	42.4 (43.4)	43.1 (38.8)
<3 months, n (%)	75 (82.4)	72 (80.0)
≥3 months, n (%)	7 (7.7)	11 (12.2)
Missing, n (%)	9 (9.9)	7 (7.8)
NEI VFQ-25 score, mean (SD)		
Total	77.8 (15.4)	75.6 (16.4)
Near activities	70.0 (21.4)	69.7 (18.4)
Distance activities	76.9 (19.8)	76.3 (20.0)
Vision dependency	86.8 (21.6)	81.9 (24.5)

* Not reported for the laser group and native Hawaiian or other Pacific Islander for the aflibercept group.
† Fewer than 10 disc areas of retinal non-perfusion.
‡ Ten or more disc areas of retinal non-perfusion.

4.6 Quality assessment of the relevant randomised controlled trials

Table 18 presents a quality assessment of VIBRANT, which was completed to the highest standard with adequate randomisation and blinding procedures. Please see **Error! Reference source not found.** in Appendix **Error! Reference source not found.** for a detailed quality assessment.

Table 18: Quality assessment results for VIBRANT

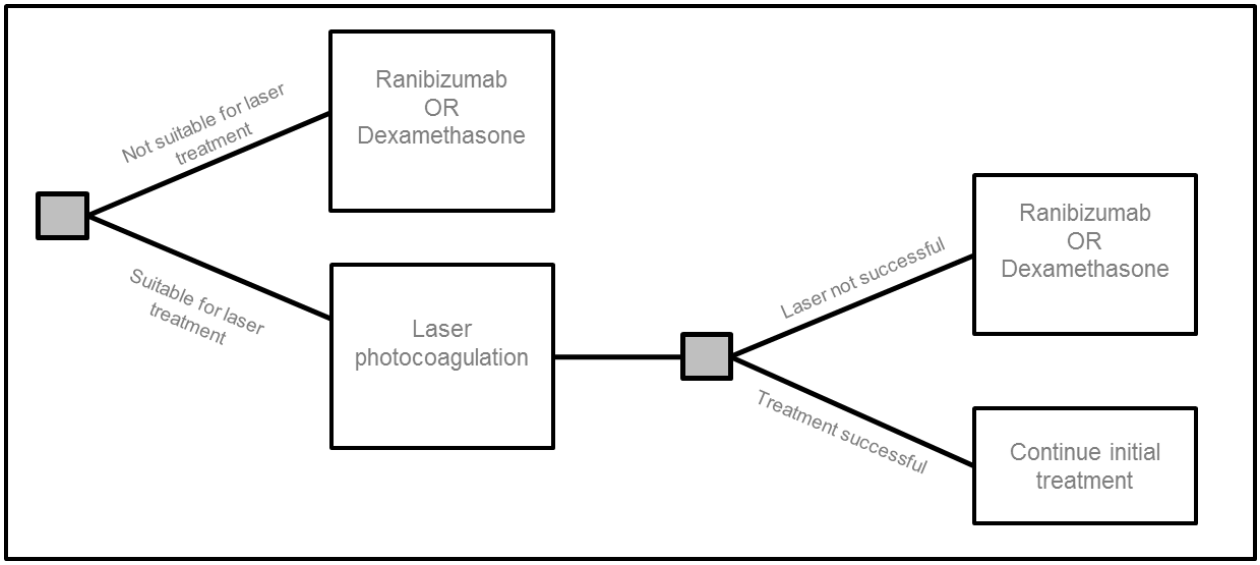
Trial number (acronym)	VIBRANT study (NCT01521559)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No, Full analysis sets were reported (includes all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment). The aflibercept FAS included all 91 randomised patients (100%) and the laser FAS included 90 of the 92 randomised patients (97.8%). Sensitivity analyses included FAS observed values.

4.6.1.1 Comparability of the VIBRANT study to clinical practice in England and Wales

As described in section 3.3.3 and section 3.6.2 there are two main treatment pathways in England and Wales i.e. there is a mix of treatment according to NICEs guidance (Figure 7) and the pathway recommended by the Royal College of Ophthalmology. The two arms of the VIBRANT study are well designed to provide data on the efficacy and safety of

aflibercept 1) if used as a second-line treatment option (the current position for newer treatments as per NICE guidance) and 2) if used as a first-line treatment option (the current recommendation for newer agents from the Royal College of Ophthalmology.

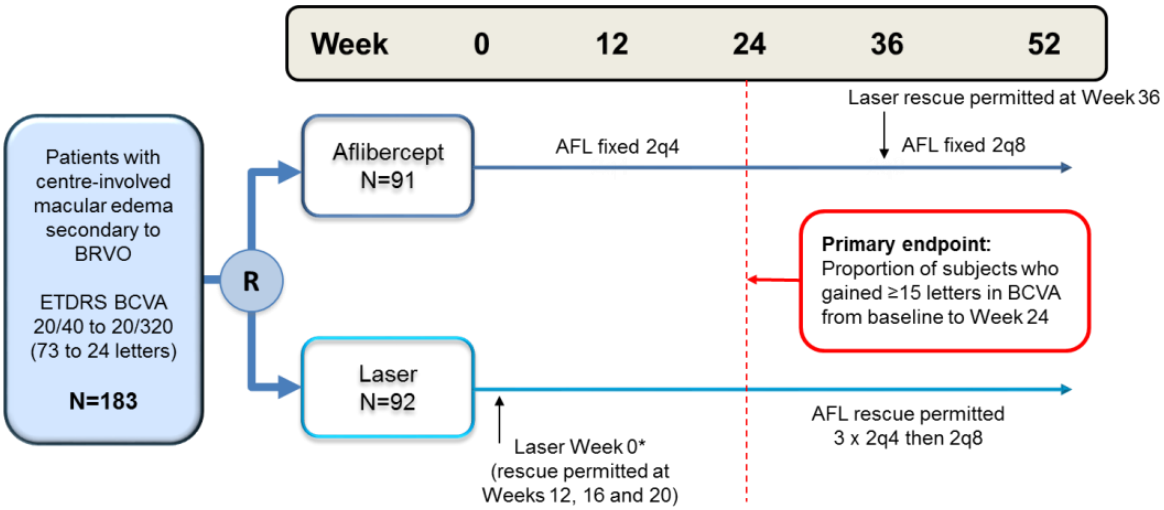
Figure 7. NICE treatment pathway



Aflibercept as a second-line treatment option (current recommendation for newer treatments (TA283, TA 229)

In the VIBRANT study, patients randomised to laser who do not obtain sufficient benefit (rescue criteria from VIBRANT are outlined in Table 11) were switched to second-line treatment with aflibercept (see Figure 8). This design therefore provides evidence on the efficacy of aflibercept as it could be used in clinical practice. There is a limitation in the design of the trial in that no comparative data for patients switching from laser to ranibizumab or dexamethasone is available. However this limitation has been overcome by conducting an indirect comparison for the purposes of the cost-effectiveness analysis (see section 4.10).

Figure 8. VIBRANT trial design



Treatment pathway as recommended by the Royal College of Ophthalmology (RCO)

The RCO recommends the newer treatments as first-line options and laser photocoagulation is recommended if other treatments are unsuccessful or unavailable. In this respect the aflibercept arm of the VIBRANT study provides evidence for aflibercept as a first-line treatment.

In the VIBRANT study, patients who did not achieve sufficient benefit on aflibercept had laser photocoagulation at week 36. These patients received a further two aflibercept injections. There are a couple of limitations in the design of the trial in that laser was initiated at week 36, in clinical practice this may occur earlier. In addition, whereas patients requiring laser photocoagulation in the VIBRANT trial received a couple more aflibercept injections, in clinical practice this treatment might be stopped straight away.

4.7 Clinical effectiveness results of VIBRANT

Efficacy Summary

The primary endpoint in VIBRANT was the proportion of patients gaining ≥15 letters from baseline to week 24. Secondary endpoints included the change from baseline in BCVA score at week 24 and the change from baseline in central retinal thickness (CRT). Vision-related quality of life was also assessed. In the second phase of the study the efficacy of a reduced frequency of aflibercept injections was assessed.

Baseline to week 24 (phase I)

Primary endpoint

At week 24 significantly more patients receiving aflibercept versus grid laser photocoagulation had gained 15 letters or more in BCVA from baseline i.e. 52.7% patients vs. 26.7%, p=0.0003.

Secondary endpoints

The mean improvement from baseline BCVA at week 24 was 17.0 letters in the aflibercept group and 6.9 letters in the GLP group (P<0.0001). The mean reduction in CRT from baseline at week 24 was 280.5 µm in the aflibercept group and 128.0 µm the GLP group. The adjusted difference between the groups was -148.6 (95%CI: -179.8 to -117.4, p<0.0001).

Both groups experienced a clinically relevant improvement vision-related quality of life, as measured by the mean NEI VFQ-25 (National Eye Institute Visual Functioning Questionnaire-25) total score at week 24. Although the mean score was higher in the aflibercept group than the GLP group, the difference was not statistically significant (p=0.083).

Efficacy results in all evaluable subgroups (e.g. age, gender, race, region, and baseline disease characteristics [BCVA, retinal perfusion status] were consistent with the results in the overall population.

Week 24 to week 52 (phase II)

At week 24 the frequency of aflibercept injections in the aflibercept group was reduced to every 8 weeks. Rescue treatment according to pre-specified criteria could be given to all patients as required, for the remainder of the study. This resulted in 67 patients in the GLP group receiving rescue aflibercept treatment and nine patients in the aflibercept group receiving an active GLP treatment in the study eye. Continued aflibercept treatment in the aflibercept group maintained the beneficial effects on visual and anatomic variables. The initiation of aflibercept rescue treatment in eligible patients in the laser group at week 24 produced beneficial effects in terms of gain in letters and the proportion of patients gaining 15 or more letters, although the size of the improvements were smaller than in the aflibercept group where aflibercept treatment had been initiated earlier (i.e. from baseline).

Table 19 shows the location of the efficacy results as outlined in section 4.3.4.

Table 19: Efficacy outcome measures – location in document

Efficacy Outcome Measure	Location
Primary outcome (proportion gaining ≥ 15 letters) at week 24	Table 20 - page 70
- sensitivity analysis of primary endpoint	Table 21-page 71
- subgroup analysis of primary endpoint	Figure 14,Table 28 – Pages 82,83
Secondary efficacy endpoints (baseline to w24):	
- Change in BCVA	Table 22 page 72; Figure 9 - page 73
- Change in CRT	Table 22 page 72; Figure 10 – page 74
- Change in NEI VFQ 25 total score	Table 22 page 72; Figure 11 – page 75
- subgroup analysis of mean change in BCVA	Figure 15 – page 84
- subgroup analysis of secondary endpoints by perfusion status & BCVA category	Table 29 - page 86
- subgroup analysis of mean change in CRT	Figure 16 – page 85
Additional efficacy endpoints	
- change in NEI VFQ 25 subscales to w24	Page 75
- proportion gaining ≥ 15 letters to w52	Table 25 – page 78
- change in BCVA letters to w52	Table 26 – page 79; Figure 12 – page 79
- change in CRT to w52	Table 27 – page 80; Figure 13– page 81
- Retinal perfusion and retinal ischaemia status at w24 and w 52	Appendix **Error! Reference source not found.**
- time to first gain of ≥ 15 letters and time to first sustained gain of ≥ 15 letters at w24 and w52	Appendix **Error! Reference source not found.**
- retinal fluid status as assessed by OCT to w24 and w52	Appendix **Error! Reference source not found.**
- change from baseline in EQ-5D questionnaire at w24 and 52	Appendix **Error! Reference source not found.**
- change in NEI VFQ 25 total score to w52	Appendix **Error! Reference source not found.**
- change in NEI VFQ 25 subscales to w52	Appendix **Error! Reference source not found.**

4.7.1 Primary outcome: proportion of patients gaining ≥ 15 ETDRS letters in BCVA at week 24 from baseline

Aflibercept 2Q4 was shown to be superior to grid laser photocoagulation treatment for the primary endpoint. The difference in the proportion of patients with at least a 15-letter vision gain between the aflibercept and laser groups was 26.1% (adjusted difference 26.6% [95% confidence interval (CI) 13-40%; p=0.0003] (Table 20).

Table 20: Proportion of patients gaining ≥15 letters in BCVA at w24 from baseline (FAS, LOCF) (8;24)

	Laser (N=90) n (%)	**Aflibercept (N=91) n (%)**
Week 24 Patients who gained at least 15 letters in BCVA	24 (26.7)	48 (52.7)
Difference (aflibercept vs. laser)		26.1%
Adjusted difference (%) (95% CI) [a]		26.6 (13.0, 40.1)
p-value [b]		0.0003

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

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

These findings were confirmed by all supportive/sensitivity analyses (PPS, OC, multiple imputation (Table 21)

Table 21: Sensitivity analyses of the proportion of patients gaining ≥15 letters in BCVA at week 24 from baseline (27)

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

LOCF=last observation carried forward method (used to impute missing data)
[a] Difference was aflibercept group minus laser [+ aflibercept] group; confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200).
[b] P-value using 2-sided Cochran-Mantel-Haenszel test adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200).
[c] Calculated from the average of 100-multiple imputed data i.e.mean number of responses in a 100 imputed datasets
[d] Calculated using Mantel-Haenszel weighting scheme adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200) for each imputed data, then obtained the average of the results.
[e] Calculated from CMH test adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤20/200 and BCVA >20/200) for each imputed data, then calculated the p-value after Wilson Hilferty transformation.

4.7.2 Secondary Efficacy endpoints (baseline to week 24)

Results of the hierarchical testing procedure for the three key secondary efficacy variables are shown in Table 22 (Endpoints were tested in the order they are presented in the table).

In addition to the proportion of patients gaining ≥15 letters in BCVA between baseline and week 24, statistical significance was formally achieved for the change in the number of BCVA letters read, and also the change in CRT. Thus, key visual acuity and anatomic secondary efficacy analyses support the conclusion that treatment with 2 mg aflibercept once every 4 weeks provides greater, clinically meaningful efficacy at week 24 compared to laser treatment. The difference in the change in NEI-VFQ-25 total score for aflibercept and laser groups was not statistically significant at 24 weeks.

Table 22: Secondary efficacy variables – Changes from baseline to weeks 24 in VIBRANT (FAS; LOCF) (8;24)

	Week 24	
	Laser (N=90) n (%)	**Aflibercept (n=91) n (%)**
Change in BCVA (ETDRS letter score)		
Mean change (± SD)	6.9 (± 12.91)	17.0 (± 11.88)
LS mean change in BCVA	3.2	13.7
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [c]		10.5 (7.1, 14.0)
p-value [c]		<0.0001
Change in CRT (by OCT, in µm)		
Mean change (± SD)	-128.0 (± 195.02)	-280.5 (± 189.7)
LS mean change in CRT	-98.9	-247.5
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [c]		-148.6 (-179.8, -117.4)
p-value [c]		<0.0001
Change in NEI-VFQ-25 total score		
Mean change (± SD)	6.3 (± 12.341)	7.7 (± 11.081)
LS mean change in NEI-VFQ-25 total score	2.7	5.3
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [c]		2.6 (-0.3, 5.5)
p-value [c]		0.0833

ANCOVA = analysis of covariance; BCVA = best corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; LOCF = last observation carried forward; LS = least squares; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire 25; OCT = optical coherence tomography; SD = standard deviation;

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

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

[c] Difference was aflibercept group minus laser [+ aflibercept] group. Point estimate, 95% CI and p value were based on an ANCOVA model with baseline measurement as covariate and treatment group, region, and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200) as fixed factors.

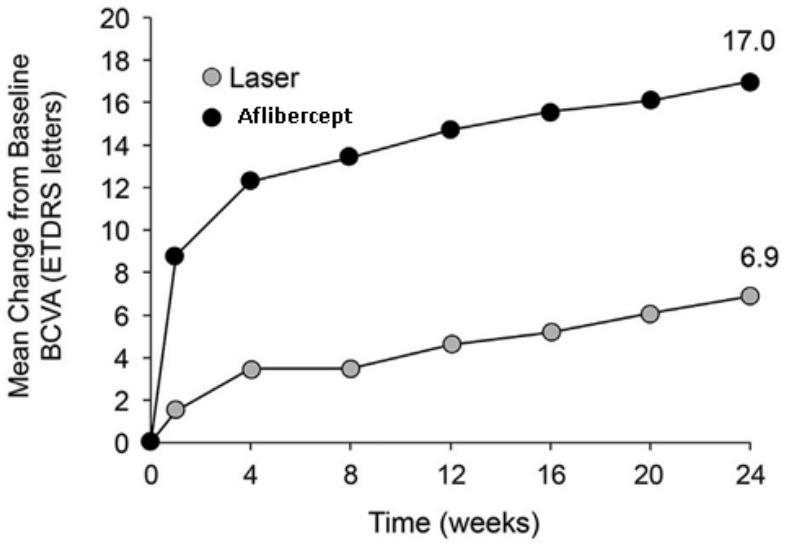
Note: A hierarchical testing procedure controlled the week 24 analyses for multiplicity, ordered as shown. Aflibercept administered as 2 mg every 4 weeks through week 24. Laser treatment administered on day 1; rescue laser treatment possible after week 12. Last observation carried forward (LOCF) method was used to impute missing data.

Change in BCVA (ETDRS letter score) from baseline to week 24 (8;24)

The mean change from baseline in BCVA in the aflibercept group compared with the laser group was 17.0 versus 6.9 ETDRS letters (P < 0.0001) at week 24, respectively (Table 22). The aflibercept group demonstrated a robust and rapid increase in BCVA, from the first post-baseline measurement at week 1 and continuing through week 24. At week 24, improvement from baseline for BCVA was observed in both dose groups; however, the magnitude of increase in the aflibercept group for mean change and least squares (LS) mean change in BCVA score from baseline to week 24 (17.0 and 13.7 letters, respectively) greatly exceeded that of the laser group (6.9 and 3.2 letters, respectively). The difference in mean change BCVA score between the aflibercept and laser groups by treatment, adjusted by region and baseline BCVA score, was 10.5 (95% CI=7.1 to 14.0, p<0.0001). A

sensitivity analysis of the change from baseline in BCVA score at week 24 performed on the FAS using OC data demonstrated similar results to those in the FAS LOCF.

Figure 9: Mean change from baseline in BCVA (ETDRS letter score) to week 24 (FAS; LOCF) (24)



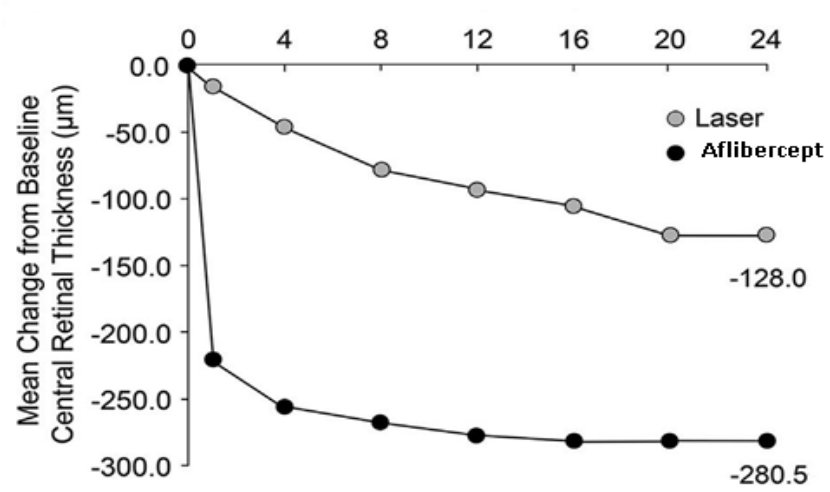
BCVA=Best Corrected Visual Acuity;
Aflibercept group: aflibercept 2 mg every 4 weeks through week 24.
Laser group: laser treatment administered on day 1; rescue laser treatment possible after week 12.

4.7.3 Change in Central Retinal Thickness (CRT) from Baseline to week 24 (8;24)

The mean reduction from baseline CRT in the aflibercept and laser groups was 280.5 versus 128.0 µm ($P < 0.0001$) at week 24, respectively. The changes observed in CRT were consistent with the improvements seen in visual acuity variables. Aflibercept treatment achieved a robust early reduction in CRT, which was seen at the first post-baseline measurement at week 1 and which was maintained through week 24. At week 24, reductions in CRT were apparent in both treatment groups, however the magnitude of the decrease in the aflibercept group greatly exceeded that in the laser group. The difference in CRT reduction between the aflibercept and GLP groups by treatment, adjusted by region and baseline BCVA score, was -148.6 (95% CI= -179.8 to -117.4, $p<0.0001$).

All supportive analyses conducted to assess the robustness of these results confirmed the findings of the main analysis at week 24.

Figure 10: Mean change from baseline in CRT up to week 24 (FAS; LOCF)

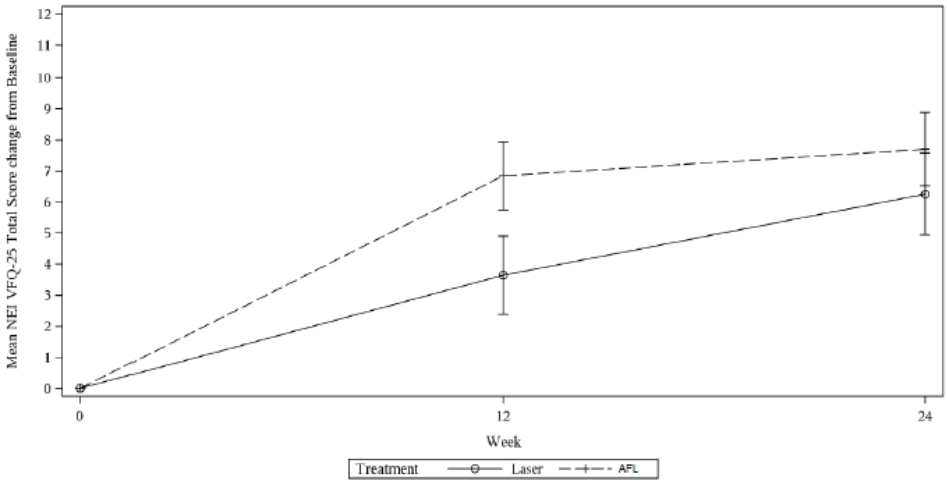


CRT=central retinal thickness;
Aflibercept group: Aflibercept 2 mg every 4 weeks through week 24.
Laser group: laser treatment administered on day 1; rescue laser treatment possible after week 12.

4.7.4 Change from Baseline in National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) Total Score to week 24 (8;24)

At week 24, the mean change from baseline in the NEI-VFQ-25 total score showed clinically meaningful improvements in both treatment groups and was slightly higher in the aflibercept group compared to the laser group (7.7 vs. 6.3, respectively). The difference in the change from baseline in NEI VFQ-25 total score between the aflibercept and laser groups by treatment, adjusted by region and baseline BCVA score, was 2.6 (95% CI= -0.3 to 5.5, p=0.0833), which was not a statistically significant difference. In the VIBRANT study the worst-seeing eye was the study eye in 98% of patients. As the NEI VFQ-25 score is correlated most closely with vision in the better-seeing eye this result is not unexpected.

Figure 11: Mean (SE) Change from Baseline in the NEI-VFQ-25 Questionnaire Total Score through Week 52 (FAS; LOCF) (27)



NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire 25; AFL = aflibercept.
Note: Last observation carried forward (LOCF) method was used to impute missing data.

4.7.5 Additional Efficacy Endpoints

Additional efficacy endpoints that are directly related to the key primary and secondary outcomes are presented below. Other additional endpoints are available in Appendix **Error! Reference source not found.**. Table 19 shows the location of the endpoints presented.

4.7.6 Change from baseline to week 24 in scores for National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) subscales (24)

Overall, differences between treatment groups were seen for Distance Activities and for Near Activities but not for Visual Dependency.

In the aflibercept and laser groups, the mean change in subscale scores from baseline to week 24 was 11.2 versus 4.3 for near activities (P = 0.0032), 9.6 versus 4.4 for distance activities (P = 0.0047), and 4.7 versus 6.9 for visual dependency (P = 0.9276), respectively.

4.7.7 Results at Week 52

The efficacy achieved at week 24 in the aflibercept group was generally maintained through week 52, even with the treatment interval increasing from monthly to every 8 weeks during this time period.

Eligible patients (n=67 [74%]) in the laser + aflibercept group benefited from the start of aflibercept rescue treatment from week 24. Between weeks 24 and 52, there was improvement in this group. Compared with the 26.7% of eyes that gained ≥15 in letter score between baseline and week 24, a total of 41.1% gained ≥15 in letter score between baseline and week 52. The mean change from baseline BCVA letter score was 12.2 at week 52 compared with 6.9 at week 24. Despite the substantial visual gains between weeks 24 and 52, visual outcomes in the laser/aflibercept group were statistically inferior to those in the aflibercept group at week 52, suggesting that early treatment after presentation of macular oedema after BRVO might be important for optimal visual outcomes.

4.7.8 Proportion of patients gaining ≥ 15 ETDRS letters in BCVA from baseline to week 52

Measurement of the primary endpoint at week 52 was an additional efficacy endpoint in the VIBRANT study, in order to explore the longer term effect of aflibercept treatment and adjustment of its administration from every 4 weeks to every 8 weeks from week 52. From week 24, patients in the laser group could receive aflibercept as a rescue treatment if they fulfilled at least one of the pre-specified rescue treatment criteria (see Table 11). Sixty seven patients (74.4%) from the laser group received aflibercept rescue treatment between weeks 24 and 52. Patients in aflibercept group could receive laser rescue treatment at week 36 if they fulfilled at least one of the pre-specified rescue treatment criteria. Nine patients from the aflibercept group received laser rescue treatment (see Table 23 and Table 24).

Table 23. Proportion of aflibercept patients requiring rescue laser

	N=91
>50µm increase in CRT on OCT compared to the lowest previous measurement	[redacted]
New or persistent cystic retinal changes or sub-retinal fluid on OCT or persistent diffuse edema in the central subfield on OCT	[redacted]
Loss of 5 or more letters from the best previous measurement due to BRVO in conjunction with any increase in retinal thickness in the central subfield on OCT from the best previous measurement	[redacted]
Total	**9 (10%)**

Table 24. Proportion of laser patients requiring rescue aflibercept

	N=90
>50µm increase in CRT on OCT compared to the lowest previous measurement	[redacted]
New or persistent cystic retinal changes or sub-retinal fluid on OCT or persistent diffuse edema in the central subfield on OCT	[redacted]
Loss of 5 or more letters from the best previous measurement due to BRVO in conjunction with any increase in retinal thickness in the central subfield on OCT from the best previous measurement	[redacted]
Total	**67 (74%)**

At week 52, the proportion of patients who had gained at least 15 letters in BCVA was 57.1% (52/91) in the aflibercept group versus 41.1% (37/90) in the laser + aflibercept group (adjusted difference 16%, nominal p=0.0296), demonstrating the superiority of administration of aflibercept starting from baseline when compared with laser plus the potential addition of aflibercept for the second half of the study. The visual acuity improvement observed in the aflibercept group at week 24 was maintained, even after reducing the treatment frequency to once every 8 weeks between week 24 and week 48. All supportive analyses conducted to assess the robustness of these results at week 52 confirmed the findings of the main analysis.

Table 25: Proportion of patients gaining ≥15 letters in BCVA at weeks 24 and 52 from baseline (FAS, LOCF) (8;24)

	Laser (N=90) n (%)	Aflibercept (n=91) n (%)
Week 24		
Patients who gained at least 15 letters in BCVA	24 (26.7)	48 (52.7)
Difference (aflibercept vs. laser)		26.1%
Adjusted difference (%) (95% CI) [a]		26.6 (13.0, 40.1)
p-value [b]		0.0003
Week 52 (Additional efficacy endpoint)	**Laser + aflibercept**	**Aflibercept**
Patients who gained at least 15 letters in BCVA	37 (41.1)	52 (57.1)
Difference (aflibercept vs. laser) (%)		16.0
Adjusted difference (%) (95% CI) [a]		16.2 (2.0, 30.5)
p-value [b]		0.0296 (nominal)

[a] Difference was aflibercept group minus laser [+ aflibercept] group; confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200).
[b] P-value using 2-sided Cochran-Mantel-Haenszel test adjusted by regions (Japan vs. North America) and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200).

4.7.9 Change from baseline in BCVA (ETDRS letter score) at week 52 (8;25;26)

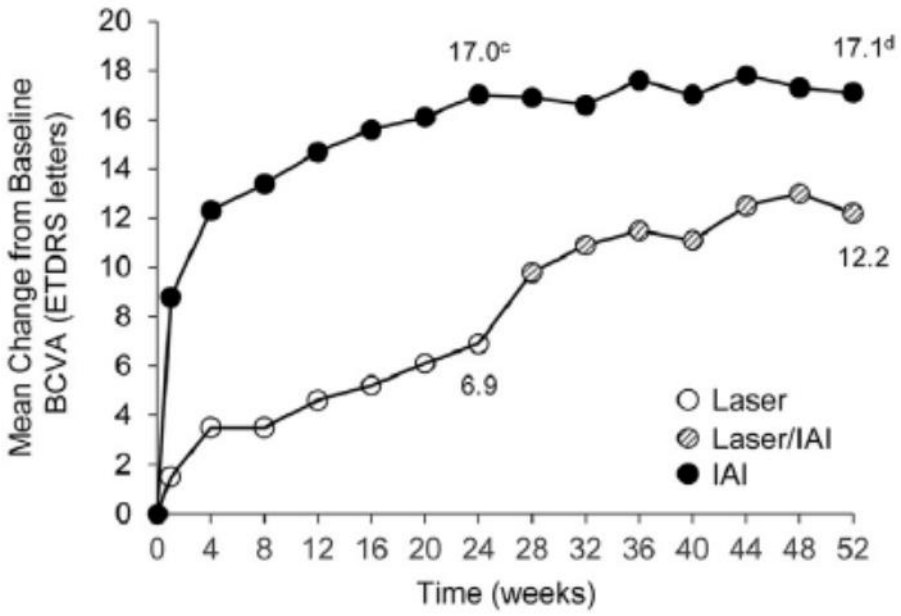
At week 52, improvement from baseline for BCVA had occurred in both dose groups; however, the magnitude of increase in the aflibercept group for mean change and least squares (LS) mean change in BCVA score from baseline to week 52 (17.1 and 12.4 letters, respectively) was higher than that of the Laser + aflibercept group (12.2 and 7.1 letters, respectively). The difference in mean change in BCVA score between the aflibercept and laser + aflibercept groups by treatment, adjusted by region and baseline BCVA, was 5.2 (95% CI=1.7 to 8.7, p=0.0035) (Table 26). Patients in the Laser + aflibercept group who were eligible for rescue treatment with aflibercept starting at week 24 gained 5.3 letters (mean change) in BCVA from week 24 to week 52. Mean changes (with standard error [SE]) over time through Week 52 are visually depicted in Figure 12.

Table 26: Change in BCVA letter score from baseline to week 52 (FAS, LOCF) (8;24;25;27)

	Laser (N=90) n (%)	Aflibercept (n=91) n (%)
Week 24		
Mean change (± SD)	6.9 (± 12.91)	17.0 (± 11.88)
LS mean change in BCVA	3.2	13.7
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [a]		10.5 (7.1, 14.0)
p-value [a]		<0.0001
Week 52 (Additional efficacy endpoint)	**Laser + aflibercept**	**Aflibercept**
Mean change (± SD)	12.2 (± 11.94)	17.1 (± 13.07)
LS mean change in BCVA	7.1	12.4
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [a]		5.2 (1.7, 8.7)
p-value [a]		0.0035 (nominal)

ANCOVA = analysis of covariance; BCVA = best corrected visual acuity; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; SD = standard deviation;
[a] Difference was aflibercept group minus laser [+ aflibercept] group. Point estimate, 95% CI and p value were based on an ANCOVA model with baseline measurement as covariate and treatment group, region, and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200) as fixed factors.

Figure 12: Mean change from baseline in BCVA (ETDRS letter score) up to week 52 (FAS; LOCF) (25)



BCVA=Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study;
IAI: aflibercept group, aflibercept 2 mg every 4 weeks through week 24, then every 8 weeks through week 48.
Laser/IAI: laser treatment administered on day 1; rescue laser treatment possible after week 12 and aflibercept (IAI) rescue treatment (administered in 67 of 90 patients) possible after week 24.
[c] P < 0.0001 vs. laser group
[d] P = 0.0035 vs. laser group

4.7.10 Change in Central Retinal Thickness (CRT) from Baseline to week 52

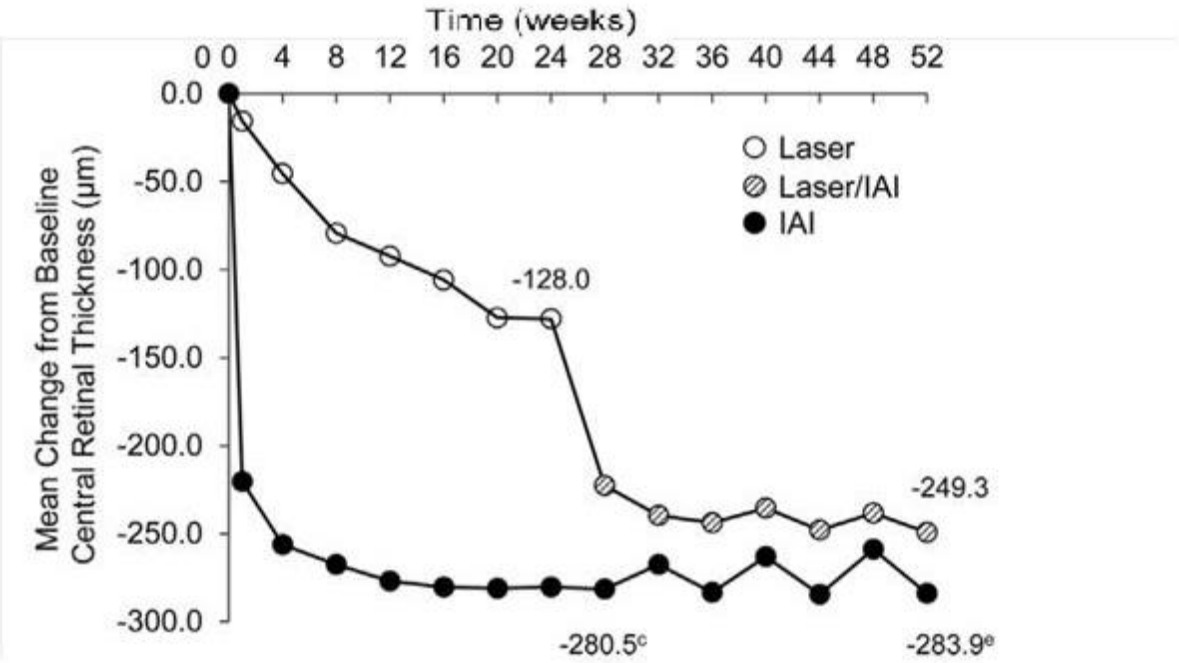
At week 52 reductions in CRT were similar in both dose groups with the aflibercept group showing a mean change of -283.9 µm and a LS mean change of -243.2 µm and the Laser + aflibercept group showing a mean change of -249.3 µm and a LS mean change of -213.7 µm (Table 27). After the start of rescue aflibercept treatment in eligible patients in the Laser + aflibercept group beginning at week 24, a robust early reduction in CRT was seen that was similar to the one observed at week 1 in the aflibercept group.

Table 27: Change in CRT (by OCT, in µm) from baseline to week 52 (FAS, LOCF) (8;24;25;27)

	Laser (N=90) n (%)	**Aflibercept (n=91) n (%)**
Week 24		
Mean change (± SD)	-128.0 (± 195.02)	-280.5 (± 189.7)
LS mean change in BCVA	-98.9	-247.5
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [a]		-148.6 (-179.8, -117.4)
p-value [a]		<0.0001
Week 52 (Additional efficacy endpoint)	**Laser + aflibercept**	**Aflibercept**
Mean change (± SD)	-249.3 (± 189.8)	-283.9 (± 189.1)
LS mean change in BCVA	-213.7	-243.2
Difference in LS mean vs. Laser [+aflibercept] (95% CI) [a]		-29.5 (-54.7, -4.4)
p-value [a]		0.0218

ANCOVA = analysis of covariance; CI = confidence interval; CRT = central retinal thickness; LOCF = last observation carried forward; LS = least squares; OCT = optical coherence tomography; SD = standard deviation;
[c] Difference was aflibercept group minus laser [+ aflibercept] group. Point estimate, 95% CI and p value were based on an ANCOVA model with baseline measurement as covariate and treatment group, region, and baseline BCVA (BCVA ≤ 20/200 and BCVA > 20/200) as fixed factors.

Figure 13: Mean change from baseline in CRT up to week 52 (FAS; LOCF) (25)



IAI: aflibercept group, aflibercept 2 mg every 4 weeks through week 24, then every 8 weeks through week 48. Laser/IAI: laser treatment administered on day 1; rescue laser treatment possible after week 12 and aflibercept (IAI) rescue treatment (administered in 67 of 90 patients) possible after week 24.
[c] P < 0.0001 vs. laser group
[e] P = 0.0218 vs. laser group

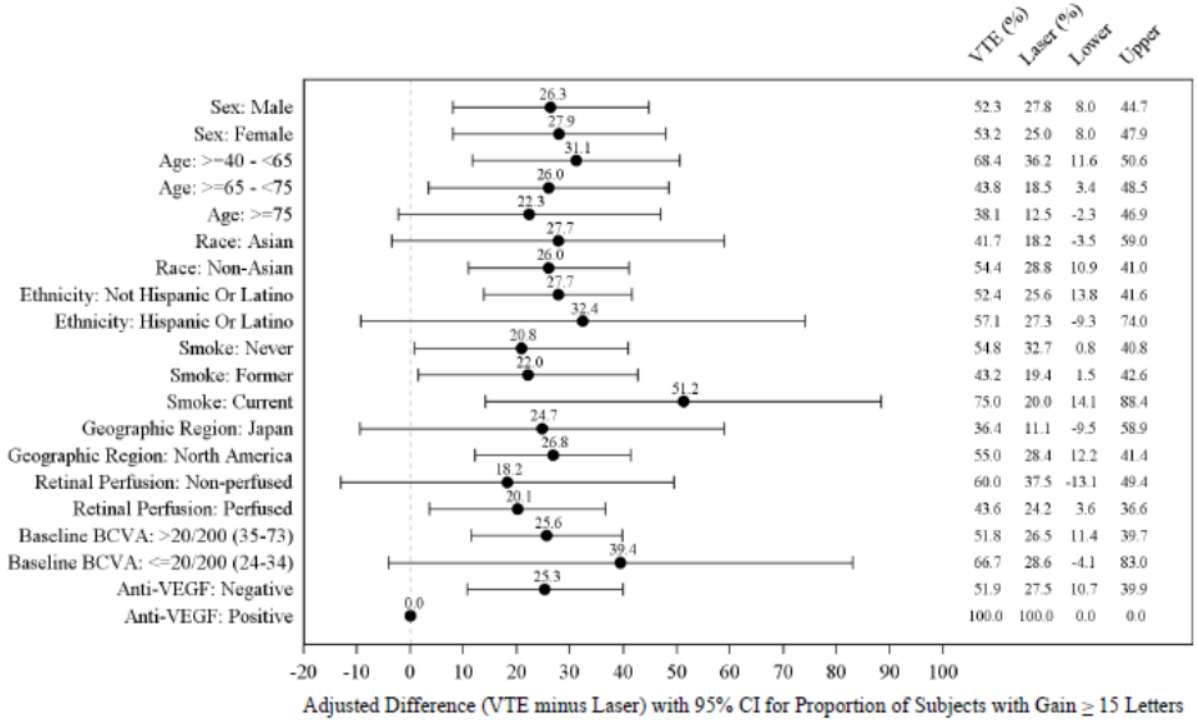
4.8 Subgroup analysis

Subgroup analyses were carried out to assess whether the effectiveness of aflibercept was consistent across all tested categories of patients regardless of baseline characteristics e.g. gender, perfusion status, BCVA category.

4.8.1 Subgroup analysis of primary endpoint

Results of the subgroup analyses demonstrated that the superiority of aflibercept over laser treatment for the primary endpoint was consistent across the subgroups examined (Figure 14, Table 28), though some subgroups had too few patients to draw useful conclusions. Results using the OC analysis were similar to those using LOCF.

Figure 14: Proportion of Patients Gaining at Least 15 Letters in BCVA at Week 24 Subgroup Analysis by Forest Plot (LOCF) (FAS) (8)



BCVA=Best Corrected Visual Acuity; VTE=aflibercept.
Anti-VEGF: Negative, Anti-VEGF Positive = subjects with negative/ positive status for antibodies against anti-VEGF Trap
VTE (%) / Laser (%) = proportion of patients at week 24 in the VTE / laser group.
Lower / Upper = lower / upper bound of 95% confidence interval for difference
Note: Last observation carried forward (LOCF) method was used to impute missing data.

Table 28: Subgroup analysis of proportion of patients who gained at least 15 letters in BCVA at week 24 from baseline (FAS, LOCF) (28)

Subgroup	Laser N=90 n/N (%)	Aflibercept N=91 n/N (%)	Difference	Adjusted Difference (%) (95% CI) [1]	CMH test p-value [2]
Overall population	**24/90 (26.7)**	**48/91 (52.7)**	**26.1%**	**26.6 (13.0, 40.1)**	**0.0003**
By perfusion status					
'Non-perfused' retina	6/16 (37.5)	12/120 (60.0)	22.5%	18.2 (-13.1, 49.4)	0.2939
'Perfused' retina	15/62 (24.2)	24/55 (43.6)	19.4%	20.1 (3.6, 36.6)	0.0241
By Baseline BCVA Category					
>20/200 (35-73)	22/83 (26.5)	44/85 (51.8)	25.3%	25.6 (11.4, 39.7)	0.0007
≤20/200 (24-34)	2/7 (28.6)	4/6 (66.7)	38.1%	39.4 (-4.1, 83.0)	0.1400

N=nominator, m=denominator

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

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

4.8.2 Subgroup analyses of secondary endpoints

4.8.2.1 Subgroup analysis of 'Mean change from baseline to week 24 in BCVA':

In general, the results of the subgroup analyses of the change from baseline to week 24 in BCVA score were consistent with those seen in the overall population (Figure 15 and Table 29) although some subgroups had too few patients to make any useful comparisons. For the subgroup of patients with a baseline BCVA ≤ 20/200 (24-34 letters), the adjusted difference (aflibercept minus GLP) in BCVA letters was numerically different from other subgroups (27.1 letters), however the 95% CI was wide (6.2 to 48.0 letters) in this small subgroup (13 patients).

Figure 15: Change from baseline to week 24 in BCVA Score Subgroup Analysis by Forest Plot (LOCF) (FAS) (27)

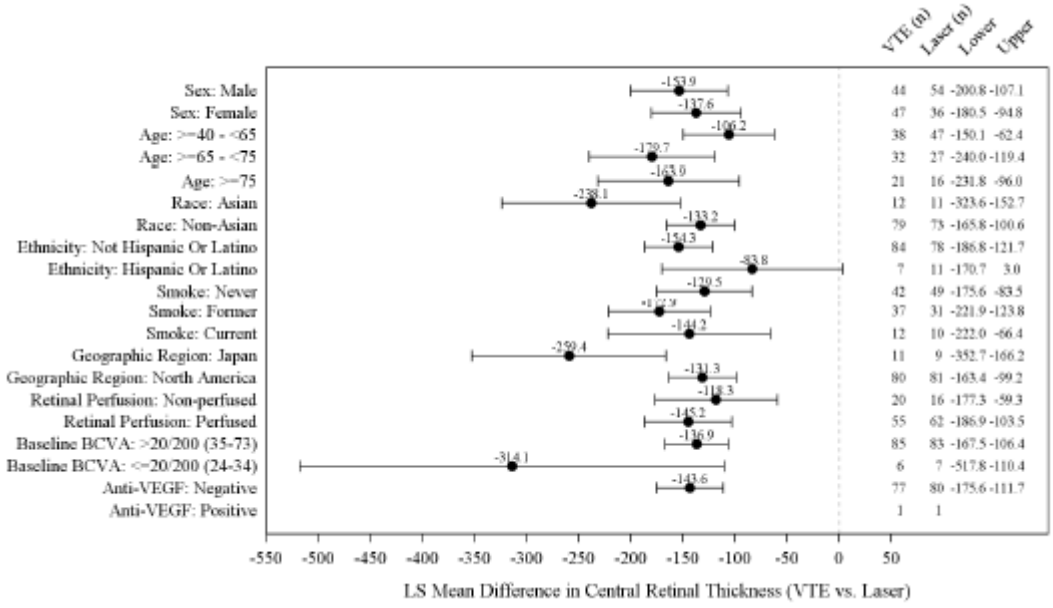
[Academic/commercial in confidence information removed]

BCVA=Best Corrected Visual Acuity; LS=least squares; VTE=aflibercept.
Anti-VEGF: Negative, Anti-VEGF Positive = patients with negative/ positive status for anti-VEGF Trap antibodies with neutralising activity; VTE (n) / Laser (n) = number of patients at week 24 in the VTE / laser group; Lower / Upper = lower / upper bound of 95% confidence interval for difference
Note: Last observation carried forward (LOCF) was used to impute missing data.

4.8.3 Subgroup analysis of 'Mean change in CRT from baseline to week 24':

In general, results in the BCVA and perfusion status subgroups for the outcome of change from baseline to week 24 in CRT were consistent with those seen in the overall population (FAS LOCF and FAS OC) (see Figure 16 and Table 29)

Figure 16: Change from baseline in Central Retinal Thickness at week 24 by subgroup (27)



VTE = aflibercept

Table 29: Subgroup analysis of key secondary endpoints from baseline to week 24 (FAS, LOCF) (24;28)

	Subgroup	Treatment	n	Baseline Mean	Week 24 Mean	Mean Change	LS Mean Change	Difference (95% C.I) [1]	p-value [1]
Change in BCVA (ETDRS letter score) from baseline to week 24	**Overall population**	LSR AFL	**90** **91**	**57.7** **58.6**	**64.6** **75.6**	**6.9** **17.0**	**3.2** **13.7**	**10.5 (7.1, 14.0)**	**<0.0001**
	By perfusion status								
	'Non-perfused' retina	LSR AFL	16 20	53.1 54.2	64.4 73.3	11.3 19.1	7.7 14.7	7.0 (-1.4, 15.3)	0.1008
	'Perfused' retina	LSR AFL	62 55	59.4 61.0	65.1 75.3	5.7 14.3	-1.8 7.3	9.1 (4.9, 13.3)	<0.0001
	By Baseline BCVA Category								
	>20/200 (35-73)	LSR AFL	83 85	60.0 60.7	66.9 76.4	6.9 15.7	5.1 14.3	9.2 (5.8, 12.6)	<0.0001
	≤20/200 (24-34)	LSR AFL	7 6	30.9 30.0	38.1 64.5	7.3 34.5	-0.2 26.9	27.1 (6.2, 48.0)	0.0168
Change in Central Retinal Thickness (CRT) from Baseline to week 24	**Overall population**	LSR AFL	90 91	553.5 558.9	425.5 278.5	-128.0 -280.5	-98.9 -247.5	-148.6 (-179.8, -117.4)	<0.0001
	By perfusion status								
	'Non-perfused' retina	LSR AFL	16 20	559.8 622.1	382.4 268.5	-177.4 -353.7	-199.0 -317.2	-118.3 (-177.3, -59.3)	0.0003
	'Perfused' retina	LSR AFL	62 55	535.1 515.4	431.2 284.7	-103.9 230.7	-42.0 -187.2	-145.2 (-186.9, -103.5)	<0.0001
	By Baseline BCVA Category								
	>20/200 (35-73)	LSR AFL	83 85	547.0 548.8	416.8 281.2	-130.2 -267.6	-110.6 -247.5	-136.9 (-167.5, -106.4)	<0.0001
	≤20/200 (24-34)	LSR	7	630.4	527.7	-102.7	-84.4		

	Subgroup	Treatment	n	Baseline Mean	Week 24 Mean	Mean Change	LS Mean Change	Difference (95% C.I) [1]	p-value [1]
		AFL	6	702.0	239.5	-462.5	-398.5	-314.1 (-517.8, -110.4)	0.0069
Change from Baseline in National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) Total Score to week 24	**Overall population**	LSR	**87**	**75.4**	**81,7**	**6.3**	**2.7**		
		AFL	**88**	**77.5**	**85.2**	**7.7**	**5.3**	**2.6 (-0.3, 5.5)**	**0.0833**
	By perfusion status								
	'Non-perfused' retina	LSR	15	73.3	79.6	6.2	3.4		
		AFL	19	72.9	86.0	13.0	8.2	4.8 (-2.3.11.9)	0.1810
	'Perfused' retina	LSR	60	75.7	82.0	6.4	4.7		
		AFL	53	78.6	85.4	6.8	6.9	2.1 (-1.7,5.9)	0.2688
	By Baseline BCVA Category								
	>20/200 (35-73)	LSR	82	75.4	81.6	6.2	2.0		
		AFL	82	77.6	85.2	7.6	4.6	2.6 (-0.4, 5.6)	0.0942
	≤20/200 (24-34)	LSR	5	76.0	82.9	6.9	10.7		
		AFL	6	76.3	85.1	8.8	11.4	0.7 (-13.1, 14.5)	0.9065

[1] Difference is aflibercept groups minus Laser. Point estimate, 95% confidence interval (C.I.), and p-value are based on ANCOVA model with baseline measurement as covariate and treatment group, region and baseline BCVA (BCVA <= 20/200 and BCVA > 20/200) as fixed factors.
LSR – Laser photocoagulation, AFL - aflibercept

4.9 Meta-analysis

Evidence of the efficacy of aflibercept in the treatment of visual impairment due to macular oedema secondary to BRVO is available from one RCT (VIBRANT). Hence meta-analysis was not carried out.

4.10 Indirect and mixed treatment comparisons

Summary

Data on the relative efficacy and safety of aflibercept compared with laser photocoagulation is available from the VIBRANT study. However, no head to head data comparing aflibercept with ranibizumab or dexamethasone intravitreal implant are available. A systematic literature review was conducted to identify RCTs investigating the efficacy and safety of aflibercept and other active treatments in adult patients with visual impairment due to BRVO in order to conduct an indirect comparison. Twelve publications relating to 9 unique studies were identified. After assessment of heterogeneity 5 studies were excluded leaving 4 studies for inclusion in the base case evidence network. Excluded studies were included in sensitivity analyses.

The outcomes considered were gaining ≥15 letters, losing ≥15 letters, BCVA change from baseline, adverse events and discontinuation. Data availability limited the comparison to two outcomes i.e. proportion of patients gaining 15 or more letters from baseline and change in visual acuity from baseline. The NMA base case and sensitivity analysis results showed no evidence of a statistically significant difference between aflibercept and ranibizumab with the 95% credible intervals crossing zero for both the proportion of patients gaining 15 or more letters and change in letters from baseline. For the comparison with dexamethasone there was evidence that aflibercept was more effective in terms of patients gaining 15 or more letters from baseline (FEM results).

4.10.1 Search strategy

Data on the relative efficacy and safety of aflibercept compared to laser photocoagulation is available from the VIBRANT trial. However, there is no head-to-head data available for the other comparators; ranibizumab and dexamethasone. Therefore, in absence of this data, a systematic literature review was undertaken to identify relevant RCTs for deriving the relative efficacy and safety of aflibercept versus ranibizumab and dexamethasone intravitreal implant via indirect comparison.

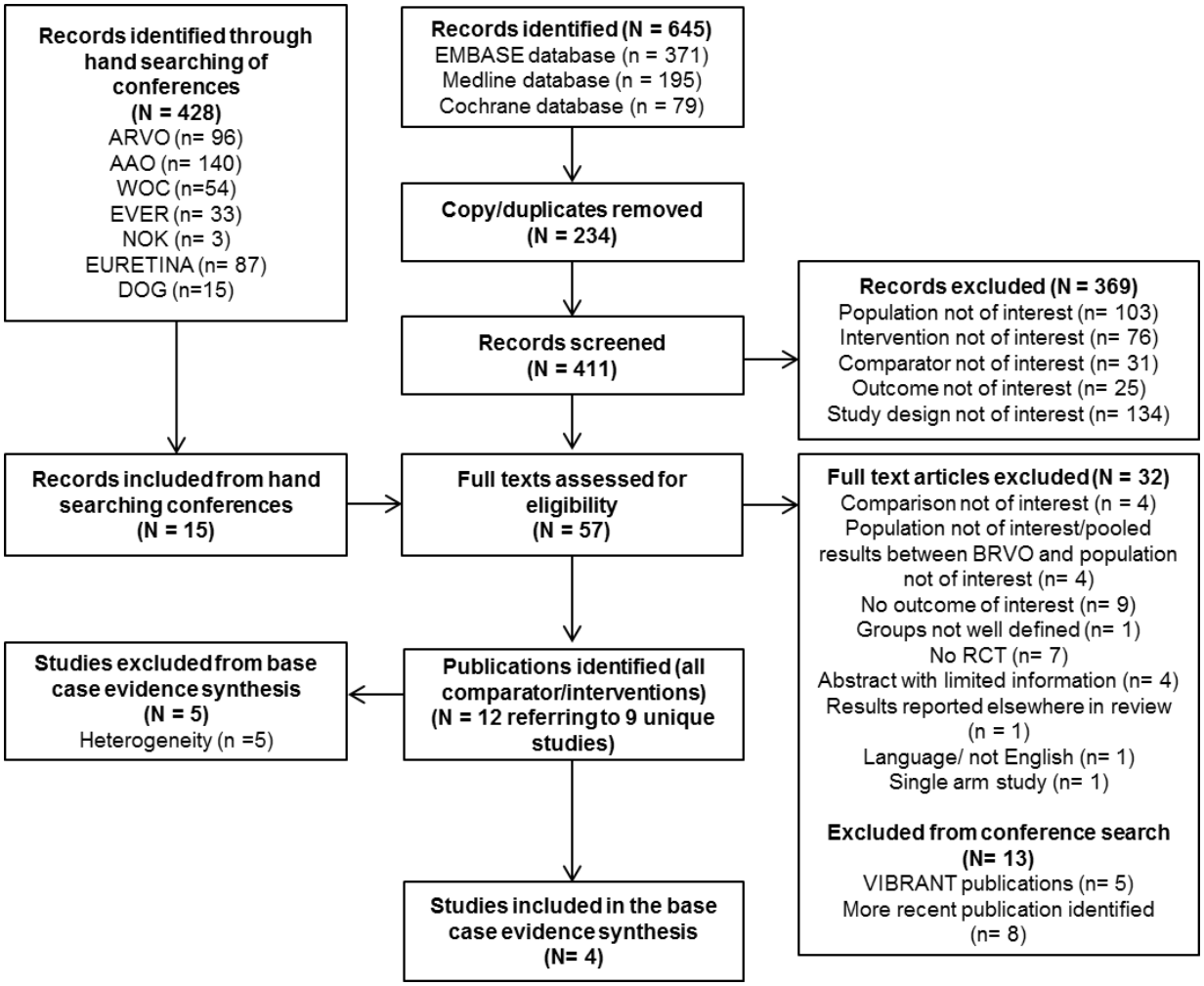
The search to identify the clinical data was part of the broader systematic literature review described in section 4.1. Please refer to section 4.1 for details of the search strategy and the inclusion and exclusion criteria used. Literature search results are reported below.

The outcomes considered were gaining ≥15 letters, losing ≥15 letters, BCVA change from baseline, adverse events and discontinuation. These were identified as clinically significant in patients affected by BRVO. In addition, the proportion of patients gaining ≥15 letters, and BCVA change from baseline were the primary and secondary outcomes of the VIBRANT trial.

4.10.2 Study selection

The results of the search are illustrated below using the PRISMA Flow diagram (Figure 17).

Figure 17. PRISMA diagram for evidence synthesis



The database search yielded 645 hits, of which 234 were duplicates, leaving 411 records to be reviewed against the eligibility criteria. 369 publications were excluded based on title or abstract leaving 42 publications requiring full text review. Hand searching of conferences identified 428 records of which 15 were assessed for eligibility. In total 57 full texts were assessed for eligibility. A list of the 32 publications from the database search and the 13 conference publications excluded at full-text stage, along with the reasons for exclusion is provided in Appendix **Error! Reference source not found.**. In total 12 publications, relating to 9 unique studies, were identified for possible inclusion in the NMA (see Table 30). Out of the 9 studies 5 were excluded from the base case evidence network for reasons of heterogeneity (further details of heterogeneity assessment are in section 4.10.3.1 - 4.10.4). Excluded studies were included in sensitivity analyses. The network evidence diagrams for the base case are in Figure 18 and Figure 19.

Table 30. Studies assessed for qualitative synthesis

Study	Intervention and comparators			Time of endpoint	Sample size (no. eyes)	Reason for exclusion	Primary Publication (n=9)	Secondary publication (n=3)
Studies included in the base case NMA								
1. VIBRANT	Aflibercept	Laser	-	6 mo	181	-	Campochiaro 2015 (24)	-
2. BRAVO	Ranibizumab 0.3mg + laser	Ranibizumab 0.5mg + laser	Sham + laser	6 mo	397	-	Campochiaro 2010 (35)	Brown et al 2011 (37) Varma et al 2012 (38) Thach et al 2014 (39)
3. BRIGHTER	Ranibizumab 0.5mg	Ranibizumab 0.5mg + laser	Laser	6 mo	354	-	Mones 2015(40) , Regnier 2014 (41)	-
4. COMRADE-B	Ranibizumab 0.5mg	Dexamethasone 0.7mg	-	6 mo	241	-	Regnier 2014 (41)	-
Studies excluded from the base case NMA (included in sensitivity analysis)								
5. Azad, 2012	Ranibizumab 0.5mg + laser	Ranibizumab 0.5mg + laser	Laser	6 mo	30	Heterogeneity	Azad 2012 (42)	-
6. Parodi, 2008	Laser	Observation	-	24 mo	31	Heterogeneity	Parodi 2008 (43)	-
7. Pichi, 2014	Dexamethasone	Dexamethasone + laser	-	6 mo	50	Heterogeneity	Pichi et al 2014 (44)	-
8. Tan, 2014	Ranibizumab 0.5mg + laser	Sham +Laser	-	12 mo	36	Heterogeneity	Tan et al 2014 (45)	-

Study	Intervention and comparators			Time of endpoint	Sample size (no. eyes)	Reason for exclusion	Primary Publication (n=9)	Secondary publication (n=3)
9. RABAMES	Ranibizumab 0.5mg	Ranibizumab 0.5mg + laser	Laser	6 months	30	Heterogeneity	Pielen et al 2015 (46)	-

Figure 18. Base case network diagram for gaining ≥15 letters

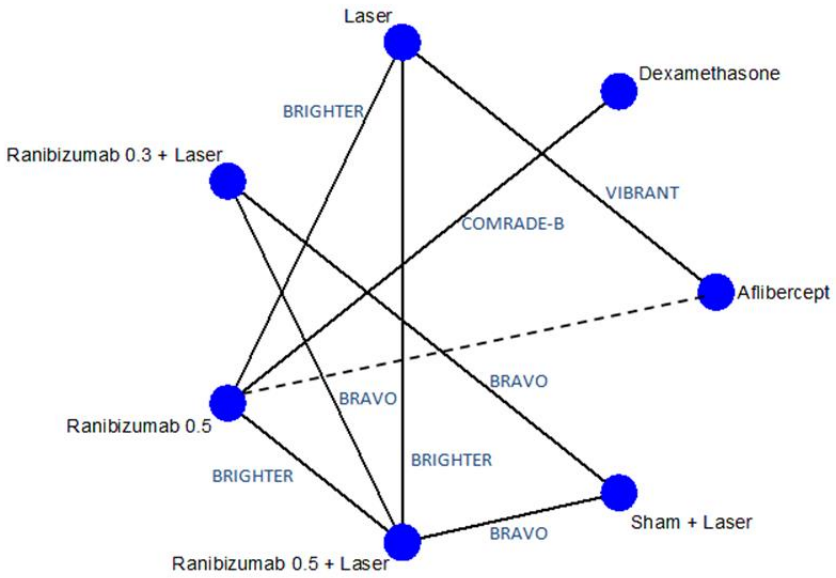
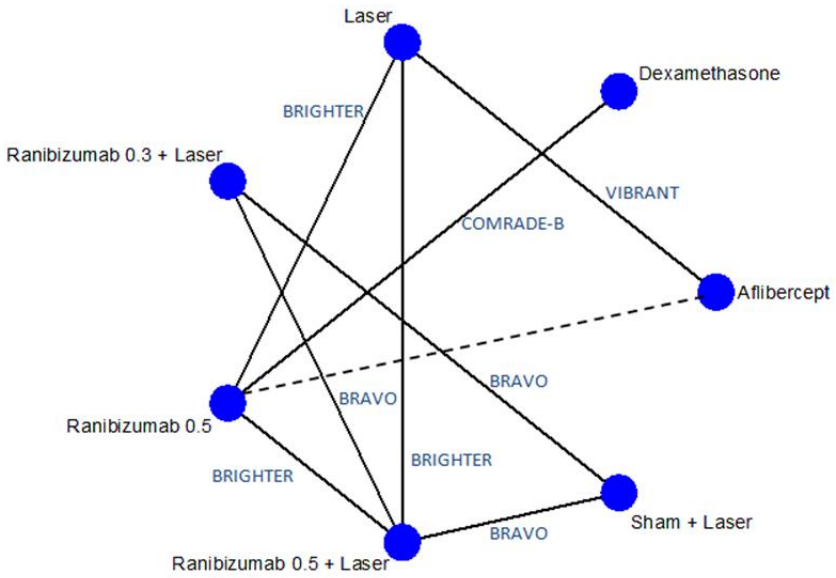


Figure 19. Base case network diagram for BCVA change from baseline



4.10.3 Methods and outcomes of included studies

4.10.3.1 Assessment of heterogeneity

The key characteristics of the studies assessed for inclusion in the NMA are provided in Table 31. The full data extraction is tabulated in appendix **Error! Reference source not found.**.

The following sources of between-study heterogeneity were considered:

1. Trial design: interventions received and dosing regimen, inclusion/exclusion criteria, sample sizes

2. Patient characteristics: disease, age at baseline, baseline BCVA, baseline CRT, duration of disease

Trial designs and patient characteristics were compared to VIBRANT for the purposes of assessing heterogeneity as this is the only RCT for aflibercept in patients with BRVO.

Table 31. Key characteristics of studies considered for inclusion in the NMA evidence network

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
Country/ region	United States, Canada, Japan	United states	Multi centre	Multi-centre	NR	Italy	Italy	Australia	Multi centre
Inclusion criteria	- Adults ≥ 18 years of age with foveal centre-involved macular oedema (ME) secondary to BRVO diagnosed within 12 months before the screening visit; - ETDRS BCVA: letter score of 73 to 24 (20/40 to 20/320) in the study eye at screening and at day 1	- Age ≥18 years of age with foveal centre-involved MO secondary to BRVO diagnosed within 12 months before the study initiation; - BCVA 20/40-20/400 Snellen equivalent using the EDTRS charts; - Mean central subfield thickness ≥ 250 µm from 2 OCT measurements	- Diagnosis of visual impairment exclusively du e to ME secondary to BRVO; - BCVA score at Screening and Baseline between 73 and 19 letters (ETDRS).	- Diagnosis of BRVO at maximum 6 months prior to - Screening; - BCVA using ETDRS charts of 20/40 to 20/400 in the study eye.	- BRVO of at least 6 weeks duration; - Perfused as confirmed on fluorescein angiography, with CMT of ≥ 250 µm, and baseline visual acuity of 20/40 or worse.	- Diagnosis of ERD secondary to ischemic BRVO; ERD involvement of the macular area; - BCVA (Snellen equivalent) of approximately 20/40 or worse on standard ETDRS charts; - Duration of BRVO no longer than 3 months; - Patients able and willing to provide written informed consent and to comply with the	Patients showing macular involved BRVO with decreased visual acuity and perfused macular oedema for at least 3 months, with baseline central retinal thickness >300 µm	- Duration of vision loss between 6 weeks and 9 months prior to baseline visits; - MO involving the centre fovea; - Macula is non-ischaemic (Less than 50 % ischaemic injury to the perifoveolar vascular zone); - BCVA score at baseline between 20 and 68 letters measured using the ETDRS charts;	Key inclusion criteria were: - Adults aged 18 years and older with chronic (>3 months, <18 months) MO secondary to branch retinal vein occlusion; - Patients who at baseline have a BCVA in the study eye between 20/320 and equivalent to 20/40, using an

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
						examination procedures.		- Mean central sub-field thickness > 250 µm by OCT at baseline visit; - Clear ocular media and adequate pupillary dilation	ETDRS chart; - Only one eye of a patient may be included
Exclusion criteria	- Current bilateral BRVO; - Uncontrolled glaucoma defined as ≥ 25 mmHg on optimal medical regimen, or previous filtration surgery in either the study eye or the fellow eye - Insufficient clearing of macular	- Prior episode of RVO; - Brisk afferent pupillary defect (i.e., obvious and unequivocal); - >10 letter improvement in BCVA between screening and day 0; - History of radical optic neurotomy or sheathotomy;	- Pregnant or nursing (lactating) women; - Stroke or myocardial infarction less than 3 months before Screening; - Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg;	- Media clarity, pupillary dilation and patient cooperation not sufficient for adequate fundus photographs; - CRT < 250 µm in the study eye; - Prior episode of RVO in the study eye;	The exclusion criteria were previous treatment for BRVO, such as intravitreal injection, sub-tenon injection, or laser photocoagulation, since the time of onset of BRVO, a history of glaucoma, macular oedema secondary to	- Detection of features and conditions able to alter BCVA , other than those associated with BRVO; - Identification of features typical of other diseases presenting ERD	Foveal haemorrhages that had not disappeared after 3 months of observation and ischaemic maculopathy detected by fluorescein angiography; patients with a history of ocular surgery and/or rubeotic or advanced glaucoma, defined as cup-to-disc ratio of 0.8 or worse; any	- Signs of significant ischaemia following BRVO; - Presence of dry or wet AMD; - Presence of diabetic retinopathy; - Any other ocular condition that would prevent improvement in VA;	Patients who at baseline: - have a relevant ocular disease potentially associated with increased intraocular VEGF levels (namely uveitis, neovascular glaucoma, neovascular age-

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
	haemorrhage that would prevent the patient from receiving laser treatment safely on day 1 (patients that meet this criterion may be rescreened once the macular haemorrhage resolves) - Uncontrolled diabetes mellitus (DM); - Use of periocular corticosteroids in the study eye within 3 months before day 1; - Previous use of intraocular corticosteroids or anti-angiogenic drugs in the	- Intraocular corticosteroid use in study eye within 3 months before day 0; - History or presence of wet or dry AMD; - Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0; - Laser photocoagulation for ME within 4 months before day; - Evidence	- Any active periocular or ocular infection or inflammation; - Uncontrolled glaucoma diagnosed at or within 6 months before Baseline in either eye; - Neovascularization of the iris or neovascular glaucoma in the study eye; - Use of any systemic antivascular endothelial growth factor (anti-VEGF) drugs within 6 months before Baseline; - Panretinal laser photocoagulati	- Active formation of new vessels in the study eye; - Anti-VEGF-treatment in the study or the fellow eye 3 months prior to Baseline; - IOP ≥ 30mmHg or uncontrolled glaucoma; patients may be re-screened after 1 month if they have undergone glaucoma treatment; - Improvement of > 10 letters on BCVA between	other causes, such as age-related macular degeneration and diabetic retinopathy.		previous treatment except for oral medication (e.g., aspirin 100 mg); patients in whom underlying cause of oedema was suspected to be different from BRVO (e.g., diabetes, vitreomacular traction).	- Treatment with intravitreal corticosteroids, intravitreal anti-VEGF agents, or macular grid laser within 3 months preceding baseline visits; - History of retinal detachment or retinal detachment surgery or pars plana vitrectomy; - Recent cataract extraction with phacoemulsification within 3 months preceding baseline, or a history of postoperative complications within the last 12 months	related macular degeneration, diabetic retinopathy, diabetic maculopathy, ocular ischaemic syndrome and others) - have a relevant malignant systemic disease possible associated with increased systemic VEGF levels (e.g. breast cancer) - had undergone treatment for macular oedema (e.g. laser, triamcinolo

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
	study eye; - Use of intraocular or periocular corticosteroids or anti-angiogenic drugs in the fellow eye within 3 months before day 1; - Previous administration of systemic anti-angiogenic medications; - Panretinal scatter photocoagulation, sector laser photocoagulation, or macular grid photocoagulation in the study eye	upon examination of any diabetic retinopathy; - Cerebrovascular accident or myocardial infarction within 3 months before day 0; - Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0	on within 3 months before Baseline or anticipated or scheduled within the next 3 months following Baseline in the study eye; - Focal or grid laser photocoagulation within 4 months before Baseline in the study eye; - Use of intra- or periocular corticosteroids within 3 months before screening; - Any use of intraocular corticosteroid implants in the study eye	Screening and Baseline				preceding baseline in the study eye (uveitis, cyclitis,etc); - Any active ocular infection or immune uveitis; - Recent CVA, MI, or major ischemic event within 3 months preceding baseline visit; - Known sensitivity to any anti-VEGF drugs and sodium fluorescein	ne, vitrectomy, etc.)
Blinding	Double blinded	Double blinded	NR	Double	NR	NR	NR	Double blinded	NR

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
				blinded					
Cross-over	Aflibercept: 10.6% Laser: 80.7%	NR	NR	NR	No	NR	NR	NR	NR
Duration of the follow up	52 weeks	12 months	24 months	6 months	6 months	24 months	6 months	12 months	6 months
Time of endpoint [+]	24 weeks	6 months	6 months	6 months	6 months	24 months	6 months	12 months	6 months
Sample size (eyes sample size)	Total: 181 AFL 2mg: 91 Laser: 90 patients	Total: 397 RAN 0.3mg: 134; RAN 0.5mg: 131 Sham: 132	Total: 354 eyes RAN 0.5mg:142 eyes RAN 0.5mg+laser:143 eyes Laser: 69 eyes	Total:241 Ranibizumab 0.5mg:124 Dexamethasone: 117	Total: 30 RAN 0.5 (1 inj)+Laser: 10; RAN 0.5 (3 inj)+Laser: 10; Laser: 10	Total: 31 Grid laser: 16 Observation: 15	Total: 50 eyes DEX: 25 eyes DEX+laser: 25 eyes	Total: 36 eyes RAN 0.5mg: 15 eyes BSC: 21 eyes	Total: 30 eyes RAN 0.5mg: 10 eyes Grid laser: 10 eyes; RBZ 0.5mg+laser: 10 eyes
Mean age (year)	65.5	66	RBZ 0.5mg: 63.9 RBZ	65.7	NR	68.1	DEX: 68; DEX+laser: 69	67.9	RBZ 0.5mg: 64.2;

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
			0.5mg+laser: 66.7 Laser: 67.1						Grid laser: 68.8; RBZ 0.5mg+laser: 65.9
BCVA measure scale	EDTRS, Snellen	EDTRS, Snellen	EDTRS	EDTRS	EDTRS, Snellen	Snellen, LogMar	LogMar	EDTRS, Snellen	EDTRS and LogMar
BCVA number of letters at baseline	AFL 2mg: 58.6; Laser: 57.7	RAN 0.3mg: 56; RAN 0.5mg: 53; Sham: 54.7	RAN 0.5mg: 58.9 RAN 0.5mg+laser: 56.7 Laser: 58.3	Ranibizumab 0.5mg:57.9 Dexamethasone: 58.4	RAN 0.5 (1 inj)+Laser: 76*; RAN 0.5 (3 inj)+Laser: 77.8*; Laser: 77.1*	Grid laser: 37*; Observation: 38*	DEX: 66*; DEX+laser: 66*	RAN 0.5mg: 39.5*; BSC: 46.2*	RAN 0.5mg: 58.5*; Grid laser: 59*; RBZ 0.5mg+laser: 64.5*
LogMar at baseline	NR	NR	NR	NR	RAN 0.5 (1 inj)+Laser: 0.18; RBZ 0.5 (3 inj)+Laser: 0.144; Laser: 0.158	Grid laser: 0.96; Observation: 0.94	DEX: 0.38; DEX+laser: 0.38	NR	RBZ 0.5mg: 0.53; Grid laser: 0.52; RBZ 0.5mg+laser: 0.41

	VIBRANT(24)	BRAVO(35)	BRIGHTER, 2014(40)	COMRADE-B(41)	Azad, 2012(42)	Parodi, 2008(43)	Pichi, 2014(44)	Tan, 2014(45)	RABAMES (46)
Baseline **Central *retinal* thickness (CRT,µm)**	AFL 2mg: 558.9; Laser: 553.5	RAN 0.3mg: 522.1; RBZ 0.5mg: 551.7; Sham: 488	RAN 0.5mg:554 RAN 0.5mg+laser: 582 Laser:558	Ranibizumab 0.5mg:537 Dexamethasone: 544	RAN 0.5 (1 inj)+Laser: 493.2; RAN 0.5 (3 inj)+Laser: 515.7; Laser: 500.2	Grid laser: 695.7; Observation: 706.5	DEX: 303; DEX+laser: 322	RAN 0.5mg: 615.6; BSC: 519.2	RAN 0.5mg: 584.2; Grid laser: 570.6; RAN 0.5mg+laser: 505.6

RAN – ranibizumab, AFL – aflibercept, NR – not reported, DEX – dexamethasone, CRT – central retinal thickness

4.10.3.1.1 Trial design – heterogeneity assessment

Inclusion criteria

Inclusion criteria were similar across most studies i.e. adults with BRVO and decreased visual criteria were selected. Parodi (2008) differed in that it enrolled patients exclusively with exudative retinal detachment secondary to BRVO which was different to the other trials.

Exclusion criteria

There were some differences in exclusion criteria across the nine studies. Existing macular haemorrhage that would prevent laser treatment at the start of the trial (baseline) was listed an exclusion in VIBRANT, Pichi 2014, and RABAMES. This exclusion was not reported for Azad and Parodi but based on the timing of the laser treatment in the trials is also assumed. In four trials no prior therapy was permitted (VIBRANT(24), Azad 2012(42), Pichi 2014(44), RABAMES(46)). In four trials prior therapy was permitted but there were differences in the required 'treatment free' period before entry (BRAVO(35), COMRADE-B(41), Tan 2014(45), BRIGHTER(40)), and in the remaining study (Parodi 2008(43)), permittance of prior treatment was not reported. No details on the proportion of patients who had received prior treatments were available.

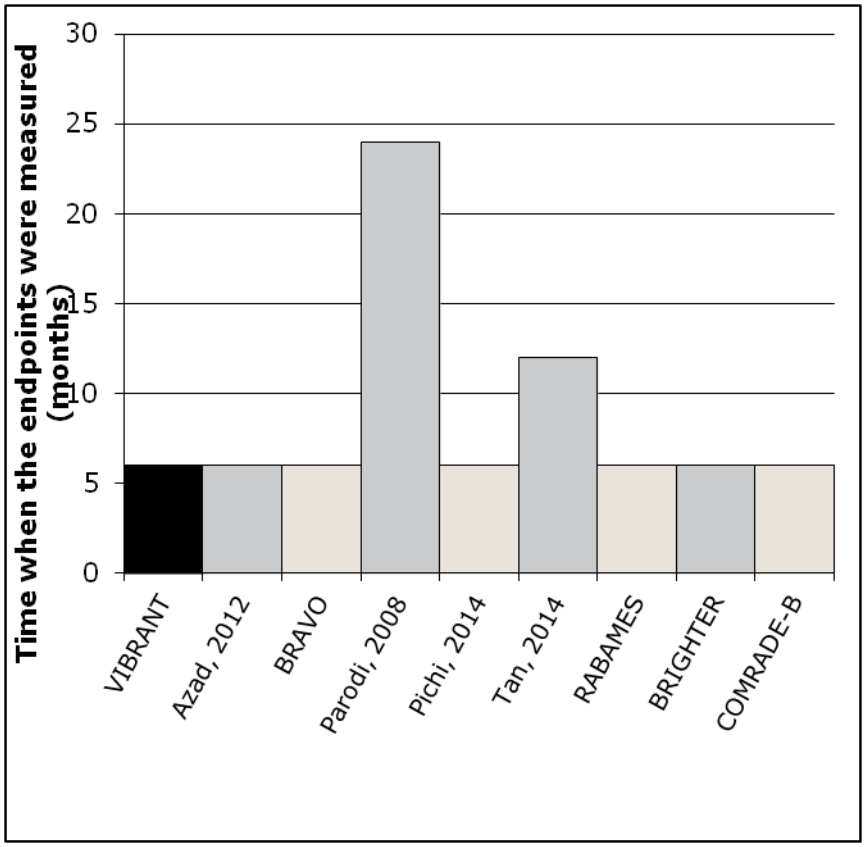
Sample sizes

There were differences in the sample sizes of the studies - four trials included over 100 study eyes whereas five trials included ≤50 study eyes (Azad 2012(42), Parodi 2008(43), Pichi 2014(44), Tan 2014(45), and RABAMES(46)).

Time at which endpoints were assessed

The timing of the endpoints across the studies is shown in Figure 20. With the exception of Parodi 2008(43) all studies reported outcomes at 6 or 12 months.

Figure 20. Time at which endpoints were measured across studies



Study location

In terms of study location, there was variation in where trials were conducted and a mix of single- and multi-centre studies.

Treatment posology

Table 32 provides details on the interventions received in each arm of the identified trials. The use of aflibercept, laser and dexamethasone across the studies was similar to what could be expected in clinical practice. For ranibizumab however there were clinically relevant variations in the regimens administered. Two trials (Azad 2012(42) and RABAMES(46)) investigated regimens that are not reflective of

its licence or clinical practice i.e. these trials investigated single injections or 3 injections of ranibizumab with observation thereafter.

Table 32. Treatment regimens investigated (up to primary endpoint)

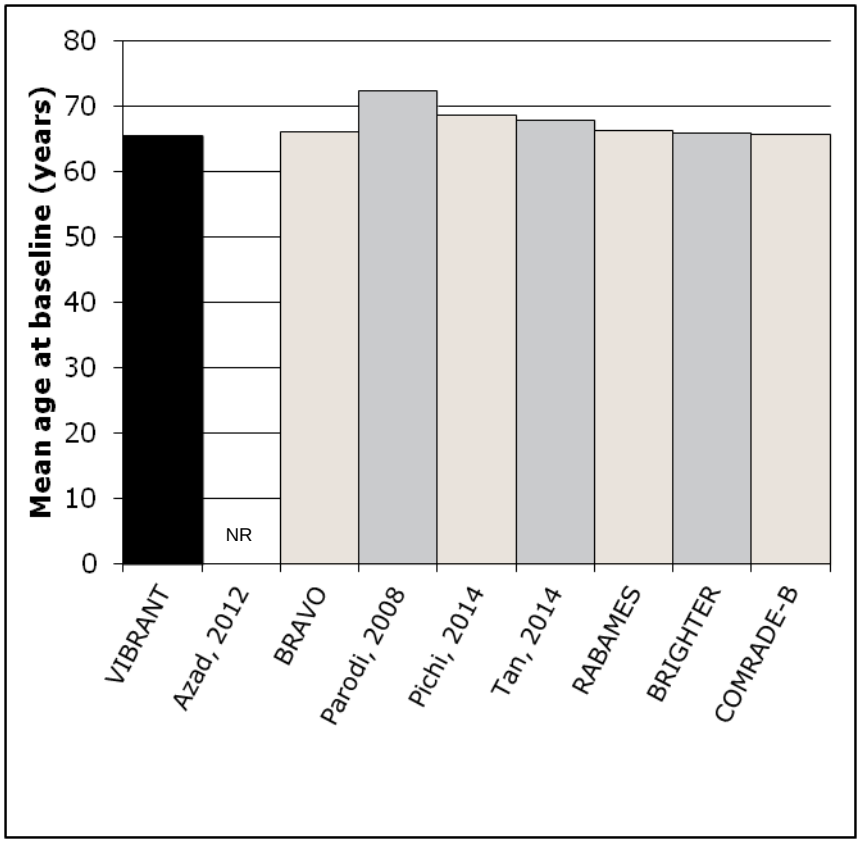
Study	Treatment arm	Treatment received
VIBRANT(24)	1	Laser at baseline with laser rescue permitted
	2	Aflibercept every month for six months and then bi-monthly
BRAVO(35)	1	Sham for 3 months then laser as required
	2	Ranibizumab 0.3 mg (monthly for six months) – laser from 3 months as required
	3	Ranibizumab 0.5 mg (monthly for six months) – laser from 3 months as required
BRIGHTER (40)	1	Laser as soon as indicated from day 0 with retreatment as required (minimum interval of 4 months)
	2	Ranibizumab (3 monthly injections) then PRN
	3	Ranibizumab (3 monthly injections) then PRN) plus laser as soon as indicated from day 0 with retreatment as required (minimum interval of 4 months)
COMRADE-B(41)	1	Dexamethasone at day 0
	2	Ranibizumab (3 monthly injections) then PRN
Azad, 2012(42)	1	Laser at day 7
	2	Ranibizumab (single treatment) plus laser at day 7
	3	Ranibizumab monthly (3 doses) plus laser treatment at day 7
Parodi, 2008(43)	1	Observation
	2	Laser at baseline and additional laser from 12 months if required
Pichi, 2014(44)	1	Dexamethasone PRN + laser at week 6-8
	2	Dexamethasone PRN
Tan, 2014(45)	1	Sham ranibizumab (monthly) plus laser if required at week 13 and 25
	2	Ranibizumab (monthly) plus laser if required at week 13 and 25
RABAMES(46)	1	Laser as required at time 0 and days 54-58
	2	Ranibizumab (3 monthly injections)
	3	Ranibizumab (3 monthly injections) and laser as required at time 0 and days 54-58

4.10.3.1.2 Patient characteristics

Mean age at baseline

There is some evidence to suggest that younger patients may have better visual acuity outcomes compared to older patients (Scott 2011(47), Jaissle 2011(48)). However, the included studies were comparable with regard to mean baseline age across studies ranging from 65.5 to 68.5 years.

Figure 21. Mean baseline age across studies



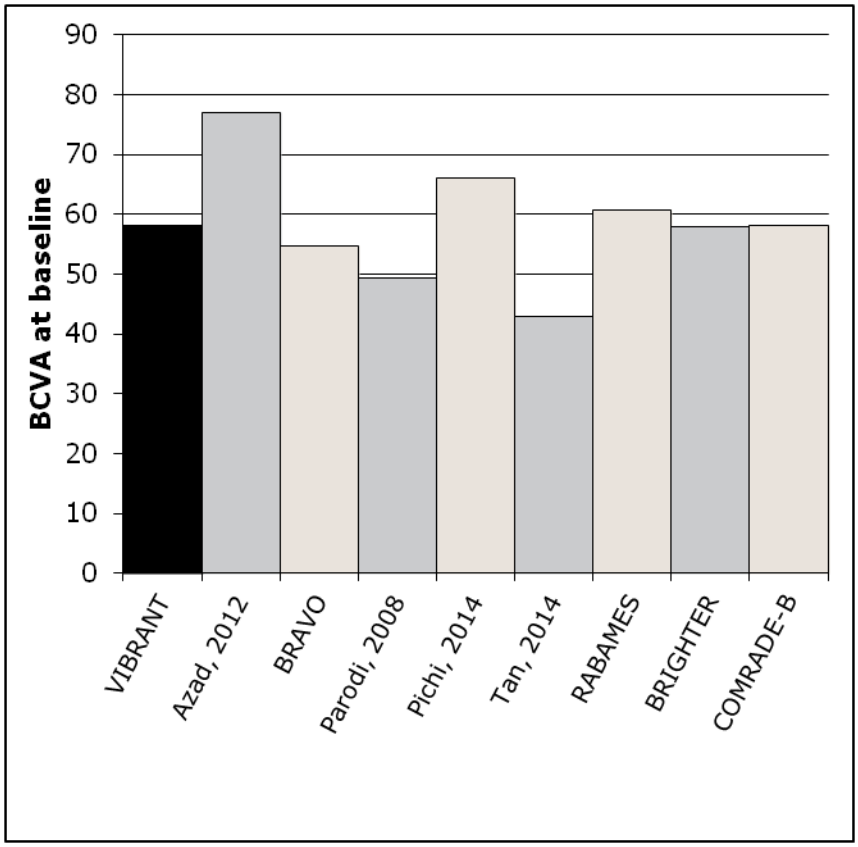
NR = not reported

Baseline BCVA

A trend towards greater absolute improvements in visual and anatomical outcomes in patients with worse baseline VA compared to those with better VA has been observed (Scott 2011(47), Jaissle 2011(48)). Therefore studies in patients with a lower baseline visual acuity may show higher treatment effects than those enrolling patients with higher baseline visual acuity.

Baseline BCVA was reported using two different scales (BCVA number of letters and LogMar) depending on the study. These two measures are comparable and an algorithm to transform LogMar into BCVA was used. The baseline BCVA following this transformation is presented in Figure 22. There was notable variation in BCVA at baseline with the range from 37 to 77. Four trials had baseline BCVA in a similar range to VIBRANT (BRAVO(35), RABAMES(46), BRIGHTER(40) and COMRADE-B(41)) with two studies having a higher BCVA at baseline (Azad 2012(42), Pichi 2014(44)) and two studies with lower BCVA at baseline (Tan 2014(45), Parodi 2008(43)).

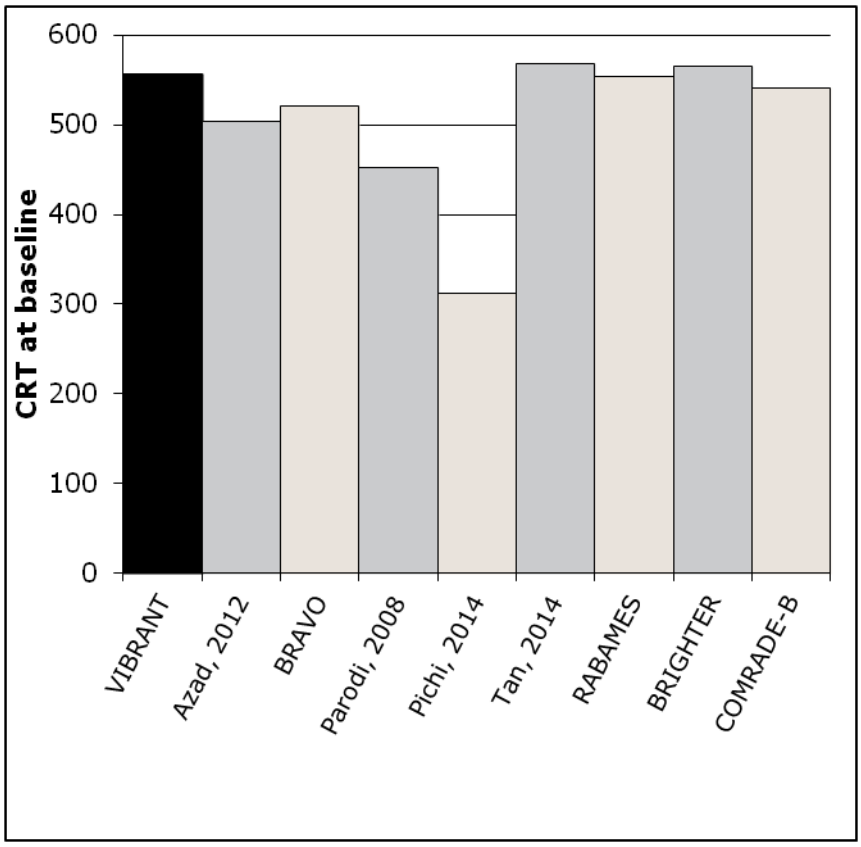
Figure 22. Mean baseline BCVA across studies



Baseline CRT

Eyes with central retinal thickness (CRT) ≥400µm at baseline show more improvement in terms of visual acuity than those with CRT of <400µm (Mitchell 2011(49)). Most of the studies were similar to VIBRANT in baseline CRT, with the exception of one study (Pichi 2014(44)) which had a baseline average CRT <400µm.

Figure 23. Mean baseline CRT (in µm) across studies

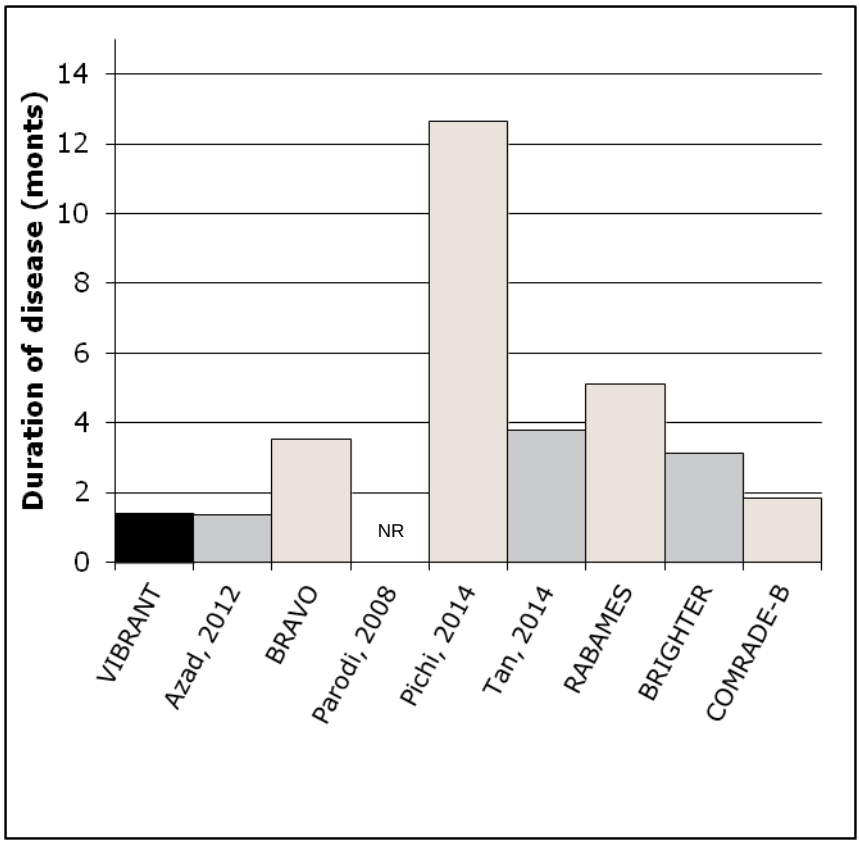


Duration of disease

There is evidence to suggest that earlier initiation of treatment from time of diagnosis with macular oedema is associated with a larger improvement in visual acuity (Scott 2011(47), Jaissle 2011(48), SCORE Study Research Group 2009(36)).

Baseline disease duration showed some variation across studies (Figure 24); however, the majority had mean disease duration of less than 4 months, with the exception of Pichi 2014(44) and RABAMES(46). Pichi 2014(44) had a substantially higher mean baseline disease duration compared to the other studies. The mean duration of disease was not reported for Parodi 2008(43) but patients with disease duration of greater than three months were excluded from the study.

Figure 24. Mean baseline disease duration across studies



4.10.3.2 Summary of heterogeneity

Table 33 provides a summary of the between-study heterogeneity identified across the studies. Heterogeneity was assessed against VIBRANT as this is the only study for aflibercept. The differences highlighted are clinically relevant and could affect efficacy and safety outcomes, thereby resulting in potential bias if used in indirect treatment comparisons. Due to heterogeneity 5 trials were excluded from the base case evidence network i.e. Azad 2012(42), Parodi 2008(43), Pichi 2014(44), Tan 2014(45) and RABAMES(46). Four studies (VIBRANT(24), BRAVO(35), BRIGHTER(40) and COMRADE-B(41) formed the basecase evidence network. The 5 excluded studies were included in several sensitivity analyses.

Table 33. Summary of heterogeneity across the studies (X indicates heterogeneity)

	BRIGHTER(40)	BRAVO(35)	COMRADE-B(41)	Azad (2012)(42)	Parodi (2008)(43)	Pichi (2014)(44)	Tan (2014)(45)	RABAMES(46)
Study population					X			
Duration of disease						X		
Baseline BCVA				X	X		X	
Baseline CRT						X		
Time point at which endpoints were measured					X			
Treatment regimen				X				X

4.10.4 Risk of bias

A quality assessment was performed to identify any ‘within-trial’ risk of bias using the NICE quality appraisal checklist. Responses to the questions in the checklist were categorized as: high risk, low risk and unclear risk of bias. The risk of bias within the studies is summarised in Table 34.

Table 34. Summary of within-trial risk of bias

	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Attrition	Outcomes	ITT
Included in basecase network							
VIBRANT(24)	Low	Low	Low	Low	Low	Low	Low
BRAVO(35)	Low	Low	Low	Low	Low	Low	Low
BRIGHTER(40)	Low	Unclear	Low	Low	Low	Low	Unclear
COMRADE-B(41)	Low	Unclear	Low	Low	Low	Low	Unclear
Excluded from basecase network							
Azad, 2012(42)	Unclear	High	Low	High	Low	Low	Unclear
Parodi, 2008(43)	Low	Low	Low	Unclear	Low	Low	Unclear
Pichi, 2014(44)	Unclear	Unclear	Low	Unclear	Low	Low	Low
Tan, 2014(45)	Low	Low	Low	Low	Low	Low	Low
RABAMES(46)	Low	Low	Low	Low	Low	Low	Unclear

The majority of studies were found to be associated with a low or unclear risk of within-study bias. However, Azad (2012)(42) was associated with a high risk of bias in terms of allocation concealment and blinding, strengthening the decision to remove this study from the base case analysis.

4.10.5 Methods and outcomes of included studies

4.10.5.1 Definition of the treatment arms in the network

There was a difference in the naming of treatment arms in some of the publications identified in the systematic literature review (SLR) and actual treatments received in the clinical trials. For example, in the BRAVO(35) trial patients were randomised to three different groups, named in the primary publication as 1) ranibizumab 0.3mg, 2) ranibizumab 0.5mg and 3) sham. However, over half of the sham group received laser treatment from 3-6 months. To avoid inappropriate grouping of treatments using simplified naming conventions taken from the publications, the evidence network was developed based on the actual treatments received. Table 35 shows the naming of the arms in the publications and the definition within the NMA. Where different treatment strengths were used, each strength was considered as a separate node in the network e.g. ranibizumab 0.3mg and ranibizumab 0.5mg.

Table 35. Definition of treatment arms in the studies included in the base case and sensitivity analysis

Study	'Naming' of the treatment arm in the publication	Actual treatment received	Treatment arm as defined in the NMA
VIBRANT(24)	Laser	Laser at baseline with laser rescue permitted	Laser
	Aflibercept	Aflibercept every month for six months and then bi-monthly	Aflibercept
BRAVO(35)	Sham	Sham for 3 months then laser as required	Sham + Laser
	Ranibizumab	Ranibizumab 0.3 mg (monthly for six months) – laser from 3 months as required	Ranibizumab + laser
	Ranibizumab	Ranibizumab 0.5 mg (monthly for six months) – laser from 3 months as required	Ranibizumab + laser
BRIGHTER(40)	Laser	Laser as soon as indicated from day 0 with retreatment as required (minimum interval of 4 months)	Laser
	Ranibizumab	Ranibizumab (3 monthly injections then PRN)	Ranibizumab
	Ranibizumab + laser	Ranibizumab (3 monthly injections then PRN) plus laser as soon as indicated from day 0 with retreatment as required (minimum interval of 4 months)	Ranibizumab + laser
COMRADE-B(41)	Dexamethasone	Dexamethasone at day 0	Dexamethasone
	Ranibizumab	Ranibizumab (3 monthly injections) then PRN	Ranibizumab
Azad, 2012(42)	Laser	Laser at day 7	Laser
	Ranibizumab + laser	Ranibizumab (single treatment) plus laser at day 7	Ranibizumab + laser
	Ranibizumab + laser	Ranibizumab monthly (3 doses) plus laser treatment at day 7	Ranibizumab + laser
Parodi, 2008(43)	Observation	Observation	Sham
	Laser	Laser at baseline and additional laser from 12 months if required	Laser
Pichi, 2014(44)	Dexamethasone + Laser	Dexamethasone PRN + laser at week 6-8	Dexamethasone + Laser
	Dexamethasone	Dexamethasone PRN	Dexamethasone
Tan, 2014(45)	Laser	Sham ranibizumab (monthly) plus laser if required at week 13 and 25	Sham + Laser
	Ranibizumab	Ranibizumab (monthly) plus laser if required at week 13 and 25	Ranibizumab
RABAMES(46)	Laser	Laser as required at time 0 and days 54-58	Laser
	Ranibizumab	Ranibizumab (3 monthly injections)	Ranibizumab
	Ranibizumab + laser	Ranibizumab (3 monthly injections) and laser as required at time 0 and days 54-58	Ranibizumab + laser

4.10.5.2 Feasibility assessment

A feasibility assessment was conducted (see Table 36) for the 9 studies to determine the comparisons that were possible for the outcomes of interest. Due to data availability only two outcomes were possible for indirect comparison i.e.

1. Proportion of patients gaining ≥15 letters from baseline, and
2. Change in BCVA from baseline.

Indirect comparisons stratified by BCVA subgroups were not feasible as the evidence available did not allow connected networks to be developed.

Table 36. Feasibility of efficacy and safety outcomes across studies (√ indicates outcome data is available)

Study	Gaining ≥15 letters	Losing ≥15 letters	Change in BCVA from baseline	Intraocular pressure	Cataract	Discontinuation	BCVA subgroups
Included in basecase network							
VIBRANT(24)	√	√	√	√	√	√	√
BRAVO(35)	√	√	√		√	√	√
BRIGHTER(40)	√		√				
COMRADE-B(41)	√		√				
Excluded from basecase network (included in sensitivity analyses)							
Azad, 2012(42)	√		√				
Parodi, 2008(43)	√	√	√				
Pichi, 2014(44)			√	√	√		
Tan, 2014(45)	√	√	√			√	√
RABAMES(46)	√	√	√		√		

4.10.5.3 Data from included studies

Table 37 provides the efficacy data from each trial used in the indirect comparison for the two comparisons that were possible. As the primary endpoint from VIBRANT was assessed at the six-month timepoint, data from the other trials is also taken from the six-month time point where available.

Table 37. Inputs used in the indirect comparison

Study	Treatment arm	Proportion of patients gaining ≥15 letters	Mean BCVA change from baseline	Source of data
Base case				
VIBRANT(24)	Aflibercept Laser	52.7 26.7	17.00 6.90	CSR
BRAVO(35)	Ranibizumab 0.3mg Ranibizumab 0.5mg Sham + Laser:	55.2 61.1 28.8	16.60 18.30 7.30	Peer-reviewed publication
BRIGHTER(40)	Ranibizumab 0.5mg Dexamethasone	61.0 37.0	17.00 9.10	Poster
COMRADE-B(41)	Ranibizumab 0.5mg Ranibizumab 0.5mg + Laser Laser	50.0 48.0 26.0	16.30 15.00 5.20	Abstract
Included in Sensitivity analyses				
Azad, 2012(42)	Ranibizumab 0.5mg + laser Ranibizumab 0.5mg + laser Laser	30.0 40.0 10.0	12.25 12.7 4.85	Peer-reviewed publication
Parodi, 2008(43)	Laser Observation	37.5 3.3	9.25 -6.50	Peer-reviewed publication
Pichi, 2014(44)	Dexamethasone Dexamethasone + Laser	NR NR	8.80 9.50	Peer-reviewed publication
Tan, 2014(45)	Ranibizumab 0.5mg Sham + Laser:	53.3 19.0	12.50 -1.60	Peer-reviewed publication
RABAMES(46)	Ranibizumab 0.5mg Ranibizumab 0.5mg + Laser Laser	70.0 70.0 20.0	17.00 6.00 2.00	Peer-reviewed publication

Full publications were used where available to source the input data. For BRIGHTER and COMRADE-B full publications are not available and therefore the inputs for these studies are from posters and abstracts and not from peer-reviewed publications. Two abstracts have been used to source the BRIGHTER data; Mones

et al 2015 (40) for the BCVA from baseline and Regnier et al 2014 (41) for the proportion of patients gaining ≥ 15 letters.

4.10.6 Methods of analysis and presentation of results

Indirect comparisons were performed for aflibercept versus ranibizumab and dexamethasone. For the dexamethasone comparison, aflibercept 2mg was compared to the dexamethasone implant with a dose of 0.7mg, based on available data. For the ranibizumab comparison, results are presented at a dose of 0.5mg as this is the only licensed dose. The outcomes considered in the analysis were restricted to gaining ≥15 EDTRS letters from baseline and mean BCVA change from baseline due to the availability of published data. Network diagrams for the base case have already been presented (Figure 18 and Figure 19).

Data on missing standard errors associated with the change in continuous outcomes from baseline were imputed using the methods described in section 16.1.3.2 of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (The Cochrane Collaboration, 2011(50)). The analyses were conducted using WinBUGS version 1.4.3. The WinBUGS code and data is provided in Appendix **Error! Reference source not found.**.

The conducted analyses consist of both continuous and binary outcomes. All baseline and intervention effect parameters were given flat (uninformative) normal (0, 1000) priors and the between-study standard deviation flat uniform distributions with an appropriately large range given the scale of measurement. A binomial likelihood with logit link function was used for binary data, and a normal likelihood with identity link was used for continuous data. The WinBUGS codes used were based on the National Institute for Health and Clinical Excellence Decision Support Unit Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials (Hoaglin, 2011(51); Jansen, 2011(52)). The methodology follows guidance from the ISPOR Task Force on Indirect Treatment Comparisons (Dias, 2011(53)).

Convergence was assessed by using the Brooks-Gelman-Rubin diagnostic in WinBUGS. In all cases a burn-in of at least 20,000 simulations was discarded. All

results have been presented based on a further sample of at least 50,000 simulations or until convergence was achieved. Lastly, we observed the Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation, to ensure that this was no more than 5% of the posterior standard deviation.

Results from both fixed and random effect models were tested for the proportion of patients gaining ≥15 letters and BCVA change from baseline. The Deviance Information Criterion (DIC) and the total residual deviance have been reported in order to choose the appropriate model for the data. The DIC provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a better model.

The results in this section are presented as tables and forest plots of the median and mean odds ratios and relative treatment differences for binary and continuous outcomes, respectively, and the associated 95% credible intervals (95% Crl). Results are presented for aflibercept compared to ranibizumab and dexamethasone implant. As previously stated, different doses were considered separately in the analysis.

4.10.7 Base-case results

4.10.7.1 Gaining ≥15 EDTRS letters from baseline results

Figure 25 and Figure 26 show the base case results for ‘gaining ≥15 letters’ for the fixed and random effect models respectively assuming aflibercept as baseline treatment.

Due to the small number of trials informing each comparison in the network, there was not enough evidence to reliably inform the heterogeneity parameter in the REM for this outcome, which led to very wide credible intervals and results from which it is difficult to draw meaningful conclusions. Based on the DIC and the fact that the REM produced implausibly large mean values (Figure 26) the FEM is preferred to the REM (DICs: FEM=71.16, REM=71.20) .

For the FEM, the median ORs suggest that response is higher for aflibercept compared to ranibizumab. However, results were not statistically meaningful with the 95% CrI crossing unity. For the mean OR the result is reversed with ranibizumab response being higher but with the 95% CrI again crossing unity.

For the comparison with dexamethasone, the FEM median OR suggests the response is substantially higher for aflibercept. The results are statistically significant with the 95% CrI ranging from 0.12 – 0.96. For the mean OR, the result is in favour of aflibercept and statistically significant.

Figure 25. Forest plot for gaining ≥15 letters from baseline- FEM

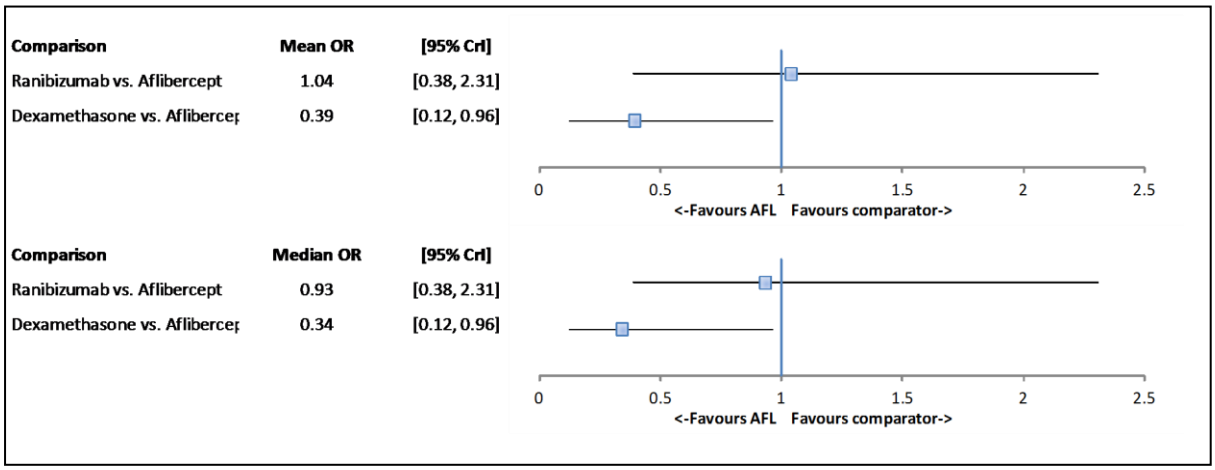
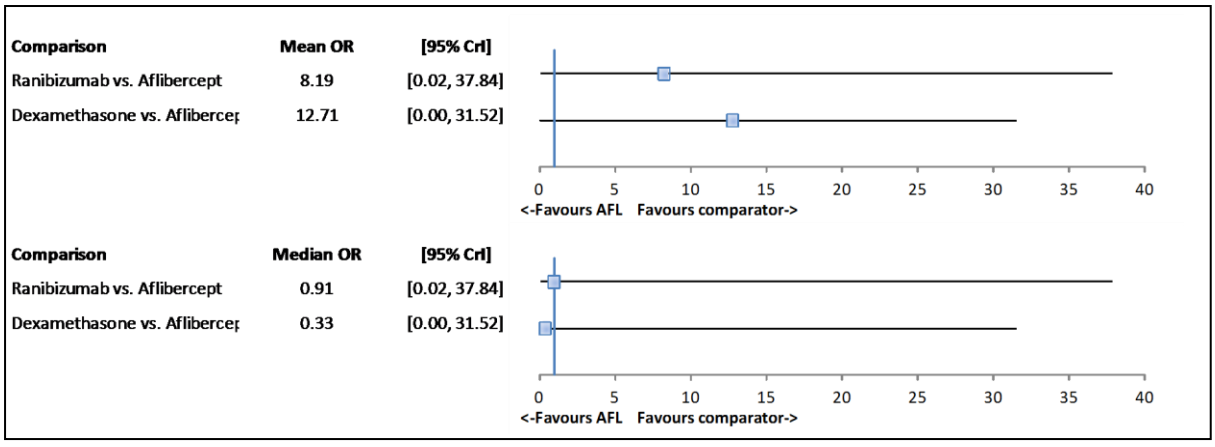


Figure 26. Forest plot for gaining ≥15 letters from baseline- REM



The preferred statistic for the measure of relative efficacy is the median as it provides a better measure of centrality when the data is highly skewed (see Figure 27 and Figure 28). For the log odds ratio which has a symmetrical distribution, both

the mean and median are in favour of aflibercept. Since the NMA is parameterised on the log odds scale this further justifies using the median odds ratio as it is invariant under any monotonic transformation (such as the logarithm or the exponential). In other words, the median of the log is the same as the log of the median. This is not the case for the mean.

Figure 27. Gaining ≥15 letters posterior distribution for the ranibizumab versus aflibercept comparison

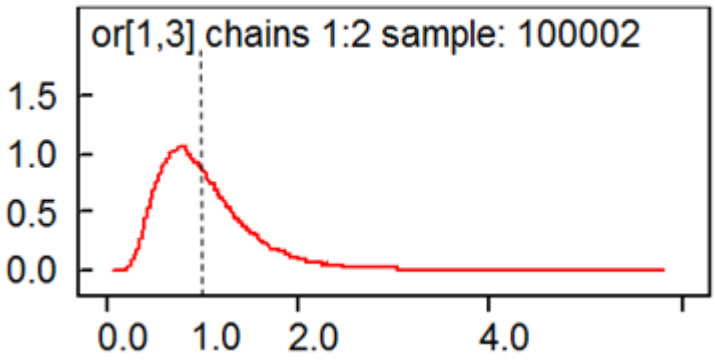
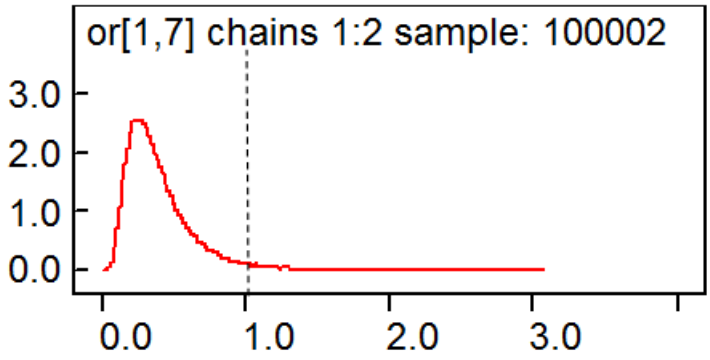


Figure 28. Gaining ≥15 letters posterior distribution for the dexamethasone versus aflibercept comparison



4.10.7.2 BCVA mean change from baseline

Figure 29 and Figure 30 show the base case results for the fixed and random effect models for both mean and median, respectively. Based on the DIC no difference is observed between the REM and the FEM (DIC: FEM= 40.89, REM= 40.42), and both REM and FEM show similar efficacy for aflibercept and ranibizumab.

When compared to dexamethasone, in the FEM model there is evidence that aflibercept leads to a greater increase in BCVA from baseline, however, in the REM the credible interval for this comparison crosses unity.

Figure 29. Forest plot for change in BCVA from baseline- FEM

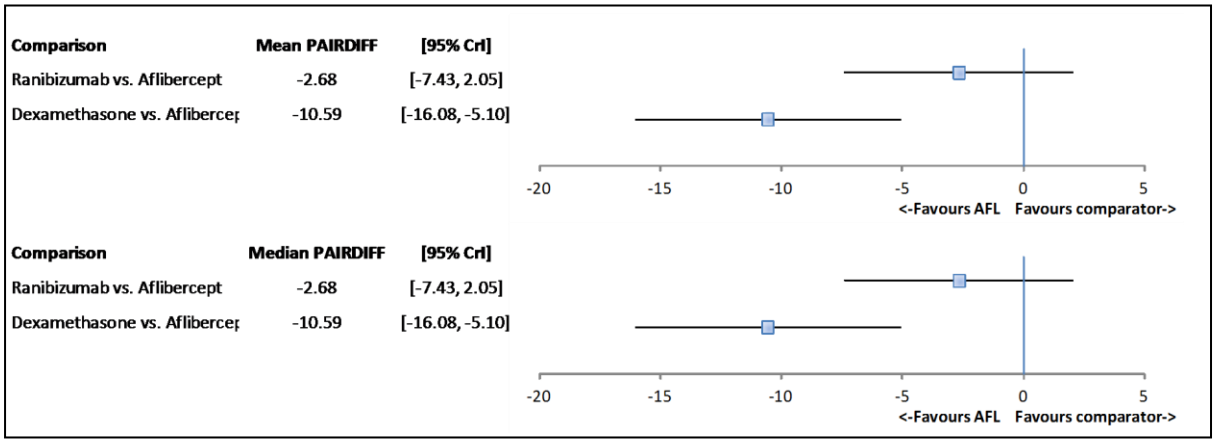
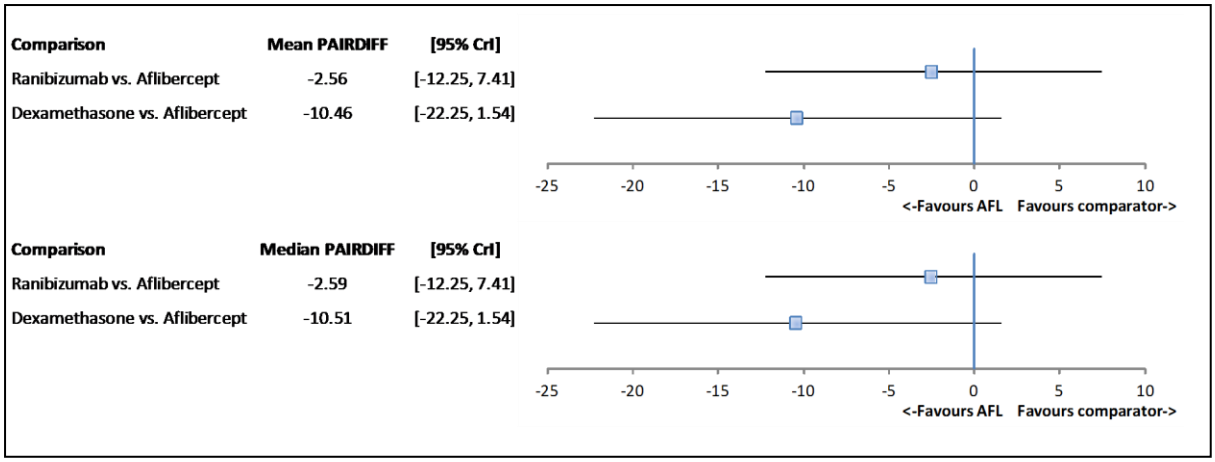


Figure 30. Forest plot for change in BCVA from baseline- REM



4.10.8 Sensitivity analyses

Four studies were considered sufficiently homogenous to be included in the base case evidence network (see 'Assessment of heterogeneity' - section 4.10.3.1). However, five studies were excluded as they were considered to have clinically relevant between-study heterogeneity that could bias the results. Several sensitivity analyses have been conducted to understand whether the inclusion of these studies would alter the base case findings. The results for sensitivity analyses for the two outcomes are presented in Table 38-Table 41 below. Inclusion of all the studies did

not alter the conclusion of there being no evidence of difference in either outcome when aflibercept is compared to ranibizumab, however the median estimate moved from numerically favouring aflibercept to numerically favouring ranibizumab. Results were mostly sensitive to the inclusion of the RABAMES(46) trial in the network more than to the inclusion/exclusion of the other identified studies. When RABAMES(46) was not included in the network the same results direction as per the base case was observed.

RABAMES(46) was a small pilot study (n=30) with a treatment regimen that was not reflective of clinical practice and was likely underpowered to detect a difference in the primary endpoint; mean change in BCVA from baseline to week 24. The results of the trial were also unexpected as the combination of ranibizumab + laser was found to be less efficacious than ranibizumab alone.

When aflibercept is compared to dexamethasone the sensitivity analyses show some differences to the base case (FEM). For the OR for gaining ≥15 letters from baseline the base case favoured aflibercept. The inclusion of RABAMES in the evidence network resulted in the credible intervals widening and crossing unity.

Table 38. Sensitivity analyses – OR of gaining ≥15 letters from baseline: ranibizumab versus aflibercept comparison (FEM)

Scenario number	Scenario	Mean	Median	2.5% CrI	97.5% CrI	DIC
1	**Base case**	**1.04**	**0.93**	**0.38**	**2.31**	**71.16**
2	Inclusion of excluded studies (Azad 2012(42), Parodi 2008(43), Pichi 2014(44), Tan 2014(45), RABAMES(46))	1.20	1.08	0.45	2.61	109.41
3	Rabames(46) excluded from 2	1.07	0.96	0.40	2.32	98.05
4	Azad 2012(42), Parodi 2008(43), Tan 2014(45) and Pichi 2014(44) excluded from 2	1.19	1.07	0.45	2.57	82.62

Figure 31. Sensitivity analyses – OR of gaining ≥15 letters from baseline: ranibizumab versus aflibercept comparison (FEM)

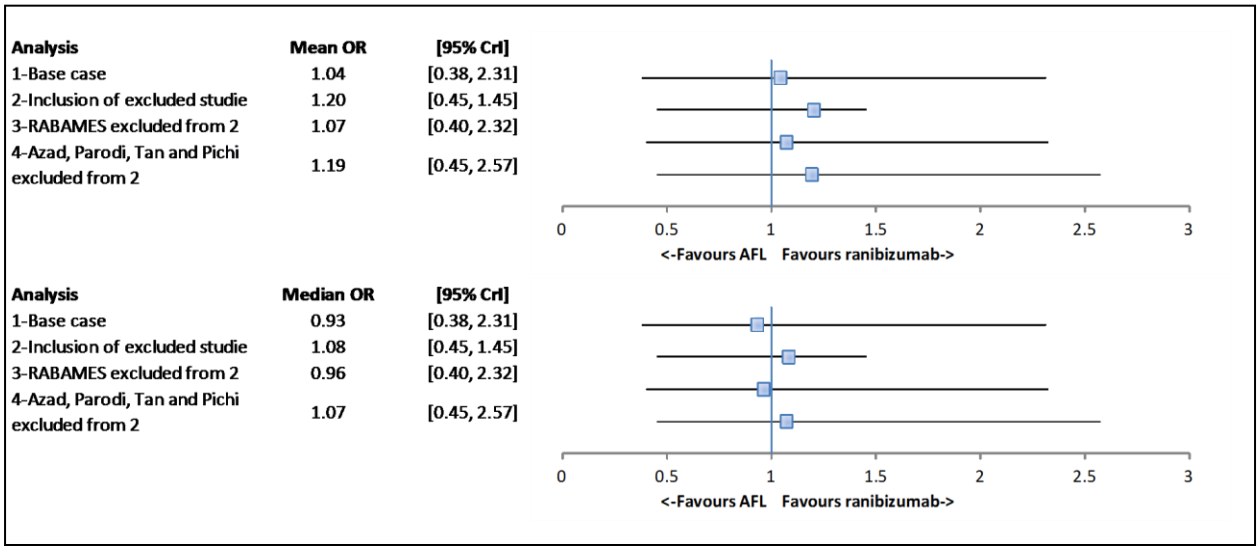


Table 39. Sensitivity analyses – OR of gaining ≥15 letters from baseline: dexamethasone versus aflibercept comparison (FEM)

Scenario number	Scenario	Mean	Median	2.5% CrI	97.5% CrI	DIC
1	**Base case**	**0.39**	**0.34**	**0.12**	**0.96**	**71.16**
2	Inclusion of excluded studies (Azad 2012(42), Parodi 2008(43), Pichi 2014(44), Tan 2014(45), RABAMES(46))	0.44	0.40	0.14	1.10	109.41
3	Rabames(46) excluded from 2	0.40	0.35	0.13	0.97	98.05
4	Azad 2012(42), Parodi 2008(43), Tan 2014(45) and Pichi 2014(44) excluded from 2	0.45	0.39	0.14	1.09	82.62

Figure 32. Sensitivity analyses – OR of gaining ≥15 letters from baseline: dexamethasone versus aflibercept comparison (FEM)

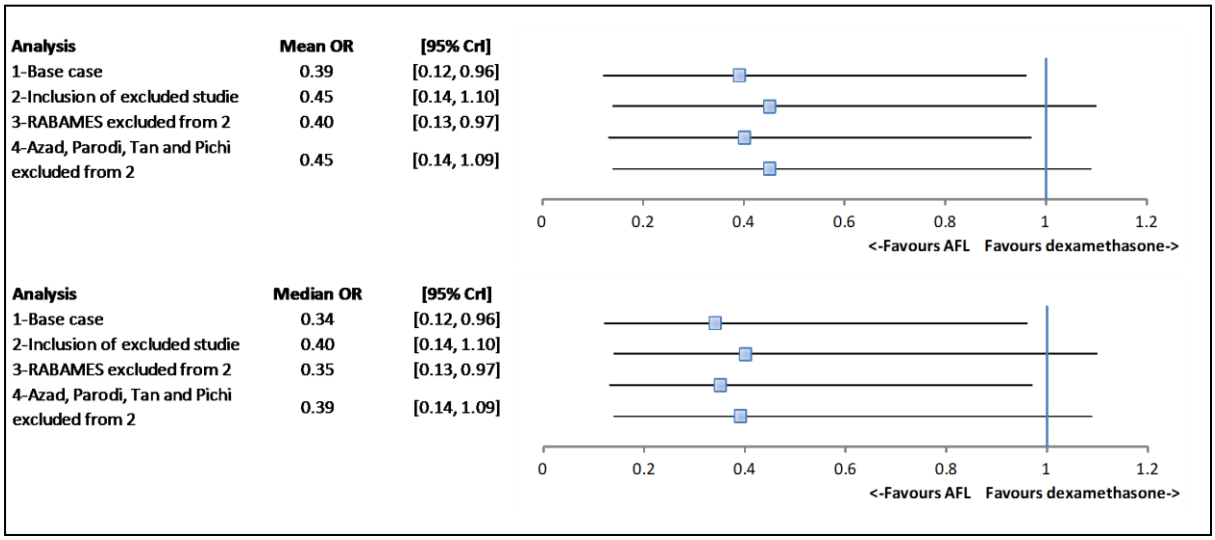


Table 40. Sensitivity analyses – change in BCVA from baseline: ranibizumab versus aflibercept comparison (FEM)

Scenario number	Scenario	Mean	Median	2.5% CrI	97.5% CrI	DIC
1	**Base case**	**-2.68**	**-2.68**	**-7.43**	**2.05**	**40.42**
2	Inclusion of excluded studies ((Azad 2012(42), Parodi 2008(43), Pichi 2014(44), Tan 2014(45), RABAMES(46))	-2.44	-2.43	-7.13	2.17	110.98
3	Rabames(46) excluded from 2	-3.21	-3.21	-8.02	1.52	90.92
4	Azad 2012(42), Parodi 2008(43), Tan 2014(45) and Pichi 2014(44) excluded from 2	-2.00	-1.99	-6.72	2.74	60.08

Figure 33. Sensitivity analyses – change in BCVA from baseline: ranibizumab versus aflibercept comparison (FEM)

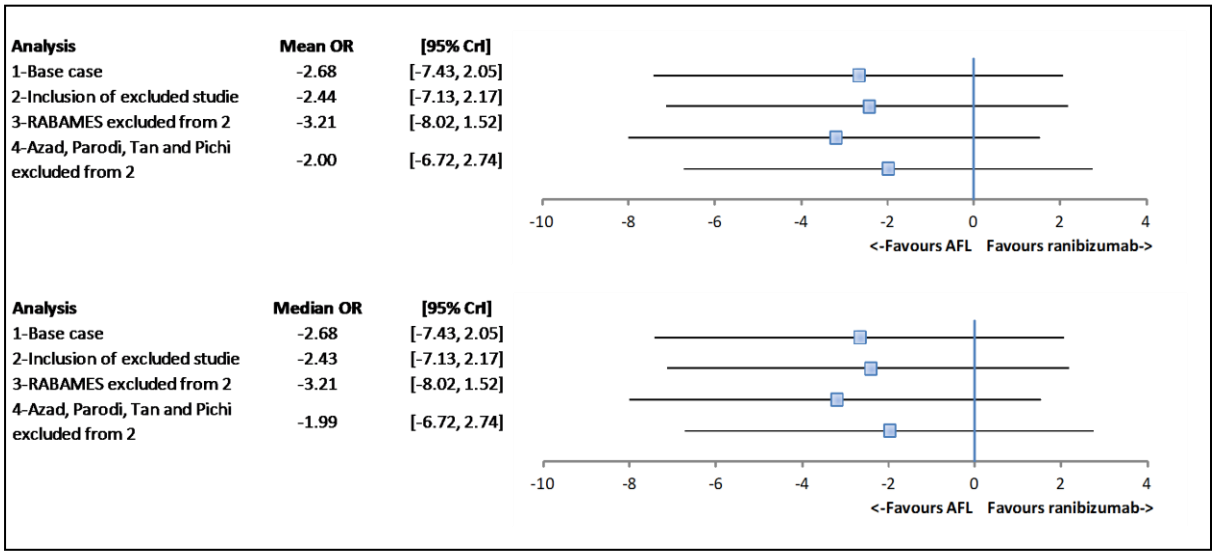
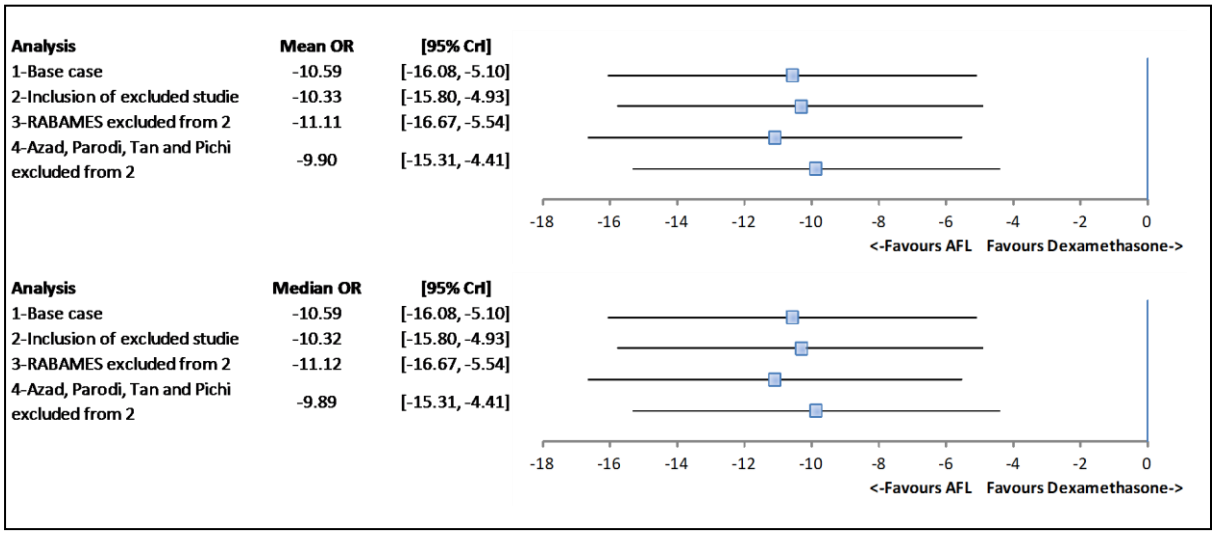


Table 41. Sensitivity analyses – change in BCVA from baseline: dexamethasone versus aflibercept comparison (FEM)

Scenario number	Scenario	Mean	Median	2.5% CrI	97.5% CrI	DIC
1	**Base case**	**-10.59**	**-10.59**	**-16.08**	**-5.10**	**40.42**
2	Inclusion of excluded studies (Azad 2012(42), Parodi 2008(43), Pichi 2014(44), Tan 2014(45), RABAMES(46)	-10.33	-10.32	-15.80	-4.93	110.98
3	Rabames(46) excluded from 2	-11.11	-11.12	-16.67	-5.54	90.92
4	Azad 2012(42), Parodi 2008(43), Tan 2014(45) and Pichi 2014(44) excluded from 2	-9.90	-9.89	-15.31	-4.41	60.08

Figure 34. Sensitivity analyses – change in BCVA from baseline: dexamethasone versus aflibercept comparison (FEM)



4.10.9 Statistical assessment of Heterogeneity

No studies making the same comparisons have been included in the base case network and therefore a statistical assessment of heterogeneity, for example calculation of I^2 statistics was not possible. This lack of multiple studies per comparison, and in general the limited number of trials conducted in patients with BRVO, meant that running a meta-regression to test the impact of baseline characteristics on the final results was attempted but found to not converge. However differences in patient's characteristics were observed across trials and this should be considered while interpreting the results.

4.10.10 Assessment of Inconsistencies in the network of evidence

There are no closed loops in the evidence network and therefore no formal test of inconsistency was necessary.

Limitations of the indirect comparison

There are some limitations of this analysis that are important to note, mainly due to the limited evidence available in the public domain:

- A relatively small number of trials in macular oedema secondary to BRVO have been conducted, and some of them are based on small sample sizes, which led to results associated with a large amount of uncertainty.

- Results from the BRIGHTER(40) trial (n=354) and the COMRADE-B(41) trial (n=241) are only available in poster and abstract format and not from peer reviewed publications.

- Data availability also limited the number of outcomes that could be included in the NMA: gaining ≥15 letters and BCVA change from baseline. No comparison of safety or comparisons in subgroups were possible as connected networks could not be developed.

- The application of additional or rescue treatments other than the randomly assigned treatment was also an issue. The time at which these treatments became available and the criteria for further treatment varied between trials.

Summary of NMA results

- Nine studies were located for possible inclusion in an evidence network. Five studies showed significant between-study heterogeneity that could affect efficacy and were excluded from the basecase evidence network. These studies were included in sensitivity analyses.

- Subgroup comparisons were not possible as a connected network could not be formed

- The FEM was the best fitting model for the comparisons

Comparison against ranibizumab

- Basecase results showed no evidence of difference in either outcome. For the outcome used in the economic model (proportion of patients gaining ≥15 letters from baseline) there was a small numerical benefit for ranibizumab in terms of the mean but a small numerical benefit for aflibercept in terms of the median. In the sensitivity analyses all comparisons continued to cross unity. Whether the median OR numerically favoured aflibercept or ranibizumab was sensitive to the inclusion/exclusion of the RABAMES(46) study.

Comparison against dexamethasone

- The basecase results for the FEM showed evidence of greater benefit for aflibercept for both efficacy comparisons. For the proportion of patients gaining 15 or more letters from baseline the inclusion of the RABAMES study lead to the CrI crossing unity.

NMA Results used in the economic model

- For the economic analysis (see section 5.3.1.2) the economic model uses the median OR estimates from the 4 studies included in the basecase network for the proportion of patients gaining 15 or more letters from baseline. Sensitivity analyses are also presented using the results obtained when all nine studies were included in the NMA.

4.11 Non-randomised and non-controlled evidence

No non-RCT evidence has been presented in this submission.

4.12 Adverse reactions

Overall, the safety data demonstrate that aflibercept has a favourable safety profile, both locally and systemically, when compared with laser therapy in patients with macular oedema secondary to BRVO. Safety outcomes were also consistent with those already seen in patients with neovascular AMD, DMO or CRVO, and suggest no association with increased risk for fatalities, APTC events, or SAEs.

Aflibercept is well tolerated in patients with BRVO over 52 weeks with no notable differences between 2Q4 and 2Q8 regimens or, with the exception of injection-related TEAEs, compared with laser photocoagulation in the incidence of ocular or non-ocular TEAEs. In general, TEAEs consistent with the injection procedure were more common in the aflibercept groups e.g. conjunctival haemorrhage, whereas TEAEs consistent with disease worsening were more common in the laser group. No cases of endophthalmitis occurred in the VIBRANT study. The most common non-ocular TEAEs were nasopharyngitis and hypertension, both of which were balanced across treatment groups. APTC events were low (2%) and only occurred in the laser group.

Safety outcomes with aflibercept were consistent with those reported in aflibercept studies in wet AMD, DMO and CRVO, confirming the validity of the safety results for aflibercept across larger cohorts.

Other than the comparison with laser photocoagulation, no direct comparison with other active agents used to treat BRVO in clinical practice was included in VIBRANT. Due to lack of data, safety comparisons were not possible in the indirect comparisons conducted. A comparable safety profile between aflibercept and ranibizumab has already been demonstrated in wet AMD. Based on the safety profile of aflibercept demonstrated in VIBRANT, it is anticipated that aflibercept will also have a comparable safety profile to ranibizumab in the treatment of BRVO. With regard to dexamethasone implant, as indicated in the RCO guidelines, the development and progression of cataracts are a complication of its use.

Evidence of the safety and tolerability profile of aflibercept in the treatment of visual impairment due to macular oedema secondary to BRVO, is provided by safety analyses and adverse event (AE) reporting from the international, multicentre, double-masked, active-controlled, 52-week phase 3 study, VIBRANT (8;24-26;28). The design, methodology, descriptions of all endpoints, and efficacy results from VIBRANT are detailed earlier in this section (section 4.3 to 4.8). The safety and tolerability of repeated intravitreal administration of aflibercept, when compared with grid laser photocoagulation for a period of up to 52 weeks was included as a secondary objective in VIBRANT.

Safety was monitored with the recording of ocular (in the study and fellow eye) and non-ocular AEs at each study visit. The term AE refers here to treatment-emergent AEs, (TEAEs) i.e. AEs which occurred or worsened after the first administration of study drug. Adverse events were summarised using the Medical Dictionary for Regulatory activities (MedDRA) (version 16.0) and were assessed for seriousness, intensity, pattern, causal relationship to study drug, and causal relationship to the injection procedure. Other safety procedures included laboratory evaluations, measurement of vital signs, and intraocular pressure (IOP) measurements.

The safety analysis population (SAF) included all randomised patients who had received any study treatment: aflibercept group n=91; laser group n=92.

A total of 112 patients in VIBRANT experienced at least one TEAE during the first 24 weeks of the study period (Laser: n=54 [58.7%]; aflibercept: n=58 [63.7%]) and 151 patients during the entire 52 weeks (Laser: n=75 [81.5%]; aflibercept: n=76 [83.5%]) (Table 42). Review of the VIBRANT safety data shows that aflibercept was generally well tolerated, without notable differences compared with grid laser photocoagulation in the incidence of ocular or non-ocular TEAEs.

Table 42: Overall adverse event profile through week 24 and week 52 (SAF) (8;24-26)

	Through week 24		Through week 52	
	Laser (N=92) n (%)	**Aflibercept (N=91) n (%)**	**Laser (N=92) n (%)**	**Aflibercept (n=91) n (%)**
Any TEAE	**54 (58.7)**	**58 (63.7)**	**75 (81.5)**	**76 (83.5)**
Non-ocular (systemic)	46 (50.0)	43 (47.3)	63 (68.5)	61 (67.0)
Ocular (study eye)	25 (27.2)	34 (37.4)	44 (47.8)	45 (49.5)
Any study drug-related AE				
Ocular drug-related (study eye)	1 (1.1)	1 (1.1)	2 (2.2)	2 (2.2)
Non-ocular drug-related	2 (2.2)	1 (1.1)	2 (2.2)	3 (3.3)
Any injection-related TEAE	**8 (8.7)**	**23 (25.3)**	**19 (20.7)**	**27 (29.7)**
Injection-related ocular TEAE	8 (8.7)	23 (25.3)	19 (20.7)	27 (29.7)
Study eye	8 (8.7)	23 (25.3)	18 (19.6)	27 (29.7)
Any laser-related TEAE	**3 (3.3)**	**2 (2.2)**	**5 (5.4)**	**2 (2.2)**
Laser-related ocular TEAE	3 (3.3)	2 (2.2)	5 (5.4)	2 (2.2)
Study eye	3 (3.3)	2 (2.2)	5 (5.4)	2 (2.2)
Any serious TEAE	**9 (9.8)**	**9 (9.9)**	**10 (10.9)**	**14 (15.4)**
Non-ocular (systemic)	9 (9.8)	8 (8.8)	10 (10.9)	13 (14.3)
Ocular (study eye)	0	1 (1.1)	0	1 (1.1)
Drug-related serious TEAE	**0**	**0**	**0**	**0**
Any injection-related serious TEAE (study eye)	**0**	**1 (1.1)**	**0**	**1 (1.1)**
Any laser-related serious TEAE	**0**	**0**	**0**	**0**
Any AEs leading to discontinuation of study drug	**0**	**3 (3.3)**	**0**	**4 (4.4) [a]**
Any death	**1 (1.1)**	**0**	**1 (1.1)**	**0**
Any APTC adjudicated events	**1 (1.1)**	**0**	**2 (2.2)**	**0**

Notes: aflibercept administered as 2mg every 4 weeks through week 24, then every 8 weeks through week 48. Laser treatment administered on day 1; rescue laser treatment possible after week 12 and aflibercept rescue treatment (67 of 90 patients) possible after week 24.

a A fourth patient was reported to have had two SAEs (central pelvic abscess and small bowel obstruction). As a consequence of these SAEs, the patient went to a hospice for a prolonged period and never continued the study treatment. The patient was documented to have discontinued the study. However, the SAEs were not documented in the clinical database as leading to discontinuation from study drug and are therefore not displayed in the source table.

Ocular TEAEs and Serious Adverse Events (SAEs)

Ocular TEAEs in the study eye were generally consistent either with disease progression or with the expected adverse consequences of the injection procedure and were mostly of mild or moderate intensity.

The incidence of ocular TEAEs in the study eye was higher in the aflibercept group compared with the laser group at week 24 (37.4% versus 27.2%), but became similar at week 52 after initiation of aflibercept rescue treatments in eligible patients in the laser group (47.8% vs. 49.5%).

The initial difference was largely accounted for by an increased frequency in injection-related TEAEs in the aflibercept group compared with the laser group.

Consistent with this, the most common ocular TEAE reported for the aflibercept group was conjunctival haemorrhage (19.8% vs. 4.3%, aflibercept vs. laser, respectively) (see Table 43). At week 52, these percentages started to become more similar (aflibercept 24.2%, laser 15.2%), reflecting the start of rescue intravitreal aflibercept injections in eligible patients in the laser group.

The most common ocular AE reported in the laser group was eye pain (week 24: 4.4% vs. 5.4%; week 52: 5.5% vs. 7.7% aflibercept vs. laser, respectively). During the first 24 weeks of the study, 3 eyes, all in the laser group, developed retinal neovascularisation; 2 of these eyes were treated with scatter laser photocoagulation. A further eye developed neovascularisation, during the week 24 to week 52 study period. This patient was in the laser group but had also received rescue aflibercept. There was no report of anterior segment neovascularisation. Other individual ocular TEAEs in the study eye were low and balanced between treatment groups.

The only serious ocular TEAE (traumatic cataract) in the study eye occurred in the aflibercept group before week 24. The SAE was considered injection procedure related, and resulted in the patient discontinuing study drug. There were no cases of endophthalmitis in either treatment group. One eye (1.1%) in the laser/aflibercept group had mild intraocular inflammation between weeks 24 and 52. Drug-related ocular TEAEs were low and similar between the treatment groups (week 52: n=2

[2.2%] aflibercept and n=2 [2.2%] laser; week 24: n=1 [1.1%] aflibercept and n=1 [1.1%] laser) and none were deemed serious.

Table 43: Ocular TEAEs in the study eye reported in ≥ 1% of patients in any treatment group through Week 52 by Preferred Term (FAS) (8;24-26;28)

MedDRA preferred term	Through week 24		Through week 52	
	Laser (N=92) n (%)	Aflibercept (N=91) n (%)	Laser (N=92) n (%)	Aflibercept (N=91) n (%)
Any ocular TEAE (study eye)	**25 (27.2)**	**34 (37.4)**	**44 (47.8)**	**45 (49.5)**
Angle closure glaucoma	0	1 (1.1)	0	2 (2.2)
Blepharitis	0	1 (1.1)	0	1 (1.1)
Cataract	0	2 (2.2)	0	3 (3.3)
Cataract cortical	0	1 (1.1)	0	2 (2.2)
Cataract subcapsular	0	1 (1.1)	0	1 (1.1)
Cataract traumatic	0	1 (1.1)	0	1 (1.1)
Conjunctival haemorrhage	4 (4.3)	18 (19.8)	14 (15.2)	22 (24.2)
Conjunctivitis allergic	0	0	2 (2.2)	1 (1.1)
Corneal abrasion	0	0	1 (1.1)	2 (2.2)
Corneal dystrophy	1 (1.1)	0	1 (1.1)	0
Corneal epithelium defect	0	2 (2.2)	0	2 (2.2)
Corneal opacity	1 (1.1)	0	1 (1.1)	0
Cystoid macular oedema	0	0	2 (2.2)	1 (1.1)
Dry eye	2 (2.2)	1 (1.1)	3 (3.3)	1 (1.1)
Eye discharge	1 (1.1)	0	2 (2.2)	0
Eye irritation	1 (1.1)	4 (4.4)	1 (1.1)	7 (7.7)
Eye pain	5 (5.4)	4 (4.4)	7 (7.7)	5 (5.5)
Eye Pruritus	0	1 (1.1)	0	2 (2.2)
Eyelid disorder	1 (1.1)	0	1 (1.1)	0
Eyelid irritation	1 (1.1)	0	1 (1.1)	0
Eyelid margin crusting	0	1 (1.1)	0	1 (1.1)
Eyelid oedema	0	1 (1.1)	0	1 (1.1)
Eyelid pain	0	0	0	1 (1.1)
Foreign body sensation in eyes	0	3 (3.3)	0	3 (3.3)
Injection site pain	0	1 (1.1)	0	1 (1.1)
Intraocular pressure increased	0	2 (2.2)	1 (1.1)	4 (4.4)
Lacrimation increased	0	3 (3.3)	0	3 (3.3)
Macular degeneration	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)
Macular fibrosis	2 (2.2)	1 (1.1)	2 (2.2)	3 (3.3)
Macular oedema	2 (2.2)	1 (1.1)	3 (3.3)	1 (1.1)
Ocular discomfort	1 (1.1)	0	1 (1.1)	0
Ocular hyperaemia	2 (2.2)	2 (2.2)	3 (3.3)	2 (2.2)
Optic disc haemorrhage	1 (1.1)	0	1 (1.1)	0
Optic disc vascular disorder	0	0	0	1 (1.1)
Photophobia	0	0	1 (1.1)	1 (1.1)
Posterior capsule opacification	1 (1.1)	0	1 (1.1)	0
Procedural complication	1 (1.1)	0	1 (1.1)	0
Punctate keratitis	0	0	0	1 (1.1)
Retinal exudates	1 (1.1)	0	2 (2.2)	0
Retinal haemorrhage	1 (1.1)	1 (1.1)	1 (1.1)	3 (3.3)
Retinal neovascularisation	3 (3.3)	0	4 (4.3)	0
Retinal pigment epitheliopathy	0	0	1 (1.1)	0

MedDRA preferred term	Through week 24		Through week 52	
	Laser (N=92) n (%)	Aflibercept (N=91) n (%)	Laser (N=92) n (%)	Aflibercept (N=91) n (%)
Retinal vascular disorder	1 (1.1)	0	2 (2.2)	1 (1.1)
Retinal vein occlusion	1 (1.1)	0	1 (1.1)	0
Retinopathy	0	0	1 (1.1)	0
Retinopathy hypertensive	1 (1.1)	0	1 (1.1)	0
Vision blurred	1 (1.1)	1 (1.1)	3 (3.3)	2 (2.2)
Visual acuity reduced	1 (1.1)	0	1 (1.1)	1 (1.1)
Visual acuity tests abnormal	0	1 (1.1)	0	1 (1.1)
Vitreous detachment	0	2 (2.2)	2 (2.2)	2 (2.2)
Vitreous floaters	0	1 (1.1)	0	1 (1.1)
Vitreous haemorrhage	1 (1.1)	0	3 (3.3)	1 (1.1)

Fellow eye

There were a low number of ocular TEAEs reported in the fellow eye at week 24 (7.6% laser group; 11.0% aflibercept group), increasing to reports in 19.6% (laser group) and 25.0% (aflibercept group) of patients by week 52. None of the TEAEs in the fellow eye were reported to be drug-related, injection-related or serious.

Injection-related TEAEs and SAEs

At week 24, the incidence of injection-related ocular TEAEs in the study eye was higher in the aflibercept group (25.3%) than in the laser group (8.7%), which was consistent with the expected adverse consequences of the injection procedure. By week 52, the difference between groups was smaller (aflibercept 29.7%, laser 19.6%), reflective of the start of aflibercept rescue injections in eligible patients in the laser group.

Injection-related TEAEs included conjunctival haemorrhage (most common ocular TEAE), eye pain, eye irritation, and foreign body sensation in eyes.

One injection-related ocular TEAE was considered serious (aflibercept: traumatic cataract).

Laser-related TEAEs and SAEs

The incidence of ocular laser procedure-related TEAEs in the study eye was low and similar between treatment groups: 3 [3.3%] laser and 2 [2.2%] aflibercept) through week 24 and 5 [5.4%] laser and 2 [2.2%] aflibercept) through week 52.

Non-ocular TEAEs and SAEs

The incidence of non-ocular TEAEs was similar in both groups at week 24 (47.3% aflibercept vs. 50.0% laser), and week 52 (67.0% aflibercept vs. 68.5% laser), suggesting that aflibercept treatment did not have an impact on non-ocular TEAEs (see Table 44) Non-ocular AEs that occurred in ≥5% of aflibercept and laser patients at week 24 were hypertension (6.6% and 10.9%, respectively) and nasopharyngitis (6.6% and 5.4%, respectively). A similar pattern was seen at 52 weeks.

Serious non-ocular TEAEs occurred with a similar frequency in the aflibercept and laser groups during the study (8.8% and 9.8% from baseline to week 24, respectively; 14.3% and 10.9% from baseline to week 52, respectively). Over the 52 weeks of study, serious non-ocular TEAEs that occurred in >1 patient were acute renal failure (1 patient [1.1%] in each treatment group), anaemia (2 patients [2.2%] in the aflibercept group), dehydration (2 patients [2.2%] in the laser group), hypertension (1 patient [1.1%] in each treatment group), and pneumonia (1 patient [1.1%] in the laser group and 2 patients [2.2%] in the aflibercept group).

Table 44: Non-ocular TEAEs reported in ≥2% of patients in any treatment group through Week 52 by Primary System Organ Class and Preferred Term in the VIBRANT study (8;24-26;28)

System organ class MedDRA preferred term	Through week 24		Through week 52	
	Laser (N=92) n (%)	Aflibercept (N=91) n (%)	Laser (N=92) n (%)	Aflibercept (N=91) n (%)
Any non-ocular TEAE	**46 (50.0)**	**43 (47.3)**	**63 (68.5)**	**61 (67.0)**
Blood & Lymphatic system disorders	**2 (2.2)**	**1 (1.1)**	**2 (2.2)**	**3 (3.3)**
Anaemia	1 (1.1)	1 (1.1)	1 (1.1)	3 (3.3)
Gastrointestinal disorders	**7 (7.6)**	**4 (4.4)**	**8 (8.7)**	**10 (11.0)**
Abdominal pain	2 (2.2)	0	2 (2.2)	0
Constipation	0	1 (1.1)	0	2 (2.2)
Diarrhoea	2 (2.2)	0	2 (2.2)	0
Gastroesophogeal reflux disease	0	1 (1.1)	0	2 (2.2)
General disorders & administration site conditions	**5 (5.4)**	**1 (1.1)**	**7 (7.6)**	**3 (3.3)**
Asthenia	2 (2.2)	0	2 (2.2)	0
Immune system disorders	**3 (3.3)**	**0**	**4 (4.3)**	**1 (1.1)**
Drug hypersensitivity	1 (1.1)	0	2 (2.2)	0
Infections and infestations	**15 (16.3)**	**19 (20.9)**	**28 (30.4)**	**30 (33.0)**
Bronchitis	4 (4.4)	2 (2.2)	6 (6.6)	
Gastroenteritis viral	1 (1.1)	0	1 (1.1)	3 (3.3)
Influenza	1 (1.1)	3 (3.3)	2 (2.2)	4 (4.4)
Nasopharyngitis	1 (1.1)	6 (6.6)	8 (8.7)	8 (8.8)
Oral herpes	5 (5.4)	0	2 (2.2)	0
Pneumonia	2 (2.2)	0	2 (2.2)	2 (2.2)
Sinusitis	2 (2.2)	1 (1.1)	4 (4.3)	4 (4.4)
Upper respiratory tract infection	1 (1.1)	4 (4.4)	0	4 (4.4)
Urinary tract infection	0	1 (1.1)	7 (7.6)	3 (3.3)
	2 (2.2)			
Injury, poisoning & procedural complications	**6 (6.5)**	**3 (3.3)**	**10 (10.9)**	**9 (9,9)**
Contusion	1 (1.1)	0	2 (2.2)	1 (1.1)
Laceration	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
Muscle strain	1 (1.1)	1 (1.1)	2 (2.2)	2 (2.2)
Road traffic accident	2 (2.2)	0	3 (3.3)	0
Investigations	**9 (9.8)**	**11 (12.1)**	**18 (19.6)**	**17 (18.7)**
Blood cholesterol increased	1 (1.1)	2 (2.2)	1 (1.1)	2 (2.2)
Blood creatine phosphokinase increased	0	0	3 (3.3)	0
Blood glucose increased	0	0	1 (1.1)	2 (2.2)
Blood pressure increased	4 (4.3)	3 (3.3)	5 (5.4)	4 (4.4)
Blood pressure systolic increased	4 (4.3)	3 (3.3)	2 (2.2)	2 (2.2)
Blood triglycerides increased	1 (1.1)	2 (2.2)	4 (4.3)	0
Eosinophil count decreased	2 (2.2)	0	0	2 (2.2)
Haematocrit decreased	0	0	0	2 (2.2)
Haemoglobin decreased	0	0	0	2 (2.2)
Monocyte count decreased	0	0	0	2 (2.2)
White blood cells urine positive	0	0	1 (1.1)	2 (2.2)
Metabolism & Nutrition	**8 (8.7)**	**2 (2.2)**	**12 (13.0)**	**8 (8.8)**

System organ class MedDRA preferred term	Through week 24		Through week 52	
	Laser (N=92) n (%)	Aflibercept (N=91) n (%)	Laser (N=92) n (%)	Aflibercept (N=91) n (%)
disorders				
Dehydration	2 (2.2)	0	2 (2.2)	0
Diabetes mellitus	0	0	1 (1.1)	3 (3.3)
Hypercholesterolaemia	2 (2.2)	0	2 (2.2)	2 (2.2)
Hyperlipidaemia	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
Hypertriglyceridaemia	1 (1.1)	0	2 (2.2)	0
Musculoskeletal and connective tissue disorders	**9 (9.8)**	**5 (5.5)**	**16 (17.4)**	**7 (7.7)**
Arthralgia	0	2 (2.2)	2 (2.2)	2 (2.2)
Back pain	0	1 (1.1)	3 (3.3)	2 (2.2)
Joint swelling	0	0	2 (2.2)	0
Osteoarthritis	1 (1.1)	0	2 (2.2)	0
Nervous system disorders	**9 (9.8)**	**2 (2.2)**	**14 (15.2)**	**5 (5.5)**
Dizziness	1 (1.1)	0	2 (2.2)	2 (2.2)
Headache	3 (3.3)	0	3 (3.3)	0
Syncope	0	0	2 (2.2)	0
Psychiatric disorders	**1 (1.1)**	**1 (1.1)**	**1 (1.1)**	**2 (2.2)**
Anxiety	0	1 (1.1)	0	2 (2.2)
Renal & urinary disorders	**4 (4.3)**	**4 (4.4)**	**6 (6.5)**	**6 (6.6)**
Urine abnormality	0	0	1 (1.1)	2 (2.2)
Respiratory, Thoracic & Mediastinal disorders	**5 (5.4)**	**6 (6.6)**	**8 (8.7)**	**10 (11.0)**
Chronic obstructive pulmonary disease	0	1 (1.1)	0	2 (2.2)
Cough	2 (2.2)	1 (1.1)	2 (2.2)	3 (3.3)
Dyspnoea	0	2 (2.2)	0	3 (3.3)
Vascular Disorders	**11 (12.0)**	**7 (7.7)**	**16 (17.4)**	**11 (12.1)**
Hypertension	10 (10.9)	6 (6.6)	15 (16.3)	10 (11.0)

Deaths

No deaths occurred in the aflibercept group during the 52 weeks of study. One death (pneumonia) was reported in the laser group, occurring before week 24.

Additional Adverse Events of interest: Arterial Thromboembolic Events (ATE) Based on Anti-Platelet Triallists' Collaboration (APTC) endpoint

ATEs, as defined by APTC criteria, include non-fatal myocardial infarction (MI), non-fatal ischaemic or haemorrhagic stroke, or vascular death (including deaths of unknown cause). APTC events are the most clinically important arterial thromboembolic events because they can represent irreversible morbidity or mortality. Potential ATEs were evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC (54).

In VIBRANT, there were no reported APTC events in the aflibercept group and 2 reported APTC events in the laser group (non-fatal stroke, non-fatal MI), one of which occurred before administration of aflibercept (non-fatal stroke).

Intraocular pressure (IOP)

There was generally no effect on mean change or threshold values of IOP over time.

Immunogenicity

There was no meaningful antibody response and no significant immunogenicity associated with intravitreal administration of 2 mg aflibercept in the VIBRANT study. Two patients had a positive anti-drug antibodies (ADA) assay (1 in the laser group and 1 in the aflibercept group), both positive at baseline and at week 24 with low ADA titres (i.e., 30, the minimum for the assay), demonstrating no titre increase from baseline. In addition, none of the samples that were positive in the ADA assay demonstrated neutralising activity.

Other investigations

No noteworthy trends relative to treatment, treatment duration or treatment exposure were observed for blood chemistry, haematology, or urinalysis parameters; or for heart rate, body temperature, blood pressure or ECG.

Adverse events leading to withdrawal

Four patients from the aflibercept group discontinued study treatment as a result of AEs. Of the 4 events, 2 were ocular and in the study eye (traumatic cataract and increased IOP). The non-ocular events were metastatic breast cancer in one patient and central pelvic abscess and small bowel obstruction in another patient. There were no AEs leading to discontinuation in the laser group.

Subgroup analyses

The subgroup analyses of safety supported the results seen in the overall population; however, several of the subgroups were too small to draw useful conclusions.

4.13 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence: clinical benefits and harms

Evidence to support the use of aflibercept for the treatment of macular oedema secondary to BRVO is provided by results from VIBRANT, a large, prospective, phase 3, randomised, double-masked, active-controlled, study. In this study, 183 patients with Best Corrected Visual Acuity between ≤73 and ≥24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters were randomised to aflibercept or laser photocoagulation. The primary endpoint was the proportion of patients gaining ≥15 letters from baseline to week 24 in Best Corrected Visual Acuity. Secondary endpoints included the change from baseline in BCVA score at week 24 and the change from baseline in central retinal thickness (CRT).

The proportion of patients gaining ≥ 15 letters in best corrected visual acuity at week 24 was significantly greater in the aflibercept group compared to the laser group (52.7% vs. 26.7%, p=0.0003). Aflibercept was also superior to laser in the number of letters gained from baseline and improvements in anatomic secondary endpoints such as reduction in central retinal thickness. The improvement in letters gained from baseline in the aflibercept group (+17 letters) was considered clinically relevant as it represents a gain of 3 lines on a vision chart - a change that is important to patients. Both functional and anatomic improvements were achieved rapidly starting at month 1 and continued to increase with most of the effect reached by month 3, which is in line with the goal of treatment to shorten duration of oedema, thereby reducing the risk for retinal damage and increasing the chances of vision recovery. In contrast, patients receiving laser treatment improved at a consistent slower rate from baseline onwards.

Improvements were also seen with regards to retinal ischaemia and retinal perfusion. Furthermore, analysis of retinal fluid status of patients at the end of the week 24,

showed that, compared to laser, significantly more patients receiving aflibercept were classified as ‘dry’ across the entire centre subfield as well as for the foveal centre only.

The benefits in terms of visual acuity and anatomic variables observed at week 24 in the aflibercept group were maintained throughout the 52 weeks of the study, despite the injection frequency of aflibercept being reduced to every other month, from week 24. In addition, eligible patients in the laser group benefited from the start of aflibercept rescue treatment at week 24. A high number of patients from the laser group required rescue aflibercept treatment during weeks 24 to 52 (67 out of 90 patients), which enabled further improvements in visual outcomes, above and beyond that achieved by laser alone in the first 24 weeks, however, patients in this group were still unable to achieve the significant clinical effects observed in the aflibercept group, who had received prompt and fixed monthly doses of aflibercept from the start of VIBRANT. This is consistent with the 12-month results in the BRAVO trial with ranibizumab (37) and emphasises the importance of patients receiving effective treatment modalities from diagnosis, with minimal delays, in order to achieve optimal visual improvement. This point is also made in the recently updated management guidelines for RVO published by the Royal College of Ophthalmologists (RCO) (6), where it is highlighted that ‘*a delay of six months in initiating anti-VEGF therapy in this condition also results in an inferior visual outcome compared to prompt treatment at diagnosis*’. The RCO also now recommend restriction of the use of laser as first - line treatment in BRVO only to patients unsuitable or unwilling to receive anti-VEGF therapy. This recommendation is supported by the BVOS study (7) in which only 40% of patients had a final visual acuity of 6/12 at 36 months despite macular laser treatment.

The efficacy and safety of aflibercept was corroborated across subgroup and sensitivity analyses, indicating the robustness of the results in a broad spectrum of patients. A small number of patients with non-perfused retinas were included in the VIBRANT study. The magnitude of the benefit observed in this group of patients was similar to patients with perfused retinas (see Figure 14) although the confidence intervals were wide.

The beneficial clinical profile of aflibercept was accompanied by an acceptable safety profile, both locally and systemically, when compared with laser therapy in patients with macular oedema secondary to BRVO. Aflibercept was well tolerated over 52 weeks with no notable differences between 2Q4 and 2Q8 regimens or, with the exception of injection-related TEAEs, compared with laser photocoagulation in the incidence of ocular or non-ocular TEAEs.

In general, TEAEs consistent with the injection procedure were more common in the aflibercept groups e.g. conjunctival haemorrhage, whereas TEAEs consistent with disease worsening were more common in the laser group. No cases of endophthalmitis occurred in the VIBRANT study. The most common non-ocular TEAEs were nasopharyngitis and hypertension, both of which were balanced across treatment groups. APTC events were low (2%) and only occurred in the laser group.

Safety outcomes with aflibercept were consistent with those reported in aflibercept studies in wet AMD, DMO and CRVO, confirming the validity of the safety results for aflibercept across larger cohorts. Overall, on the evidence presented, the benefits of aflibercept in the treatment of visual impairment due to macular oedema secondary to BRVO outweigh any treatment related risks.

Strengths and limitations of the clinical evidence base

A strength of the evidence base is that the efficacy and safety of aflibercept in treating MO secondary to BRVO was corroborated across all subgroup and sensitivity analyses conducted, indicating the robustness of the results in a broad spectrum of patients.

All efficacy and safety assessments in the VIBRANT study are standard variables and methods utilised in clinical studies for RVO, and in ophthalmic practice (6). They are widely recognised as valid, reliable, accurate and relevant.

It was also demonstrated that BRVO patients (by administration of rescue aflibercept) can achieve some clinical benefit, even if aflibercept treatment is not initiated promptly - although this management strategy was less effective than

prompt treatment and an initial period of fixed monthly dosing, and would not be recommended as an optimal treatment approach for BRVO.

The two different dosing (and monitoring) intervals studied for aflibercept i.e. monthly or 8-weekly provided information on the viability of a longer interval between monitoring and/or dosing, although, during marketing approval discussions, the CHMP considered that the study design was unsuitable to identify the optimal treatment frequency for BRVO patients (8). A fixed regimen, as used in VIBRANT, was considered by the CHMP to be unnecessary. On that basis, a similar regimen, as agreed for CRVO, i.e. initial fixed monthly dosing until stabilisation of vision to be followed by a flexible regimen, was considered more appropriate in absence of suitable data. The posology recommendations were also aligned with what is recommended for other anti-VEGF inhibitors in the same indication.

A limitation to the evidence is that laser photocoagulation is the only 'active' comparator in VIBRANT. At the time of the study design laser therapy was considered to be the standard of care, whereas now in clinical practice, ranibizumab, another intravitreal anti-VEGF treatment, is commonly used as 'standard of care' in England. An indirect comparison with ranibizumab, the only other intravitreal anti-VEGF treatment licensed for BRVO, has been included in this submission [see section 4.10], in order to put the results of VIBRANT into the context of current clinical practice. The results of the Network Meta-Analysis (NMA) showed no statistically significant difference in terms of the proportion of patients gaining 15 or more BCVA letters from baseline or in terms of the number of letters gained from baseline in the comparison against ranibizumab. In the comparison against dexamethasone aflibercept was superior in terms of gaining 15 letters from baseline.

Relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice

Population

'Adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion' is the population considered within this appraisal. The key inclusion criteria for VIBRANT study entry were patients ≥ 18 years of age, with BRVO or HRVO causing oedema involving the centre of the macula if the occlusion occurred within 12 months, and visual impairment (BCVA of 20/40 to 20/320). Therefore the population included within the clinical studies is reflective of the population defined in the appraisal scope.

The VIBRANT study was a multicentre trial conducted in North America (~90% of patients) and Japan (~10% of patients). There were no clinical trial centres in the UK, however the majority of patients in the trial were white (>70%). Typically, the risk of RVO increases with age and there is a similar distribution amongst men and women. In VIBRANT, 54% patients were male, and the total population ranged in age from 42 to 94 years, with a mean age of 65.5 years. The demographic and baseline characteristics of patients in VIBRANT were therefore broadly representative of a UK population of patients with BRVO.

Furthermore, the efficacy and safety of aflibercept was consistent across subgroups including age, gender, ethnicity, race, or baseline disease characteristics, demonstrating that a wide range of patients with BRVO, typical of those presenting in clinical practice in England, can benefit from aflibercept.

Comparators

In VIBRANT, aflibercept treatment was compared with the standard of care at the time of study design i.e. GLP. As can be seen from the results of VIBRANT, laser photocoagulation has limited effect on improving vision. Some of the difficulties encountered with laser treatment mean that treatment may not be able to take place, for example if there is too much bleeding, previous damage or scarring. Repeat

treatment may also cause macular scarring. An advantage of intravitreal pharmacological treatment of BRVO is that it does not carry the same risk of operator/clinical error and sudden or permanent visual loss, it avoids the potential destructive effects of laser photocoagulation in the long term, and importantly, repeat treatments are not limited. Moreover, laser requires the maintenance and servicing of machines, replacing of gas and lenses, repair or replacement in the case of breakdown, training and an appointed safety officer.

Laser photocoagulation is one of several comparators stated in the decision problem. As discussed already, since the design and conduct of VIBRANT, new treatments for MO secondary to BRVO have been approved by NICE for use only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage: dexamethasone intravitreal implant (July 2011, NICE TA229) and most recently, ranibizumab (May 2013, TA283) (9;55). The positioning of ranibizumab in its NICE appraisal i.e. after laser, or only if laser unsuitable, is now at odds with the recent guidelines for BRVO from The Royal College of Ophthalmologists where the positioning of laser and ranibizumab in the treatment pathway has been switched - laser is now restricted to patients unsuitable or unwilling to receive anti-VEGF therapy (6).

Intervention

Dose per injection in VIBRANT was 2mg intravitreally. This is the same dose per injection utilised in aflibercept treatment of wet AMD, CRVO and DMO. The posology used in the trial - initial monthly injections during the first 24 weeks, followed by a 2Q8 regimen to week 52 – has been adjusted for clinical practice, in line with that agreed for CRVO, i.e. initial fixed monthly dosing until stabilisation of vision to be followed by a flexible regimen. The posology recommendations were also aligned with what is recommended for other anti-VEGF inhibitors in the same indication.

Outcomes

The main impact of BRVO is the rapid loss or change in vision due to macular oedema (56). Outcome measures in VIBRANT were therefore based around assessment of treatment effects on vision and the ability of aflibercept to halt, slow or reverse disease progression. Improvements in these measures are of direct relevance and benefit to a patient with BRVO. Improvements in vision can mean the difference between independent and dependent living, improved wellbeing or depression, and also mean patients are less at risk of falls or accidents due to visual problems (57-59).

Also, the VIBRANT study did not exclude patients with excessive capillary non-perfusion (defined as > 10 disc areas [DA]). This expands the relevance of the results of all outcomes described below, since both patient-types (non-ischaemic and ischaemic) can be expected in clinical practice.

The primary efficacy endpoint in VIBRANT was an assessment on the ability of aflibercept to improve visual function i.e. *the proportion of patients who gained at least* 15 letters in the *ETDRS letter score at 6 months (week 24) compared to baseline*. During assessment, letters are read from standard eye-charts, commonplace worldwide and used routinely in ‘eye tests’ in clinical practice in the UK.

The primary endpoint was met in VIBRANT - aflibercept treatment was found to be significantly superior to grid laser photocoagulation.

Secondary endpoints included mean change in BCVA as measured by ETDRS letter score, which further assessed the effects of aflibercept on vision, and an anatomical endpoint of mean change in CRT provided information on the morphological effects of aflibercept. Superiority of aflibercept treatment compared to laser treatment was demonstrated for both of these endpoints.

Alongside the significant decrease in central retinal thickness, aflibercept induced further positive morphological changes to study eyes, as assessed by the endpoints ‘Proportion of patients with a decrease in retinal ischaemia’, ‘post-baseline retinal

perfusion status', and 'retinal fluid status'. Aflibercept treatment resulted in improved retinal perfusion and a decrease in retinal ischaemia, with greater improvement in retinal fluid status (i.e. absence of intra-retinal fluid or sub-retinal fluid) when compared with laser treatment.

The safety profile and patient tolerability of aflibercept were also evaluated at every study visit throughout the VIBRANT study. All AEs were assessed for seriousness, intensity, pattern, study drug action, drug treatment, causal relationship to study drug, and causal relationship to the injection procedure. Aflibercept was well tolerated throughout the 52-week study duration. No deaths occurred in the aflibercept group during the study. One death (pneumonia) was reported in the laser group, occurring before week 24.

Importantly, the positive effects of aflibercept on all measured efficacy and safety outcomes were shown to be durable throughout the year-long study. The clinical experience of aflibercept in BRVO is entirely in line with both trial and market experience of treatment of other eye conditions with aflibercept, such as CRVO, wet AMD and DMO.

End of life criteria

It is not intended for aflibercept, in the indication proposed within this submission, to be considered as a 'life-extending treatment at the end of life'.

4.14 Ongoing studies

There are no further studies, or updated analyses of existing studies, that are anticipated to provide data relevant to this submission in the next 6 to 12 months.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Search overview

A systematic literature search was performed which aimed to identify economic evaluations in the area of BRVO and RVO.

The search was conducted on October 7th 2015 using the following electronic databases;

- Embase (1988 – October 7th 2015)
- Medline (including Medline (R) in process (1946 – October 7th 2015))
- Econlit
- NHS EED

The search strings used for each database are presented in section 8, appendix **Error! Reference source not found.**.

In addition, a search was conducted to identify relevant economic evaluation conference abstracts and posters on November 23rd 2015. The following congress was searched:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (European meeting): http://ispor.org/

The search strategy, search terms and results for the congress search are detailed in appendix **Error! Reference source not found.**.

The inclusion and exclusion criteria are shown in Table 45. The interventions included in the search were aflibercept, ranibizumab, dexamethasone, laser and placebo/BSC/sham/observation.

The study designs included in the search were; papers presenting cost-effectiveness, cost-utility, cost-minimisation, cost-consequence and cost-benefit analyses, costing studies and resource use studies.

The search was restricted to publications from 2000 and limited to English language.

Table 45. Eligibility criteria for economic evaluation (and resource use) search

Economic evidence	Inclusion	Exclusion
Patient population	• Adult patients with BRVO or RVO	• Patients with CRVO, AMD and DMO
Interventions*	• Aflibercept **OR** • Dexamethasone **OR** • Ranibizumab **OR** • Laser	-
Comparators*	• Dexamethasone **OR** • Ranibizumab **OR** • Laser **OR** • Placebo/BSC/sham/observation	-
Outcome measures	• Resource use & costs	-
Study design	• Cost-benefit analysis **OR** • Cost-effectiveness analysis **OR** • Cost-minimisation analysis **OR** • Cost-utility analysis **OR** • Costing analysis **OR** • Resource use study	• Editorials **OR** • Notes **OR** • Comments **OR** • Letters **OR** • Systematic reviews of EE **OR** • Abstracts not providing sufficient data for extraction**
Restrictions	• Language: English • Published from 2000	• Non-English studies • Studies published prior to 2000

AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; DMO: diabetic macular oedema; RVO: retinal vein occlusion.

* Applies only to cost-benefit, cost-effectiveness, cost-utility and cost-minimisation studies.

** If full text publication not available.

5.1.2 Methods and process

After the removal of duplicates, the titles and abstracts of all references identified from the search were independently reviewed by two researchers. The suitability of the articles was evaluated against the eligibility criteria shown in Table 45. Full texts of the studies selected were reviewed and the same eligibility criteria applied. In the

event of a disagreement regarding inclusion the inclusion status of the publication were resolved either through “reconciliation” (discussion between the two reviewers) and/or through “arbitration” by a third independent reviewer. All papers included after the full text review were retained for data extraction. Data extraction was carried out by one reviewer and checked by another.

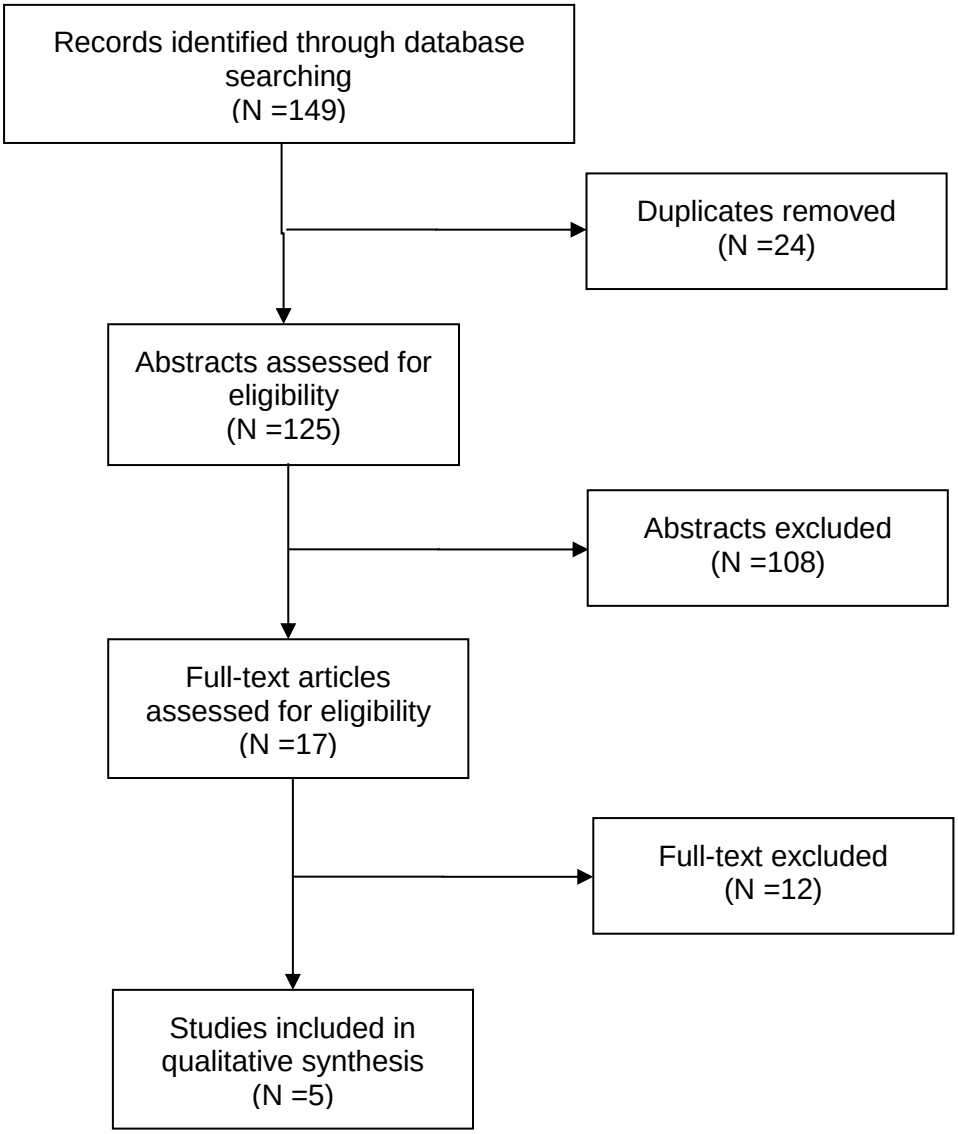
A quality assessment on the individual studies was conducted on the included studies as per the NICE guidance quality checklist. This checklist focuses on selection bias, performance bias, measurement bias and attrition bias.

5.1.3 Results

5.1.3.1 Search results

The economic evaluation and resource use search yielded a total of 149 hits, of which 24 were duplicates, leaving 125 records to be reviewed against the eligibility criteria. After screening the 125 titles and abstracts, 17 studies were selected for full-text review. Of these, 5 were retained for data extraction. The 12 studies excluded at the full text stage, and the primary reasons for exclusion are detailed in appendix **Error! Reference source not found.** - **Error! Reference source not found.**. The process of study selection and the final results of the search are illustrated using the PRISMA Flow diagram below (Figure 35).

Figure 35. PRISMA flow diagram for the economic (and resource use) search



5.1.3.2 Included studies

Table 46 lists the 5 studies that were selected for data extraction. These included three cost-utility analyses (CUA) (Brown et al. 2002(60), Smiddy et al. 2011(61), Taylor et al. 2014(62)) and two costing studies reporting resource use data (Fekrat et al. 2010(63) and Augustin et al. 2012(64)). One study reported a cost-effectiveness analysis alongside a cost-utility analysis (Smiddy et al. 2011(61)).

Table 46. Economic evaluation search included studies

Authors	Year	Title	Journal
Cost-utility analysis and/or cost-effectiveness analysis			
Brown et al.	2002	Incremental cost-effectiveness of laser therapy for visual loss secondary to branch retinal vein occlusion	Ophthalmic Epidemiology
Smiddy et al.	2011	Economic considerations of macular edema therapies	Ophthalmology
Taylor et al.	2014	A United Kingdom-based economic evaluation of ranibizumab for patients with retinal vein occlusion (RVO)	Journal of Medical Economics
Resource use			
Augustin et al.	2012	Treating retinal vein occlusions in France, Germany, and Italy: An analysis of treatment patterns, resource consumption, and costs	European Journal of Ophthalmology
Fekrat et al.	2010	Resource use and costs of branch and central retinal vein occlusion in the elderly	Current Medical Research and Opinion

This section of the submission will discuss the cost-utility and cost-effectiveness studies identified in the search. The resource use studies are further detailed in section 5.5.1.1.

5.1.3.2.1 Cost-utility and cost-effectiveness included studies

Brown et al. 2002(60), Smiddy et al. 2011(61) and Taylor et al. 2014(62) published cost-utility and cost-effectiveness economic evaluations. A summary on the studies is provided in Table 47. A full data extraction and summary of each study is provided in appendix **Error! Reference source not found.**.

In terms of setting, Brown et al. 2002(60) and Smiddy et al. 2011(61) were focused on the US setting and Taylor et al. (62) on the UK setting. The US studies were from a payer perspective and the UK study was from the perspective of the National Health Service. Brown et al. 2002(60) included patients with MO secondary to BRVO. Smiddy et al. 2011(61) and Taylor et al. 2014(62) included patients with MO associated with BRVO. However, Taylor et al. 2014(62) presented results separated

for two populations with observation the comparator in the BRVO population, and laser as the comparator for a CRVO population. In terms of model characteristics, a lifetime horizon was taken by both Brown et al. 2002(60) and Taylor et al. 2014(62) whereas a 1 year horizon was used in Smiddy et al. 2011(61). Furthermore, a two eye model was used by Brown et al. 2002(60), however the other two studies do not report this model characteristic.

Laser is compared to observation by both Brown et al. 2002(60) and Smiddy et al. 2011(61) with an ICER of $4,439 and $1,572 respectively. There was a notable difference in incremental outcome between these studies; 0.198 and 0.033 QALYs gained for Brown et al. 2002(60) and Smiddy et al. 2011(61) respectively. Brown(60) assigned utility values by BCVA level where as Smiddy et al. 2011(61) assigned a utility gain of 0.03 for each line of vision gained. Furthermore, Brown et al. 2002(60) discounted by 3% whereas Smiddy et al. 2011(61) applied no discount rate. Incremental costs are not able to be compared as this was not reported in Smiddy et al. 2011(61).

Ranibizumab is also compared to observation in Smiddy et al. 2011(61) and Taylor et al. 2014(62) with an ICER of $13,554 and £15,710 respectively. Furthermore, Taylor et al. 2014(62) compared ranibizumab to laser with an ICER of £17,103.

Smiddy et al. 2011(61) also compares intravitreal corticosteroids, dexamethasone, pegaptanib and bevacizumab which are all compared to observation. This study also performed a cost-effectiveness analysis which shown a range between $494 per line saved for bevacizumab compared to observation and $4,898 per line saved for pegaptanib compared to observation.

These three studies were based on models that differ significantly in terms of structure and underlying assumptions. None of these models explore the impact of VA improvement in the study eye relative to fellow eye on quality of life.

Table 47. Summary of economic evaluations identified

Study	Type of evaluation	Country	Study conclusion	Population	Technology	ICER	Comparator
Brown et al. 2002(60)	Cost-utility	US	Laser therapy appears to be a cost-effective intervention for improving visual loss associated with macular oedema secondary to BRVO compared to observation alone.	MO secondary to BRVO	Laser photocoagulation	$4,439/QALY	Observation (natural history)
Smiddy et al. 2011(61)	Cost-utility	US	Compared to observation, the following therapies were shown to be cost-effective; laser, corticosteroids, bevacizumab, dexamethasone and pegaptanib and ranibizumab.	MO associated with BRVO and CRVO	Laser photocoagulation	$1,572/QALY	Observation (natural history)
					Intravitreal corticosteroid	$2,217/QALY	
					Dexamethasone	$5,536/QALY	
					Pegaptanib	$13,554/QALY	
					Bevacizumab	$824/QALY	
					Ranibizumab	$13,554/QALY	
	Cost-effectiveness				Laser	$1,539/line saved	
					Intravitreal corticosteroid	$1,131/line saved	
					Dexamethasone	$2,990/line saved	
					Pegaptanib	$4,898/line saved	
					Bevacizumab	$494/line saved	
					Ranibizumab	$13,039/line saved	
Taylor et al. 2014(62)	Cost-utility	UK	The results show ranibizumab is a cost-effective treatment for patients with MO secondary to RVO relative to current standard care for BRVO and observation for CRVO.	MO secondary to BRVO and CRVO	Ranibizumab (BRVO)	£15,710/QALY	Observation
					Ranibizumab (CRVO)	£17,103/QALY	Laser photocoagulation

MO macular oedema; BRVO branch retinal vein occlusion, CRVO central retinal vein occlusion; US United States; UK United Kingdom

5.1.3.3 Quality assessment

A full quality assessment on the individual studies based on the NICE guidance quality checklist is shown in appendix **Error! Reference source not found.**.

Overall the best reported study in terms of number of checklist elements with a 'yes' was Brown et al. 2002(60). The study design and research question were well defined and described. The data collection was lacking in some detail such as price adjustments like inflation. The least well reported study was Taylor et al. 2014(62) which lacked a lot of detail in the data collection and in explaining the choice of analysis. Some of the analysis and interpretation was not well reported. Only one of the three studies, Smiddy et al. 2011(61), addressed generalisability issues. The sensitivity analysis was not well addressed with only one study justifying the choice of variables for sensitivity analysis (Taylor et al. 2014(62)) and one study describing the ranges parameters were varied across (Brown et al. 2002(60)). Overall, the study design was reported across all studies with the justification for the type of analysis as well as the conclusions with appropriate caveats in the analysis.

5.1.4 Summary

The cost-utility and cost-effectiveness studies identified in this literature review followed a simple pair wise comparison structure. The patient pathway of BRVO patients has developed in recent years with the introduction of anti-VEGFs to the market, as reflected in the NICE treatment pathway Figure 2. The models identified in the systematic review do not fully capture the costs and outcomes of the treatment pathway.

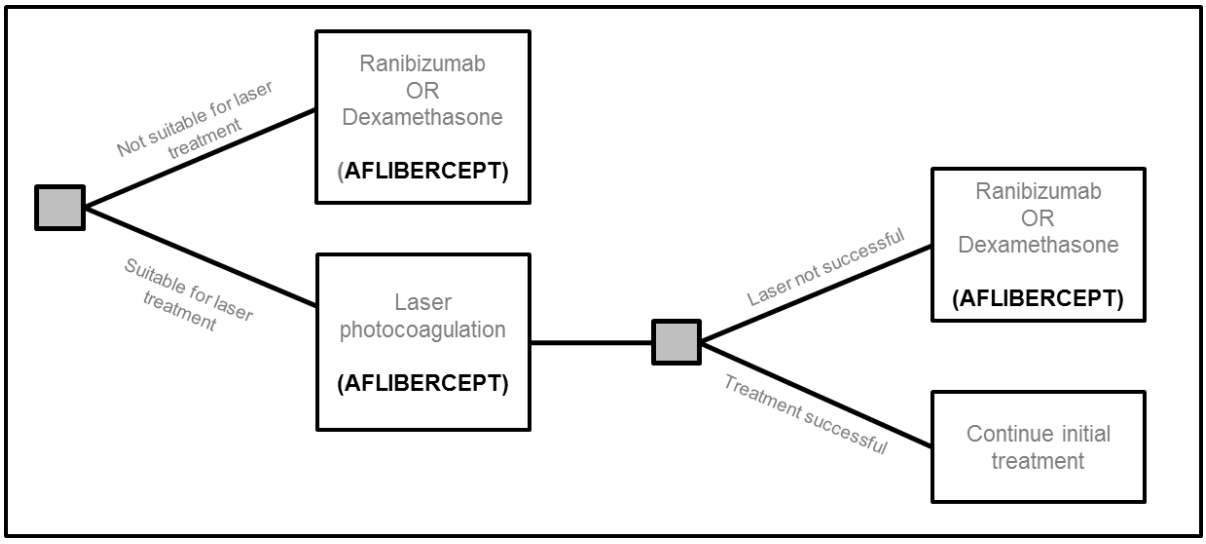
5.2 De novo analysis

Background

The results of the economic literature search (section 5.1.3) show that previous economic models relating to the treatment of BRVO have considered the costs and outcomes of single lines of therapy as pairwise comparisons e.g. ranibizumab versus laser or dexamethasone versus laser. However, the introduction of new treatments has resulted in a treatment pathway and therefore economic assessments should also consider the cost and outcomes of subsequent lines of therapy. Figure 36 shows the NICE recommended treatment pathway (grey text) where ranibizumab and dexamethasone are second-line options to first-line treatment with laser photocoagulation.

Aflibercept is indicated for the treatment of visual impairment due to BRVO without being restricted to patients for whom laser is unsuitable or where laser has not been beneficial. Therefore, according to its licence, aflibercept can be used at various points in the existing clinical pathway i.e. as an alternative to laser, ranibizumab or dexamethasone. The possible positions for aflibercept in the NICE pathway are shown in bold.

Figure 36. NICE recommended clinical pathway for BRVO



In clinical practice patients are monitored on a regular basis to assess response to treatment. Those who do not benefit from initial therapy such as laser have the

option of moving to one of the newer, more costly but more effective agents. Clinical guidelines recognise the limited benefit of laser treatment and RCTs such as VIBRANT(25) and BRAVO(35) show that a significant proportion of patients fail to achieve sufficient benefit on laser, requiring additional therapy. From an economic perspective it is therefore important to account for the costs and outcomes of the pathway of care that each patient receives.

To capture the costs and outcomes of the treatment pathway, a de novo model has been developed for this submission. The new model captures the costs and outcomes of initial treatment and second-line treatment. The general structure of the model within each line of therapy remains the same as previously accepted by NICE.

5.2.1 Patient population

Adult patients with visual impairment due to macular oedema secondary to BRVO are considered in the model. This is in line with the population included in the VIBRANT(25) trial and aflibercept's marketing authorisation.

5.2.2 Model structure

Overview

The model used in this submission is a state transition Markov model which was developed in Microsoft Excel 2007. The model is based on health states defined by different ranges of visual acuity which is an established approach in this disease area. The health states in the model account for the visual acuity of both eyes. The effect of treatment is captured in terms of changes in visual acuity which is modelled as three distinct phases 1) an 'efficacy phase' during which vision may improve 2) a 'maintenance phase' where visual acuity is stable, and 3) a 'rest of life' phase in which vision gradually deteriorates (see section 5.2.2.3 - Evolution of visual acuity).

Within the model, patients continue on their initial treatment if response to treatment is adequate and the model captures the costs and outcomes for this patient group. Patients with poor response to their initial treatment can switch treatment and the costs and outcomes for these patients are also captured (see section 5.2.2.4 - Modelling the NICE treatment pathway). Inadequate response to treatment is defined as it was in VIBRANT(25) (see 4.3.3.4).

The model considers BRVO in both the study eye (SE) and the fellow eye (FE). While most patients have unilateral BRVO (occurring only in the study eye), some patients may have bilateral BRVO (occurring in both eyes at baseline), or some may go on to develop BRVO in their other eye. The model allows for consideration of all three scenarios.

5.2.2.1 Health states

Health states are defined by the visual acuity in both the study eye and the fellow eye. The 0-100 EDTRS letter scale was divided into five visual acuity categories based on the primary efficacy endpoint from the VIBRANT study(25) i.e. the proportion of patients gaining ≥15 letters (Table 48). This is also the primary efficacy endpoint from the other studies included in the NMA. These five visual acuity categories represent the five health states for the study and fellow eyes in the model. At any model cycle, both eyes fall independently into one of these given categories.

A change of at least 15 letters in visual acuity is assumed to represent a move from one health state to another; therefore a patient gaining ≥15 letters moves to an improved health state (e.g. from VA3 to VA2 or VA3 to VA1), with the exception of patients in the VA1 state who cannot further improve. Conversely, a patient losing ≥15 letters is assumed to move to a worse visual acuity health state (e.g. from VA2 to VA3), with the exception of patients in the VA5 state who cannot worsen since they are blind. Treatment of the first and second eye is captured by separate consideration of efficacy and benefit in each eye. Discontinuation is captured by having additional states in which the patient does not receive treatment.

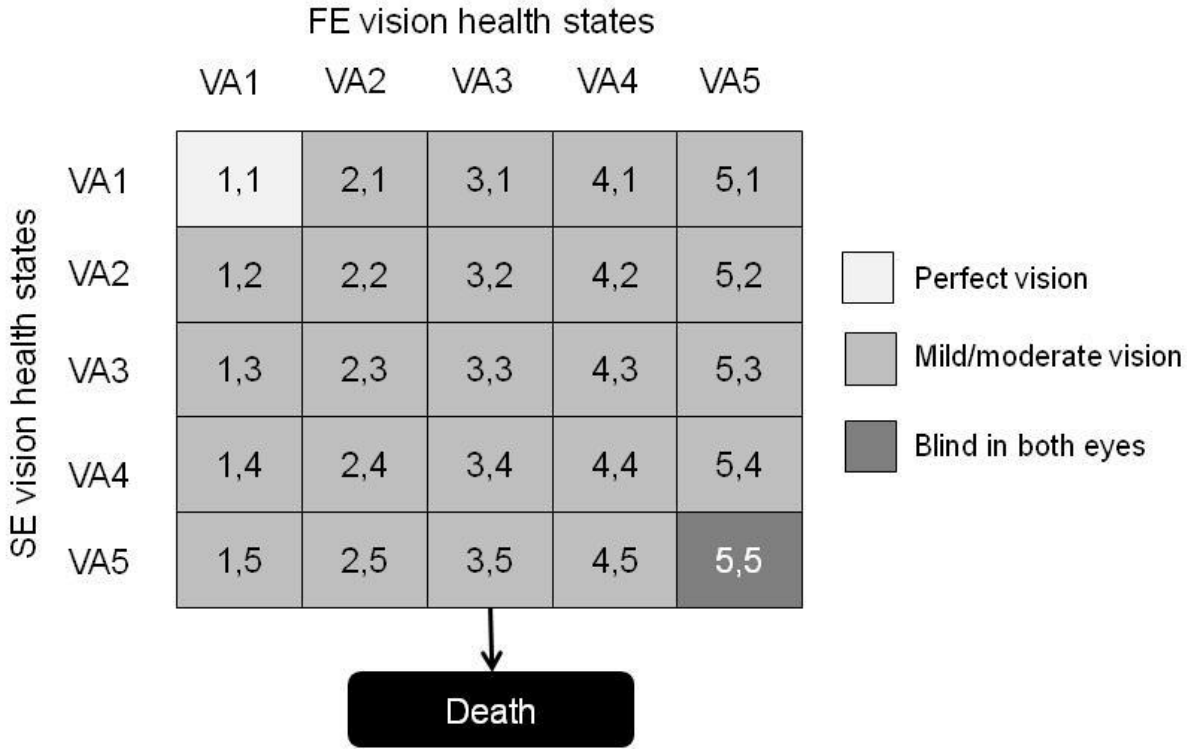
Table 48. Categorisation of vision based on EDTRS letters

BVCA category	ETDRS letters read
VA 1	≥ 80
VA 2	65 – 79
VA 3	50 – 64
VA 4	35 – 49
VA 5	< 35

VA – visual acuity

This model features a total of 26 health states, 25 for each combination of the study eye and fellow eye, and one absorbing health state representing death (Figure 37).

Figure 37. Model health states defined by vision in study eye (SE) and fellow eye (FE)



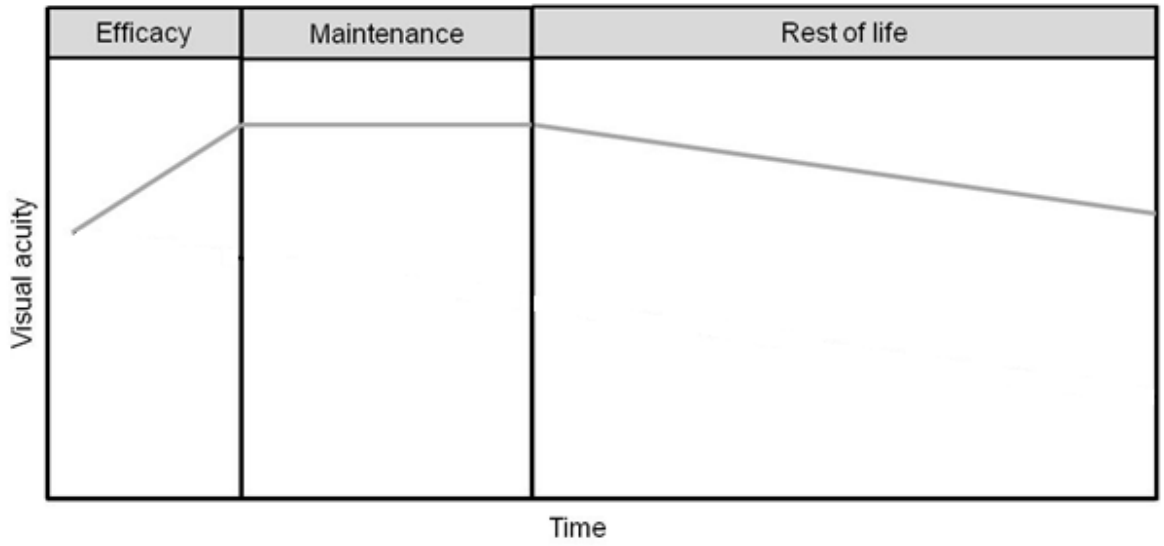
5.2.2.2 Cycle length

The model cycle is 4 weeks to reflect the time point at which data were collected in the VIBRANT trial(25) as well as the highest frequency of treatment administration (initial monthly doses for both aflibercept and ranibizumab). Half cycle correction was not applied due to this short cycle length.

5.2.2.3 Evolution of visual acuity

The change in visual acuity over time in the model is shown in Figure 38. The line indicates the change in visual acuity for an eye affected by BRVO and treated. As described in section 5.2.2.5, BRVO may develop in a patient's second eye in which case this eye is modelled in the same way as the first eye with BRVO.

Figure 38. Evolution of visual acuity



This structure is based on evidence that shows treatment leads to an initial increase in mean BCVA across a cohort followed by a plateau. This is shown in the VIBRANT trial(25) (Figure 12) and in the BRAVO trial(35) (Figure 1 from Brown 2011). The '*efficacy phase'* lasts for 1 year which allows for the efficacy of first, as well as second-line treatments, to be considered. It is the only phase in which a patients vision may improve with treatment.

After the efficacy phase, there is the '*maintenance phase'*. The results of a UK physician survey (appendix **Error! Reference source not found.**) indicate that physicians would continue to monitor and administer additional treatments if required for up to 5 years with the aim of stabilising vision. Treatment would be according to patient need based on disease activity as a function of visual acuity or anatomical parameters. In this phase there is a decreasing mean number of injections required to maintain vision (see section 5.5.2.2). BRVO is expected to resolve over this period.

Following the '*maintenance phase'* is the '*rest of life'* phase, where patients no longer require treatment for BRVO. During this period, as for the general population, there is a long-term slow decline of vision per natural history of aging patients. Each of the three phases of visual acuity is described in more detail below.

5.2.2.3.1 Efficacy phase

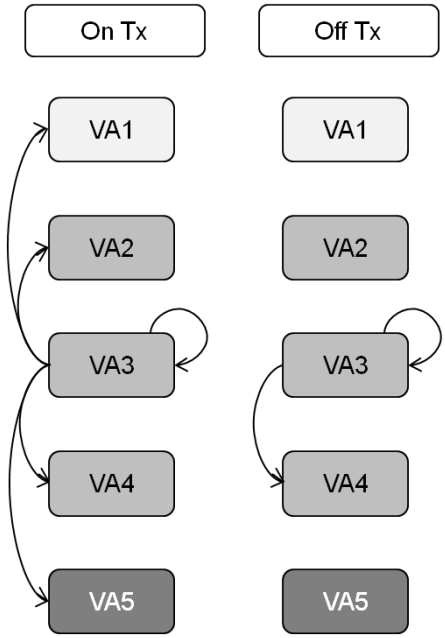
The efficacy phase is the only phase in which a patients' vision may improve. Figure 39 illustrates an example of the possible transitions in terms of changes in visual acuity using health state VA3 as an example. The following transitions are possible while patients are on treatment during the efficacy phase:

- Remain in the same health state
- Gain 15 or more letters
- Lose 15 or more letters
- Discontinue (not shown in the diagram)
- Die (not shown in the diagram)

For those patients off treatment (discontinued) in the efficacy phase, the following transitions can occur:

- Remain in the same health state
- Lose 15 letters of more
- Die (not shown in the diagram)

Figure 39. Transition between health states: efficacy phase using health state VA3 as an example



5.2.2.3.2 Maintenance phase

There is no efficacy data available for aflibercept for the maintenance phase (year 2-5). It has been assumed that the treatment benefit accrued by the end of the efficacy phase is maintained with no diminished effect until the start of the rest of life phase (from year 5 onwards). This assumption is supported by 1) the physician survey (appendix **Error! Reference source not found.**) which showed that physicians will continue to monitor and treat as necessary up to 5 years with the aim of stabilising vision 2) data for ranibizumab from the RETAIN study (n=34) which showed that efficacy was maintained out to 49 months (111). In previous HTA submissions for aflibercept, this approach to maintaining vision in the medium term has been implemented and accepted (TA346, TA294). In the base case patients who are blind (<35 letters) are assumed not to receive treatment in that eye during the maintenance phase.

Figure 40 illustrates an example of the possible transitions in terms of changes in visual acuity using health state VA3 as a starting point for patients on or off treatment.

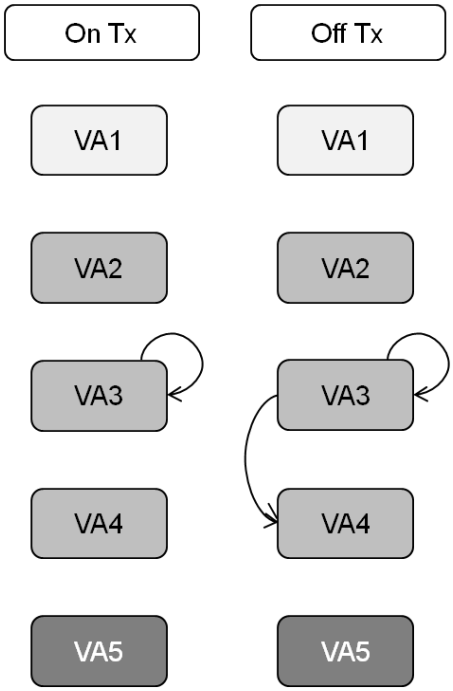
For patients who are being monitored and treated as required during the maintenance phase, the following transitions are possible:

- Remain in the same health state
- Discontinue treatment (not shown in diagram)
- Die (not shown in diagram)

For patients who are off treatment (discontinued) during the maintenance phase, the following transitions are possible:

- Remain in the same health state
- Lose 15 letters or more (patients can deteriorate by a maximum of one health state per cycle)
- Die (not shown in diagram).

Figure 40. Transition between health states: maintenance phase using health state VA3 as an example



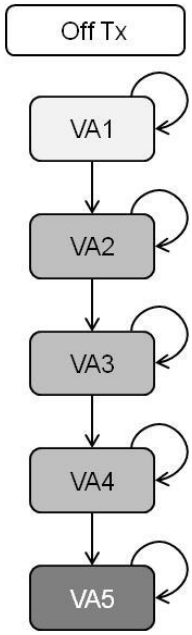
5.2.2.3.3 Rest of life phase

It is assumed that all patients still on treatment at the end of the maintenance phase discontinue treatment. In this phase a long term decline of vision occurs at a monthly rate in line with natural progression (see section 5.3.2.2). Figure 41 illustrates an example of the possible transitions in terms of changes in visual acuity using VA3 as a starting point.

During the rest of life phase, the following transitions are possible:

- Remain in the same health state
- Lose 15 letters or more (patients can deteriorate by a maximum of one health state per cycle)
- Die (not shown in diagram)

Figure 41. Transition between health states: rest of life phase



5.2.2.4 Modelling the NICE treatment pathway

The general structure of the model as it relates to NICEs treatment pathway is shown in Figure 42. Patients initiate treatment at the beginning of the model and are assigned to treatment. Patients are monitored on a regular basis for response to treatment. From month 6 the treatment pathway is determined by response to initial treatment:

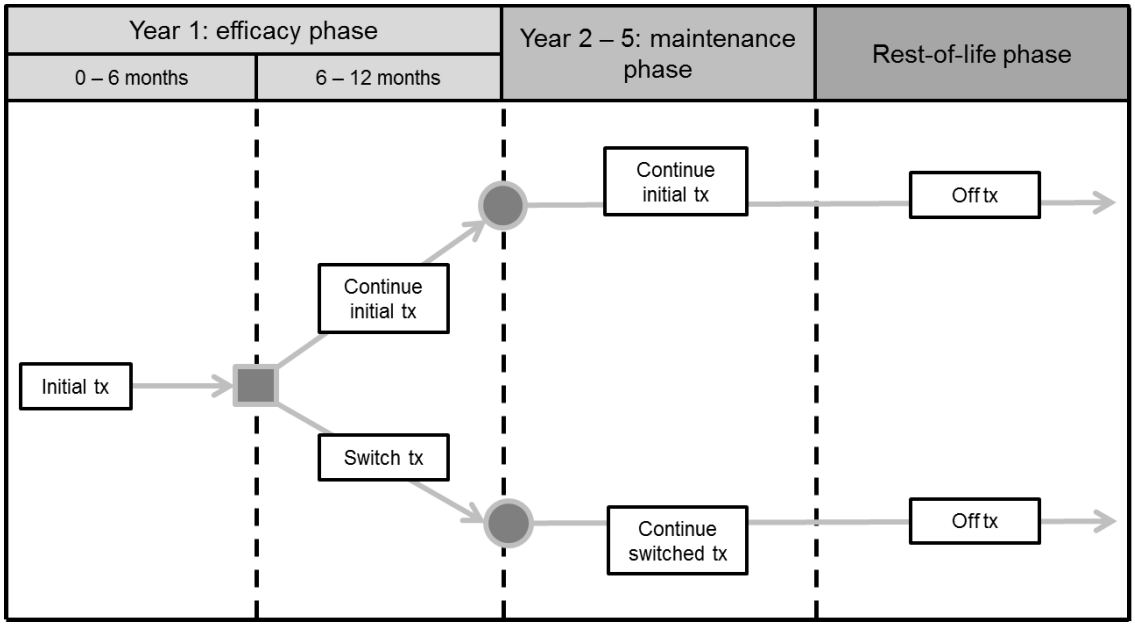
- Patients successfully managed by the initial treatment continue on that treatment from months 6 to 12.
- Patients for whom the initial treatment has not been of sufficient benefit are assumed to switch to a second-line treatment from month 6-12.

There is no further opportunity for changing therapy i.e. only first and second-line therapies are included.

All patients are assumed to continue the treatment that they are on at month 12. At year 5 monitoring and treatment is assumed to stop.

The model allows for discontinuation of treatment or death from any cycle in the 3 phases of the model. Patients who discontinue treatment are assumed not to receive any further treatment and for visual acuity to decrease according to the same rate as in the ‘rest of life phase’.

Figure 42. Structure of the treatment pathway.



5.2.2.5 Fellow eye patient pathway

BRVO can be a bilateral disease; however the Physician's Survey estimated the incidence of bilateral involvement at baseline is low at around 6.1% (appendix **Error! Reference source not found.**). The fellow eye is included in the model because quality of life is a function of both eyes. BCVA in the fellow eye is assumed to vary in the model independently of the study eye. This inclusion removes the need to make assumptions about BCVA in the fellow eye and about whether the study eye is the better or worse seeing eye. Furthermore, the fellow eye may be treated in the model. If the fellow eye is treated, the three phase approach applied to the study eye is also applied to the fellow eye. The second eye may start treatment at the start of any of the first 5 years of the model. An 5-year incidence rate of 12.3% (Physician survey – appendix **Error! Reference source not found.**) is used to generate the number of fellow eyes initiated. Initiation of treatment of the fellow eye was limited to the first five years to limit complexity in the model.

5.2.2.5.1 Example patient pathway

To describe how the different components of the model link together two patient journeys through the model are illustrated below. Although discontinuation can occur at any cycle during the model the illustrative examples below assume continued monitoring and treatment.

Patient 1 – good response to initial treatment

This patient is initiated on treatment at baseline and at six months has had good gains in vision – moving from health state VA3 (50 -64 letters) to VA2 (65-79 letters). The efficacy phase on the initial treatment continues for 12 months. From years 2-5 this initial treatment is continued with the visual acuity remaining in health state VA2 for the next 4 years. From year 5 treatment is ceased and vision deteriorates gradually over time.

Patient 2 – poor response initial treatment

This patient is initiated on treatment at baseline and during the initial six months loses visual acuity and moves down one visual acuity health state (VA3 to VA4). At month six a second-line treatment is initiated and the patient enters the efficacy phase for this treatment – moving up a visual acuity health state by month 12. From years 2-5 this second-line treatment is continued with the visual acuity remaining in heatlh state achieved at the end of the efficacy phase. From year 5 treatment is ceased and vision deteriorates gradually over time.

5.2.3 Features of the de novo analysis

Table 49 describes the key features of the model with justification.

Table 49. Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	A lifetime horizon was chosen because BRVO is a chronic disease, and time horizons that exceed typical treatment durations are a common feature of previous cost-effectiveness models in BRVO and other back-of-the-eye conditions
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case
Discount for utilities and costs	3.5%	NICE reference case
Perspective	NHS/PSS	NICE reference case
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The analysis compares aflibercept to laser, ranibizumab and dexamethasone as per the scope. Bevacizumab is included as a comparator in the scope but it is not licensed for use in the eye and no comparison against this treatment has been made. Bevacizumab has had no regulatory assessment and is not routine practice in NHS England or NHS Wales.

In terms of treatment continuation rules, the model allows the user to assume that blind patients stop treatment during the maintenance phase. All treatments included in the model have similar stopping rules in their SmPCs and therefore any impact of this in clinical practice is likely to be similar for all products.

Intervention

The intervention considered is aflibercept 2 mg administered once every four weeks until maximum visual acuity is reached and then administered according to patient need, as determined by the treating physician based on disease activity as a function of visual acuity or anatomical parameters. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). Aflibercept has marketing authorisation for adults with visual impairment due to macular oedema secondary to BRVO which is reflected in the population included in the model.

Comparators

Treatment with ranibizumab is modelled according to a 0.5mg dose. According to its licence, ranibizumab has a comparable posology to aflibercept, as described above.

Laser photocoagulation is modelled as it was administered in the VIBRANT trial i.e. based on the Combined Branch Vein Occlusion Study (CBVOS) protocol (7).

Treatment with dexamethasone is assumed to be one implant administered inta-vitreally to the infected eye. There is limited data investigating the efficacy of repeat dosing less than 6 months apart, and therefore the model assumes treatment every 6 months.

5.2.4.1 Aflibercept as a first-line treatment option

As described earlier (section 5.2), an economic assessment of aflibercept as an alternative first-line option to laser should consider the costs and effects of any changes in therapy necessitated by lack of benefit of the inititial treatment. For patients failing laser photocoagulation second-line treatment is currently ranibizumab or dexamethasone. Consequently, the comparison of aflibercept against laser compares

- Patients initiating aflibercept who have a laser procedure if they fail on aflibercept

Versus, switches to the following treatments in patients who initiate laser but fail:

- ranibizumab (comparison 1a)
- dexamethasone (comparison 1b).
- for completeness the cost-effectiveness of laser followed by aflibercept has also been assessed (comparison 1c).

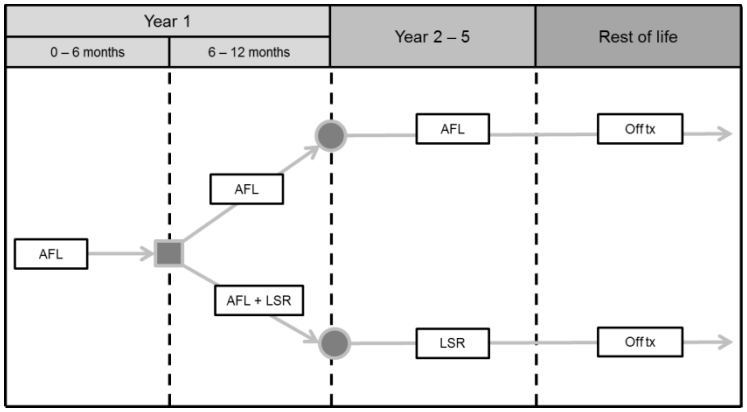
Table 50 shows the three comparisons conducted which jointly indicate the cost-effectiveness of aflibercept as a first-line alternative to laser. The pathway followed by patients in each of these comparisons are illustrated in Figure 43 to Figure 45.

Table 50. Comparisons assessing aflibercept as a first-line treatment option

Intervention pathway	Comparator pathway
Aflibercept followed by laser for treatment failures	**Comparison 1a (see also Figure 43)** Laser followed by ranibizumab for treatment failures
	Comparison 1b (see also Figure 44) Laser followed by dexamethasone for treatment failures
	Comparison 1c (see also Figure 45) Laser followed by aflibercept for treatment failures

Figure 43. Comparison 1a – aflibercept followed by laser versus laser followed by ranibizumab

Intervention – Aflibercept followed by laser



Comparator - Laser followed by ranibizumab

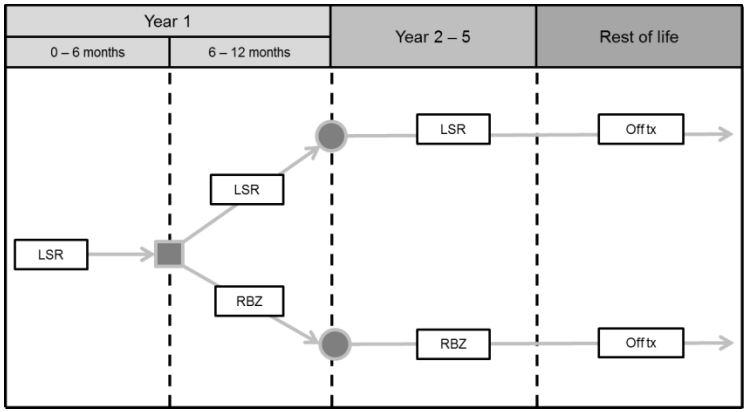
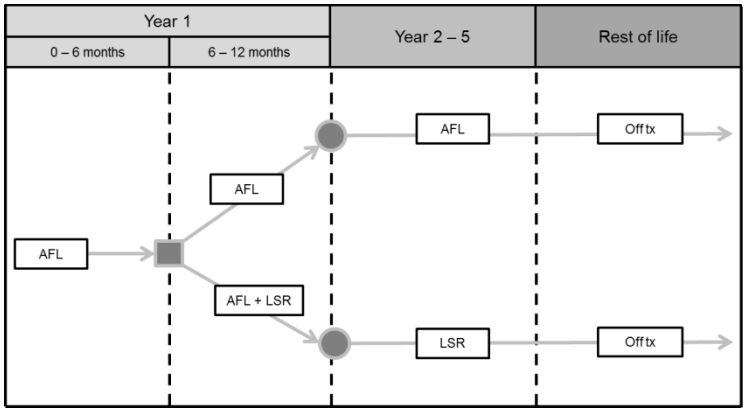


Figure 44. Comparison 1b - aflibercept followed by laser versus laser followed by dexamethasone

Intervention – Aflibercept followed by laser



Comparator - Laser followed by Dexamethasone

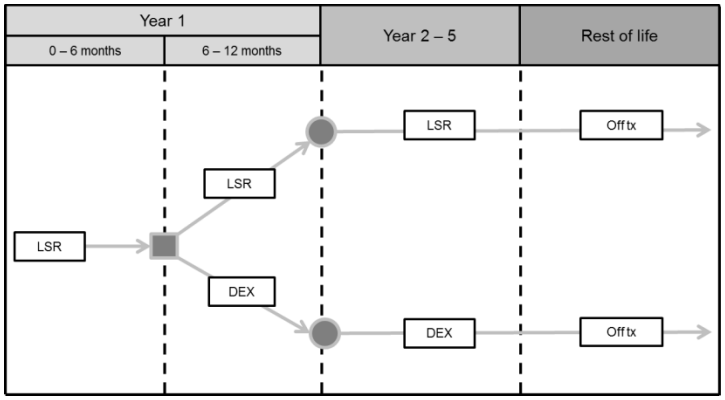
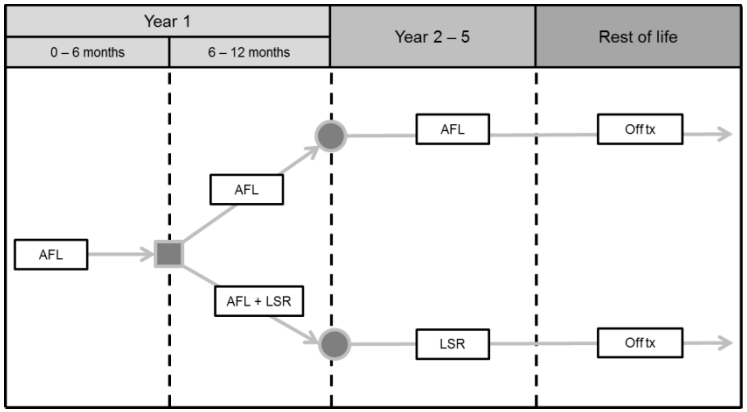
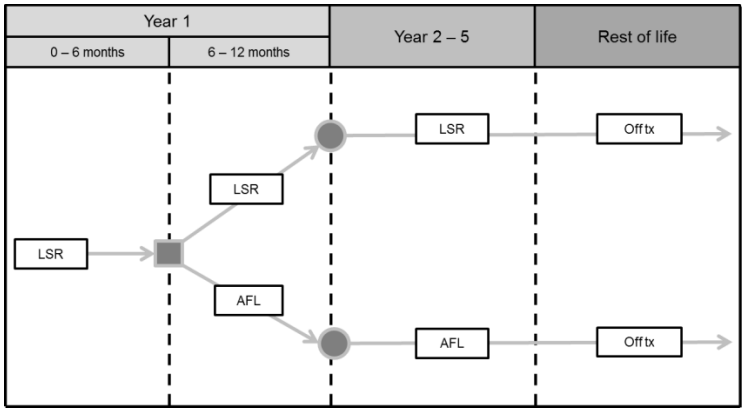


Figure 45. Comparison 1c - aflibercept followed by laser versus laser followed by aflibercept

Intervention - Aflibercept followed by laser



Comparator - Laser followed by aflibercept



5.2.4.2 Aflibercept as a second-line treatment option

To compare the cost-effectiveness of aflibercept versus ranibizumab and dexamethasone, all treatments are compared as 2nd line treatments after laser which is the current clinical pathway as recommended by NICE. As before, the comparison considers the costs and effects of the whole pathway and hence also accounts for the costs and outcomes of initial treatment. The treatment arms considered in the model for each comparison are shown in Table 51 and Figure 46 and Figure 47). Patients initiate treatment on laser for the first 6 months. From month 6-12, if patients fail laser treatment, they switch treatment to aflibercept or one of the comparators. Patients then remain on the treatment they are on at the 12 month timepoint until the end of the maintenance period but with a risk of discontinuing treatment in each cycle. If laser treatment is successful in the first six months no change in treatment occurs.

Table 51. Comparisons assessing aflibercept as a second-line treatment

Intervention pathway	Comparator pathway
Laser followed by aflibercept for treatment failures	**Comparison 2a (see also Figure 46)** Laser followed by ranibizumab for treatment failures
	Comparison 2b (see also Figure 47) Laser followed by dexamethasone for treatment failures

Figure 46. Comparison 2a - laser followed by aflibercept versus laser followed by ranibizumab

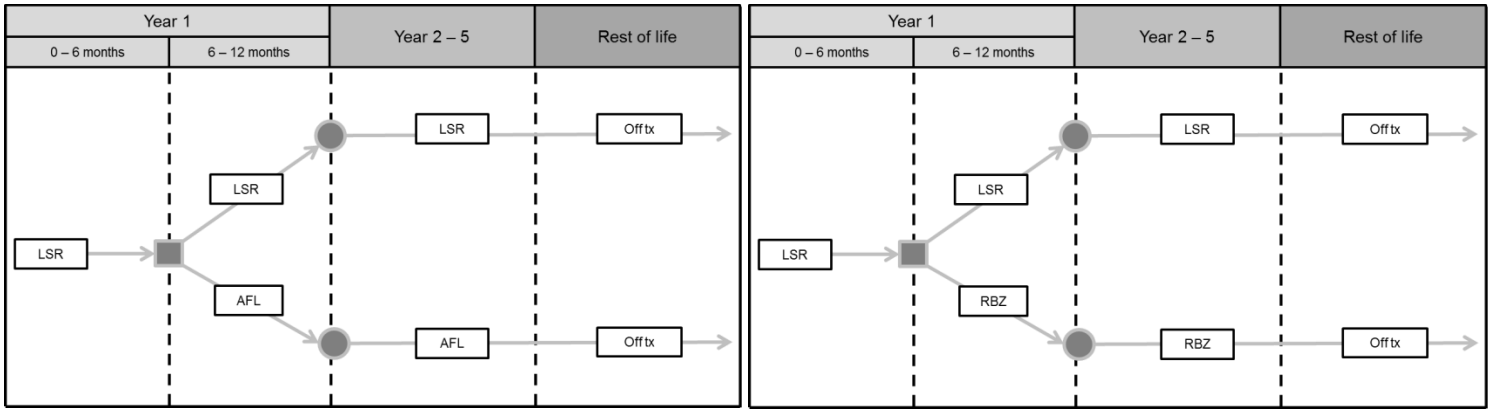
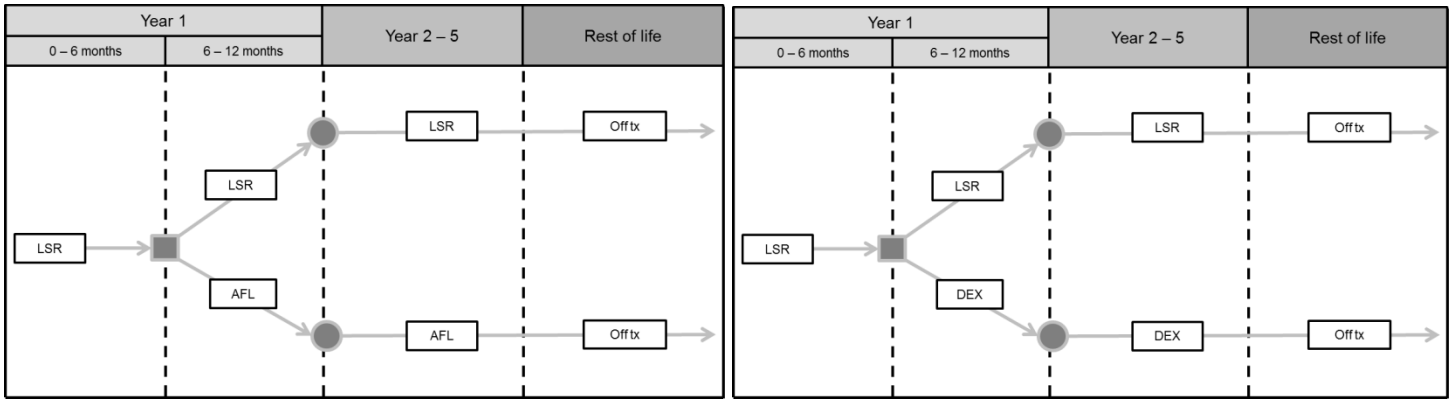


Figure 47. Comparison 2b - laser followed by aflibercept versus laser followed by dexamethasone



5.2.4.3 Clinical experts: modelling approach

Validation meetings were held with two consultant ophthalmologists from England and Northern Ireland. The meeting format was a teleconference with each expert individually where they were shown the model structure in terms of a) VA health states b) the 3 phases of visual acuity and their respective durations, and c) possible movements between the health states for each phase of the model.

The experts were asked to comment on the structure, the assumptions and how well the change in VA over time matched clinical practice. There was agreement that the model adequately reflected the change in visual acuity over time for patients initiated on therapy and reflects the pathway of care.

5.3 Clinical parameters and variables

5.3.1 Clinical inputs

5.3.1.1 Baseline population

The baseline population characteristics and discontinuation rate have been sourced from the VIBRANT trial(25) where possible, in addition the model takes into account background mortality as well as an increased mortality associated with blindness.

The baseline characteristics of patients entering the model are shown in Table 52 (source - clinical section Table 17).

Table 52. Population characteristics applied to model

Parameter	Value	95% Confidence interval	Sources
Baseline age (years)	65	52-78	VIBRANT
Proportion female (%)	45	36-54	VIBRANT

The starting vision health state distributions for the study eye and fellow eye were obtained from the VIBRANT trial(25) data (Table 53) and are assumed to be independent. The distributions were estimated from the full sample, regardless of treatment arm, and are therefore assumed to be applicable to all treatments.

Table 53. Starting health state distributions

	VA1	VA2	VA3	VA4	VA5	Total
Study eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fellow eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3.1.2 Mortality

Background mortality risk, as well as the mortality risk associated with poor vision, is incorporated into the model.

The evidence regarding whether there is an increased mortality risk associated with BRVO is conflicting (see section 3.4.1). Therefore no increased risk has been assumed. Background mortality rates, by patient age, were taken from the Office of National Statistics England and Wales life tables (Office for National Statistics 2014(69)). Within each age group (e.g. 68 years) the mortality rates for females and males were weighted according to the gender distribution in the VIBRANTstudy(25) to give the mortality rate for that particular age.

A previous submission to NICE for aflibercept in DMO (66) used a mortality hazard ratio value from Christ et al. (2008)(19) for patients with mild visual impairment, described as blind in one eye, compared with the general population. A pragmatic literature search was conducted to identify if there are any more recent and robust studies from which to source this input (see appendiex **Error! Reference source not found.**). This search identified a number of studies presenting a hazard ratio by visual acuity status for a variety of populations; however none were identified for the RVO population specifically. Christ et al (2008)(19) was chosen to source this input for two reasons; to keep consistency with past submissions and the robust nature of the study. This retrospective study analysed data from 135,581 adult respondents as part of the National Health Interview Survey in the United States. The results shown the hazard rate of mortality increased by 23% (hazard ratio: 1.23, 95% CI: 1.16-1.31) for blindness in one eye relative to no visual impairment. This study took into consideration both direct effects and indirect effects of mortality associated with visual impairment.

Based on this source, a relative risk of mortality associated with poor vision was applied to individuals blind in one eye i.e. health state VA5.

5.3.1.3 Discontinuation

Discontinuation in the model is applied throughout the efficacy and maintenance phase. The discontinuation rate for aflibercept and laser were obtained from the VIBRANT trial(25). For the other comparators, ranibizumab and dexamethasone, the discontinuation rate was assumed to be equivalent to aflibercept as this information is not available from the NMA.

Monthly discontinuation rates were calculated (Table 54).

Table 54. Monthly discontinuation rate by treatment

Treatment	Monthly probability of discontinuation	Sources
Aflibercept	0.00955	VIBRANT(25)
Laser	0.00781	VIBRANT(25)
Ranibizumab	0.00955	Assumption
Dexamethasone	0.00955	Assumption

5.3.2 Efficacy inputs

Overview of the adaptation of the VIBRANT data in the economic model

A single RCT (VIBRANT(25)) provides data on the efficacy of aflibercept (versus laser photocoagulation) in patients with BRVO. Figure 48 summarises the design of VIBRANT(25) and Figure 49 shows the possible treatment paths that patients can follow given the design.

Figure 48. Design of the VIBRANT study

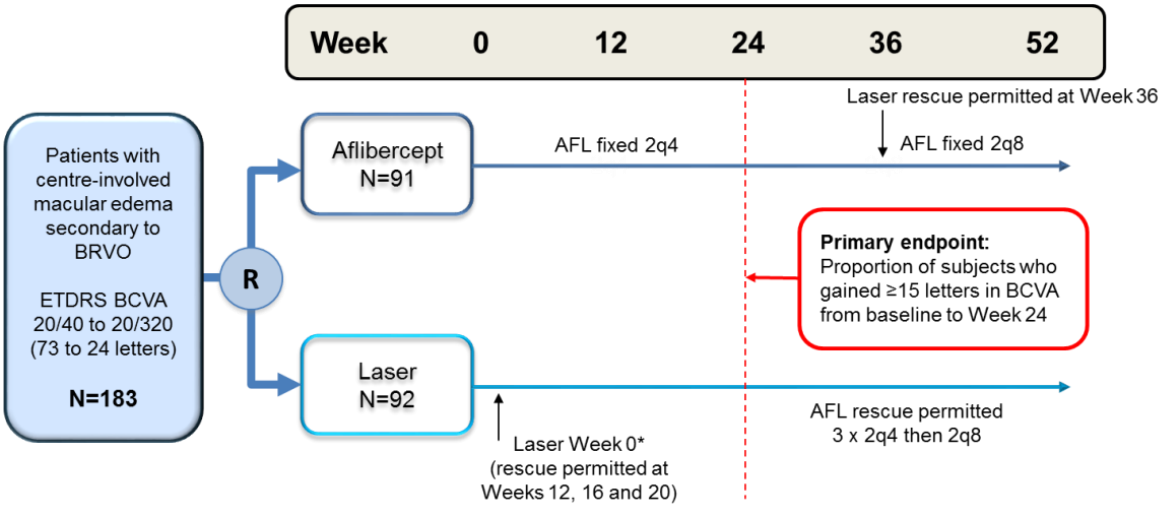
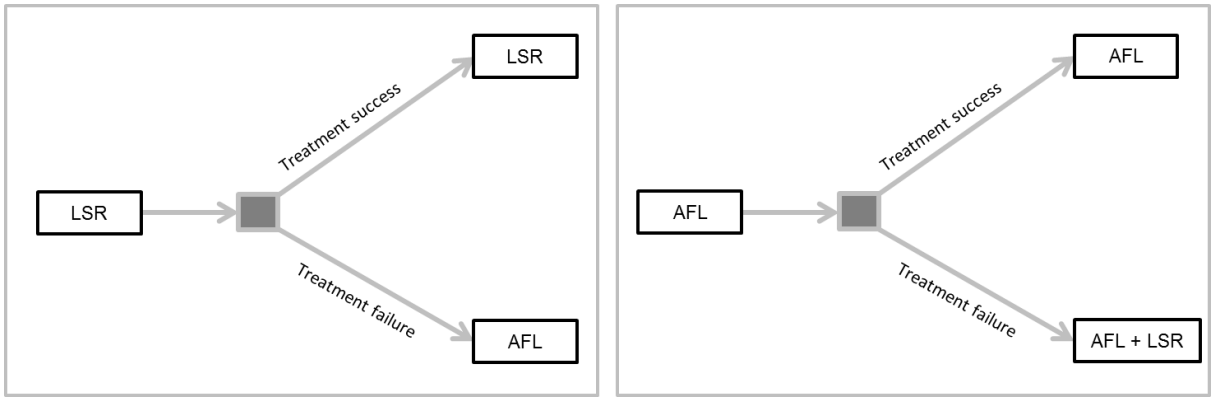


Figure 49. Potential treatment pathways from the VIBRANT study



Comparison 1c (aflibercept first-line versus laser first line)

Patient level data from VIBRANT(25) was used to calculate transition probabilities between the model health states. Transition probabilities were calculated separately 1) for first 6 months and second 6 months and 2) according to the actual treatment

received during these 6-month periods. These transition probabilities formed the inputs for comparison 1c (Table 50).

Comparisons 1a, 1b, 2a, 2b (Table 50, Table 51)

No head-to-head data is available comparing aflibercept against ranibizumab or dexamethasone. Therefore the NMA results (section 4.10) were used, together with the VIBRANT(25) data, to estimate transition probabilities for ranibizumab or dexamethasone had they been used in the VIBRANT study instead of aflibercept.

The calculation of transition probabilities is described in more detail below.

5.3.2.1 Network meta-analysis

The VIBRANT trial(25) provided head-to-head data between aflibercept and laser. However, in lieu of head-to-head trial data between aflibercept and ranibizumab and dexamethasone, the network meta-analysis detailed in section 4.10, was used to determine the efficacy inputs of the model for these comparisons.

The availability of data meant an indirect comparison was possible for the outcomes of gaining ≥15 letters BCVA and BCVA mean change from baseline. Aflibercept 2mg was compared to ranibizumab 0.5mg and dexamethasone implant 0.7mg. The structure of the model meant the binary outcome of gaining ≥15 letters BCVA was incorporated in the analysis. Table 55 shows the median odds ratios used in the model using aflibercept as the base treatment i.e. OR of 1.

Table 55. NMA results used for the calculation of transition probabilities for comparator treatments

Comparison	Median odds ratio for gaining ≥15 letters	Credible interval
Ranibizumab versus aflibercept (used in comparisons 1a and 2a - Table 50 and Table 51)	0.93	0.38 – 2.31
Dexamethasone versus aflibercept (used in comparisons 1b and 2b - Table 50 and Table 51)	0.34	0.12 – 0.96

The other efficacy input necessary in the model was the proportion of patients losing ≥15 letters. However, due to a lack of available data, this outcome could not be determined by the NMA for either the comparison with ranibizumab or dexamethasone. Therefore it was assumed this outcome was equal to aflibercept for the ranibizumab and dexamethasone comparisons i.e. ranibizumab and dexamethasone had OR of 1.0 relative to aflibercept.

5.3.2.2 Extrapolation of efficacy data

The NMA data presented in Table 55 was derived from the first 6 months of the VIBRANT trial(25) data where there was no treatment switching. This was to ensure the trial data were comparable to the other studies in the network. For use in the model, it was assumed the median odds ratio derived for the first 6 months of the trial was applicable for estimating transitions for comparator treatments in the second 6 months in the model.

5.3.2.3 Transition probabilities

Transition probabilities are expected to change over time based on the three phase approach. Therefore transition matrices have been derived for each phase separately. The following sections will describe how the transition matrices were calculated, and the associated assumptions, for each phase.

5.3.2.3.1 Efficacy phase

The efficacy phase is the only phase in which a patients' vision may improve. Transition probabilities were derived using the MSM package in R. This package allows a general multi-state model to be fitted to longitudinal data to model transition intensities. The advantage of using the MSM package is that other methods such as shift tables use the trial data to 'count' the number of transitions between time points, and therefore only represent one 'realisation' of the patient pathway rather than using the trial data to calculate the most likely, i.e. the 'averaged' pathway. Use of simple counting methods, may give extra weight to less important transitions for which the number of patients making a transition may have been unusually high or low due to chance. The MSM method also makes use of all available data and does not discard observations at intermediate time points.

The MSM package was used to derive transition probabilities for the 0-6 month period and 6-12 month period. For the post-switching phase, separate transition matrices were calculated for patients who did and did not switch.

The transition matrices for the efficacy phase derived from the VIBRANT study(25) are shown Table 56 - Table 61.

Transition probabilities for ranibizumab (comparisons 1a & 2a) and dexamethasone (comparisons 1b and 2b) were based on applying the median odds ratio derived from the network meta-analysis (Table 55) to the 6-12 months aflibercept transition probabilities (Table 58) as follows:

1) Aflibercept transition probabilities (p_{AFB}) (Table 58; 6-12 month transitions) were firstly converted to log-odds ($Logodds_{AFB}$) applying the following formula:

$$(1 + EXP\left(logit(p_{comp})\right)$$

2) The ORs obtained from the NMA for both ranibizumab and dexamethasone were converted to logoddsratio and applied to the above aflibercept log-odds matrix where appropriate (only for gaining 15 or more letters).

$$logit(p_{comp}) = logodds_{AFB} + logoddsratio_{comp}$$

3) Finally, the LogOdds matrices were converted to probabilities and applied into the model to give the transition matrices for ranibizumab (Table 62) and dexamethasone (Table 63) for the 6-12 month part of the model.

$$P_{comp} = \frac{EXP\left(logit\left(p_{comp}\right)\right)}{(1 + EXP\left(logit\left(p_{comp}\right)\right)}$$

Table 56. Transition matrices (per cycle): Aflibercept 0-6 months

		ON Treatment (cycle n)					**Off** Treatment (cycle n)				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.8224	0.2042	0.0772	0.0212	0.0224	0.9976	0.0	0.0	0.0	0.0
	VA2	0.1635	0.7533	0.3896	0.1516	0.1564	0.0017	0.9976	0.0	0.0	0.0
	VA3	0.0036	0.0317	0.5056	0.1313	0.1809	0.0	0.0017	0.9976	0.0	0.0
	VA4	0.0001	0.0005	0.016	0.6045	0.2717	0.0	0.0	0.0017	0.9976	0.0
	VA5	0.0	0.0	0.0012	0.081	0.358	0.0	0.0	0.0	0.0017	0.9989
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0011	0.0008	0.0008	0.0008	0.0008	0.0011
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 57. Transition matrices (per cycle): Laser 0-6 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.8712	0.0715	0.0108	0.0012	0.0003	0.9976	0.0	0.0	0.0	0.0
	VA2	0.1104	0.785	0.2362	0.0387	0.0063	0.0017	0.9976	0.0	0.0	0.0
	VA3	0.0094	0.1305	0.696	0.2279	0.0458	0.0	0.0017	0.9976	0.0	0.0
	VA4	0.0003	0.0042	0.045	0.621	0.1378	0.0	0.0	0.0017	0.9976	0.0
	VA5	0.0001	0.0002	0.0035	0.1026	0.8011	0.0	0.0	0.0	0.0017	0.9989
	Discontinue	0.0078*	0.0078*	0.0078*	0.0078*	0.0078*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0011	0.0008	0.0008	0.0008	0.0008	0.0011
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 58. Transition matrices (per cycle): Aflibercept 6-12 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.8805	0.112	0.0234	0.0005	0.0003	0.9975	0.0	0.0	0.0	0.0
	VA2	0.1053	0.8431	0.2731	0.0064	0.002	0.0017	0.9975	0.0	0.0	0.0
	VA3	0.0037	0.0335	0.6501	0.0331	0.0139	0.0	0.0017	0.9975	0.0	0.0
	VA4	0.0001	0.0009	0.0384	0.7868	0.5637	0.0	0.0	0.0017	0.9975	0.0
	VA5	0.0	0.0001	0.0047	0.1629	0.4096	0.0	0.0	0.0	0.0017	0.999
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0010	0.0008	0.0008	0.0008	0.0008	0.0010
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 59. Transition matrices (per cycle): Aflibercept + Laser 6-12 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.8814	0.0432	0.0432	0.0	0.0001	0.9975	0.0	0.0	0.0	0.0
	VA2	0.0909	0.7818	0.7904	0.0	0.0002	0.0017	0.9975	0.0	0.0	0.0
	VA3	0.0191	0.1664	0.1578	0.0	0.0	0.0	0.0017	0.9975	0.0	0.0
	VA4	0.0	0.0	0.0	0.9914	0.0	0.0	0.0	0.0017	0.9975	0.0
	VA5	0.0	0.0	0.0	0.0	0.9909	0.0	0.0	0.0	0.0017	0.999
	Discontinue	0.0078*	0.0078*	0.0078*	0.0078*	0.0078*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0010	0.0008	0.0008	0.0008	0.0008	0.0010
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 60. Transition matrices (per cycle): Laser 6-12 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9055	0.0743	0.0014	0.0004	0.0	0.9975	0.0	0.0	0.0	0.0
	VA2	0.0854	0.9051	0.0342	0.0004	0.0	0.0017	0.9975	0.0	0.0	0.0
	VA3	0.0006	0.012	0.9558	0.0003	0.0	0.0	0.0017	0.9975	0.0	0.0
	VA4	0.0	0.0	0.0	0.8661	0.0	0.0	0.0	0.0017	0.9975	0.0
	VA5	0.0	0.0	0.0	0.1242	0.9911	0.0	0.0	0.0	0.0017	0.999
	Discontinue	0.0078*	0.0078*	0.0078*	0.0078*	0.0078*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0010	0.0008	0.0008	0.0008	0.0008	0.0010
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 61. Transition matrices (per cycle): Aflibercept after laser 6-12 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.786	0.1087	0.014	0.0017	0.0003	0.9975	0.0	0.0	0.0	0.0
	VA2	0.1978	0.8325	0.21	0.0379	0.0057	0.0017	0.9975	0.0	0.0	0.0
	VA3	0.0058	0.0479	0.746	0.2722	0.0431	0.0	0.0017	0.9975	0.0	0.0
	VA4	0.0001	0.0006	0.0196	0.6777	0.0006	0.0	0.0	0.0017	0.9975	0.0
	VA5	0.0	0.0	0.0	0.0	0.9398	0.0	0.0	0.0	0.0017	0.999
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0010	0.0008	0.0008	0.0008	0.0008	0.0010
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 62. Transition matrices (per cycle): ranibizumab after laser 6-12 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.786	0.1019	0.0131	0.0016	0.0002	0.9975	0.0	0.0	0.0	0.0
	VA2	0.1978	0.8393	0.1982	0.0354	0.0053	0.0017	0.9975	0.0	0.0	0.0
	VA3	0.0058	0.0479	0.7588	0.2581	0.0402	0.0	0.0017	0.9975	0.0	0.0
	VA4	0.0001	0.0006	0.0196	0.6945	0.0005	0.0	0	0.0017	0.9975	0.0
	VA5	0.0	0.0	0.0	0.0	0.9431	0.0	0	0	0.0017	0.999
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0010	0.0008	0.0008	0.0008	0.0008	0.0010
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 63. Transition matrices (per cycle): dexamethasone after laser 6-12 months

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.786	0.0619	0.0076	0.0009	0.0001	0.9975	0.0	0.0	0.0	0.0
	VA2	0.1978	0.8793	0.1256	0.0209	0.0031	0.0017	0.9975	0.0	0.0	0.0
	VA3	0.0058	0.0479	0.8368	0.1682	0.0238	0.0	0.0017	0.9975	0.0	0.0
	VA4	0.0001	0.0006	0.0196	0.7996	0.0003	0.0	0.0	0.0017	0.9975	0.0
	VA5	0.0	0.0	0.0	0.0	0.9621	0.0	0.0	0.0	0.0017	0.999
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0008	0.0008	0.0008	0.0008	0.0010	0.0008	0.0008	0.0008	0.0008	0.0010
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

5.3.2.3.2 Maintenance phase

There is no efficacy data available for the maintenance phase (year 2-5) and therefore it is assumed that the treatment benefit accrued by the end of the efficacy phase is maintained with no diminished effect until the rest of life phase from year 5 onwards.

Tables Table 64 – Table 69 show the transition matrices for the maintenance phase.

Table 64. Transition matrices (per cycle): aflibercept maintenance phase

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9894	0.0	0.0	0.0	0.0	0.9972	0	0.0	0.0	0.0
	VA2	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0	0.0
	VA3	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0
	VA4	0.0	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0
	VA5	0.0	0.0	0.0	0.0	0.9891	0.0	0.0	0.0	0.0017	0.9987
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0011	0.0011	0.0011	0.0011	0.0013	0.0011	0.0011	0.0011	0.0011	0.0013
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 65. Transition matrices (per cycle): aflibercept + laser maintenance phase

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9911	0.0	0.0	0.0	0.0	0.9972	0.0	0.0	0.0	0.0
	VA2	0.0	0.9911	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0	0.0
	VA3	0.0	0.0	0.9911	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0
	VA4	0.0	0.0	0.0	0.9911	0.0	0.0	0.0	0.0017	0.9972	0.0
	VA5	0.0	0.0	0.0	0.0	0.9909	0.0	0.0	0.0	0.0017	0.9987
	Discontinue	0.0078*	0.0078*	0.0078*	0.0078*	0.0078*					
	Death	0.0011	0.0011	0.0011	0.0011	0.0013	0.0011	0.0011	0.0011	0.0011	0.0013
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 66. Transition matrices (per cycle): Laser maintenance phase

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9911	0.0	0.0	0.0	0.0	0.9972	0.0	0.0	0.0	0.0
	VA2	0.0	0.9911	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0	0.0
	VA3	0.0	0.0	0.9911	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0
	VA4	0.0	0.0	0.0	0.9911	0.0	0.0	0.0	0.0017	0.9972	0.0
	VA5	0.0	0.0	0.0	0.0	0.9909	0.0	0.0	0.0	0.0017	0.9987
	Discontinue	0.0078*	0.0078*	0.0078*	0.0078*	0.0078*					
	Death	0.0011	0.0011	0.0011	0.0011	0.0013	0.0011	0.0011	0.0011	0.0011	0.0013
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 67. Transition matrices (per cycle): aflibercept after laser - maintenance phase

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9894	0.0	0.0	0.0	0.0	0.9972	0.0	0.0	0.0	0.0
	VA2	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0	0.0
	VA3	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0
	VA4	0.0	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0
	VA5	0.0	0.0	0.0	0.0	0.9891	0.0	0.0	0.0	0.0017	0.9987
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0011	0.0011	0.0011	0.0011	0.0013	0.0011	0.0011	0.0011	0.0011	0.0013
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 68. Transition matrices (per cycle): ranibizumab after laser - maintenance phase

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9894	0.0	0.0	0.0	0.0	0.9972	0.0	0.0	0.0	0.0
	VA2	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0	0.0
	VA3	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0
	VA4	0.0	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0
	VA5	0.0	0.0	0.0	0.0	0.9891	0.0	0.0	0.0	0.0017	0.9987
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0011	0.0011	0.0011	0.0011	0.0013	0.0011	0.0011	0.0011	0.0011	0.0013
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

Table 69. Transition matrices (per cycle): dexamethasone after laser - maintenance phase

		ON **Treatment (cycle n)**					**Off Treatment (cycle n)**				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9894	0.0	0.0	0.0	0.0	0.9972	0.0	0.0	0.0	0.0
	VA2	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0	0.0
	VA3	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0	0.0
	VA4	0.0	0.0	0.0	0.9894	0.0	0.0	0.0	0.0017	0.9972	0.0
	VA5	0.0	0.0	0.0	0.0	0.9891	0.0	0.0	0.0	0.0017	0.9987
	Discontinue	0.0096*	0.0096*	0.0096*	0.0096*	0.0096*					
	Death	0.0011	0.0011	0.0011	0.0011	0.0013	0.0011	0.0011	0.0011	0.0011	0.0013
	Total	1	1	1	1	1	1	1	1	1	1

* Patients who discontinue enter the off-treatment transition matrix

5.3.2.3.3 Rest of life phase

During the rest of life phase of the model, it is assumed patients will not be monitored or treated and that BRVO has resolved. A structured literature search was conducted with the objective of identifying the long-term progression of BRVO in order to inform the rest of life phase of the model (see appendix **Error! Reference source not found.**). The search identified a study which investigated visual acuity in a British population aged ≥65 years as part of a national diet and nutrition survey (Van der pols, 2000(70)). Based on this study, patients in the model have a 2% likelihood of losing at least 10 letters per year. No studies were identified which reported an input suitable for the model for losing at least 15 letters per year and therefore it is assumed in the model that this likelihood is equivalent. The following formula was applied in order to convert the annual rate to a monthly rate to be applied per cycle in the model during the rest of life phase:

$$\textit{Monthly rate} = (1 + \text{`annual rate'})^{1/12} - 1$$

$$= (1.02)^{1/12} - 1$$

$$= 0.0017$$

The transition matrix for the rest of life phase is shown in Table 70. This is the same for all arms of the model as all patients are off treatment and following a path of natural visual deterioration.

Table 70. Transition matrices (per cycle): rest of life phase (all treatments)

		Off Treatment (cycle n)				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**
On Tx (cycle n+1)	**VA1**	0.9983	0	0	0	0
	VA2	0.0017	0.9983	0	0	0
	VA3	0	0.0017	0.9983	0	0
	VA4	0	0	0.0017	0.9983	0
	VA5	0	0	0	0.0017	1
	Discontinue					
	Death	¥	¥	¥	¥	¥

¥ – updated each year

5.3.2.3.4 Fellow eye

All fellow eyes are independently at risk of BRVO when they enter the model. The VIBRANT trial(25) did not include any patients with bilateral involvement at baseline. Therefore, the proportion of patients with bilateral involvement was estimated as 6.1% by the Physician's Survey. This value is comparable to the value of 5-6% referenced in the NICE ranibizumab submission for BRVO sourced from a published systematic review (Rogers et al 2010(71)). The base case assumes only 50% of the fellow eyes affected by BRVO are treated – this is tested in a sensitivity analysis. The fellow eye, if affected by BRVO, follows the same patient pathway as the study eye with an incidence rate applied for the first five years of the model (see section 5.3.2.3.1, 5.3.2.3.2 and 5.3.2.3.3 for the transition matrices). When the fellow eye is not affected by BRVO, a natural decline rate will be applied as per the 'Rest of life phase' (section 5.3.2.3.3). The transition matrices were determined using the MSM package, as for the SE.

5.3.2.4 Safety

Frequent ocular adverse events in the VIBRANT trial(25), as well as in the product information for the comparators, were evaluated. Adverse events that are transient, self-resolving or which are a symptom of macular oedema secondary to BRVO were not included in the analysis. Based on these criteria and expert advice, only cataracts and intraocular pressure (IOP) were included in the analysis. Observations from the trials did not identify any frequent non-ocular adverse events; consequently, these were not included in the model.

Adverse events were modeled to only occur in patients who were on treatment during the efficacy and maintenance phases. For aflibercept and laser, monthly adverse event rates were calculated from the VIBRANT trial(25) analysis at 1 year.

An indirect comparison for ranibizumab and dexamethasone was not possible due to a lack of data and therefore we assumed equivalence in the adverse event rate with aflibercept. In respect of dexamethasone this is a conservative assumption as an increasing risk of cataracts is known to be associated with increasing number of

dexamethasone injections (RCO guidelines 2015, Ozurdex Manufacturer submission(55)).

Adverse event rates were converted to monthly rates (Table 71) using the following formula:

Monthly rate = (1 + 'annual rate')$^{1/12}$ - 1

Table 71. Adverse event rates

Adverse event	Monthly rate	Sources
Aflibercept		
Cataract	0.00091	VIBRANT(25)
IOP	0.00091	VIBRANT(25)
Laser		
Cataract	0.00000	VIBRANT(25)
IOP	0.00090	VIBRANT(25)
Ranibizumab		
Cataract	0.00091	Assumption
IOP	0.00091	Assumption
Dexamethasone		
Cataract	0.00091	Assumption
IOP	0.00091	Assumption

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

The VIBRANT trial(25) collected EQ-5D data and were analysed to estimate utilities (see appendix **Error! Reference source not found.**). The data were analysed using multiple model types, using both univariate and multivariate model structures. All variables of interest were initially tested using univariate ordinary least squares (OLS) regression models and where variables were found to be significant, they were considered for inclusion in the multivariate analysis.

The results showed a significant relationship between BCVA and EQ-5D; however the relationship explained only a very small proportion of the total variance (3.2% or 3.1%). This is consistent with previous analyses and NICE guidance stating that EQ-5D is not sufficiently sensitive to changes in visual acuity. The insensitivity of the EQ-

5D to changes in BCVA has been highlighted by Fenwick et al. 2012(72), Finger et al. 2013(73), Gonder 2014(74), Loftus 2011(75) and Brown 2012(76).

Given this evidence, utility estimates based on direct valuation techniques were preferred for the base case analysis (see section 5.4.4.1).The results of the EQ-5D utility analysis are used as a sensitivity analysis which is the approach taken by a previous submission to NICE in DMO (66).

5.4.2 Mapping

No mapping studies were performed.

5.4.3 Health-related quality-of-life studies

5.4.3.1 Search Overview

Previous ophthalmology submissions across DMO and CRVO have used base case utilities taken from Czoski-Murray et al. (2009)(77), a study in age-related macular degeneration (AMD) using the time-trade off (TTO) elicitation method. While this study does not elicit values from a BRVO patient population, it is used as a standard in HTA submissions(66;68;78) as well as being recommended for use by the ERG in the ranibizumab submission for BRVO(79).

A systematic literature search was performed to answer the following research questions:

1. How does BRVO affect HRQoL?
2. What utilities are attached to different levels of VA?
3. What disutilities are associated with treatment-related adverse events?

The search was conducted on October 9th 2015 using the following electronic databases;

- Embase (1988 – October 9th 2015)
- Medline (including Medline (R) in process (1946 – October 9th 2015))
- Econlit

- NHS EED

The search strings used for each database are presented in appendix **Error! Reference source not found.**.

Furthermore, a search was conducted to identify relevant economic evaluation conference abstracts and posters on November 23rd 2015. The following congress was searched:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (North Africa and Europe only): http://ispor.org/

The search strategy, search terms and results for the congress search are detailed in section appendix **Error! Reference source not found.**.

The inclusion and exclusion criteria are shown in Table 72. No comparators or interventions were included in the search because the aim was to identify disease specific utilities, not treatment specific utilities. The outcomes were limited to utilities stratified by visual acuity to align with the health states included in the model (see section 5.2.2.1).Studies reporting utility elicitation, valuation or economic evaluations reporting utility values were included; specifically, studies containing TTO, SG, EQ-5D, HUI-3.

The search was restricted to publications from 2000 and limited to those in the English language.

Table 72. Health related quality of life eligibility criteria

Quality of life	Inclusion	Exclusion
Patient population	Adult patients with BRVO, CRVO, RVO, AMD or DMO	Patients with pathologies other than BRVO, CRVO, RVO, AMD or DMO
Interventions	-	-
Comparators	-	-
Outcome measures	• Utility values (visual acuity, treatment adverse events, BRVO complications) stratified by visual acuity or disease severity	Studies that reported utilitily values not stratified by visual acuity or disease severity of BRVO, CRVO, RVO, AMD or DMO
Study design	• Reports of utility elicitation exercises **OR** • Reports of utility validation exercises **OR** • Reports of economic evaluations using utility measures gathered during the studies.	• Abstracts not providing sufficient data for extraction*
Restrictions	• Language: English • Published from 2000	• Non-English studies • Studies published prior to 2000

AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; DMO: diabetic macular oedema; RVO: retinal vein occlusion. * If full text publication not available

5.4.3.2 Methods and processes

After the removal of duplicates, the titles and abstracts of all references identified from the search were independently reviewed by two researchers. The suitability of the articles was evaluated against the eligibility criteria shown in Table 72. Full texts of the studies selected were reviewed and the same eligibility criteria applied. In the event of a disagreement regarding inclusion the inclusion status of the publication were resolved either through “reconciliation” (discussion between the two reviewers) and/or through “arbitration” by a third independent reviewer. All papers included after the full text review were retained for data extraction. Data extraction was carried out by one reviewer and checked by another.

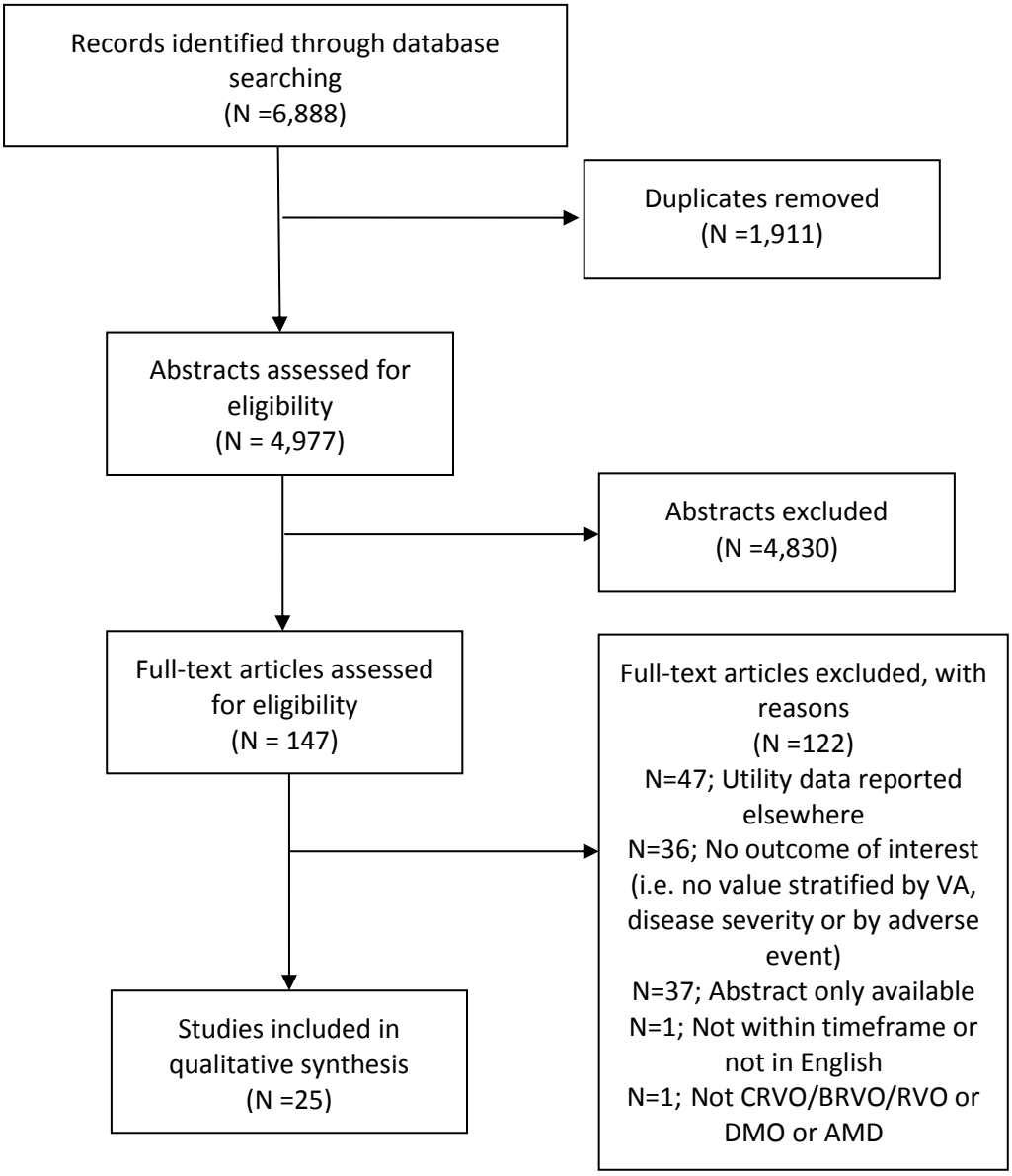
A quality assessment on the individual studies was conducted on the included studies as per the NICE guidance quality checklist. This checklist focuses on selection bias, performance bias, measurement bias and attrition bias.

5.4.3.3 Results

5.4.3.3.1 Search results

The HRQoL search yielded a total of 6,888 hits, of which 1,911 were duplicates, leaving 4,977 records to be reviewed against the eligibility criteria. A total of 4,830 abstracts were excluded with 147 studies selected for full text review. Of these, 122 were excluded and 25 retained for data extraction. The process of study selection and the final results of the search are illustrated below using the PRISMA flow diagram (Figure 50).

Figure 50. PRISMA diagram for the HRQoL search



5.4.3.3.2 Excluded studies

The list of 122 excluded studies with the primary reason for exclusion for each study is presented below in appendix **Error! Reference source not found.** – section **Error! Reference source not found.**.

5.4.3.3.3 Included studies

At the stage of full text review, 25 studies were retained for data extraction. VIBRANT(25) was one of the trials identified in the search, full details of the utilities elicited can be found in section **Error! Reference source not found.**.

Table 73. Summary of included studies for HRQoL search

Study	Country setting	Population	Method of elicitation	Methods of valuation
Aspinall et al. 2007(80)	UK	AMD patients with mean age of 77.8 years	TTO by questionnaire	NEI-VFQ-25
Au Eong et al. 2012(81)	China	AMD patients with mean age of 68.1 years	TTO and SG questionnaires administered by interviewer	EQ-5D
Brown et al. 1999(82)	USA	Associated with diabetic retinopathy and varying degrees of visual loss with a mean age of 63 years	TTO and SG	Paired, two-tailed student t-test was used to compare the means of each of the subgroups within the total sample with regard to mean TTO utility versus mean SG utility value
Brown et al. 2000(83)	USA	AMD patients with a mean age of 74.4 years	TTO and SG	-
Brown et al. 2000(84)	USA	Patients with visual loss to the level of 20/40 or worse in at least one eye and visual loss occurring predominantly secondary to AMD	TTO and SG	-
Brown et al. 2002(60)	USA	Patients with diabetic retinopathy or dry or wet AMD	TTO	-
Czoski-Murray et al. 2009(77)	UK	General population with a mean age of 32 years	TTO	HUI-3, selected items from the VF-14
Espallargues et al. 2005(85)	UK	AMD patients with mean age of 79.6 years	TTO, EQ-VAS	EQ-5D, HUI-3, SF-36, VF-14
Fenwick et al. 2012 (72)	Ireland	24.6% had no DR/DME, 11.8% had mild NPDR/DME, 23.2% had moderate NPDR/DME and 40.4% vision threatening DR. The median age was 65 years.	VisQol with health states derived from TTO	Multi-attribute utility instrument

Lee et al. 2008(86)	USA	Patients with DR, glaucoma, AMD and cataract were included	SG	-
Lotery et al. 2007 (87)	UK	AMD and general population control	-	EQ-5D, NEI-VFQ-25, HADS
Payacachat et al. 2009(88)	Australia, Netherlands, UK, USA, Canada, France, Germany, Spain	Primary dataset: patients with wet AMD from Australia, Netherlands, UK and USA Validation dataset: patients with wet AMD from Canada, France, Germany, Spain and UK	-	EQ-5D, NEI-VFQ-25
Pershing et al. 2014(89)	USA	Patients with type 1 or type 2 and DMO	TTO and SG (based on other studies)	NR
Polack et al. 2015 (90)	India	Patients with type 2 diabetes, and had either; ; no DR; mild/moderate non-proliferative DR without macular edema (NPDR), sight threatening DR, and blind due to DR	EQ-5D	-
Regnier et al. 2015 (91)	Cost-utility analysis			
Sahel et al. 2007(92)	France, Germany, Italy	AMD patients with mean age 77 years	-	NEI-VFQ-25, HUI-3, MacDQol
Shah et al. 2004 (93)	US	AMD patients with mean age of 67.5 years	TTO	-
Sharma et al. 2000(94)	USA	Associated with diabetic retinopathy and varying degrees of visual loss with a mean age of 63 years	TTO and SG	Paired, two-tailed student t-test was used to compare the means of each of the subgroups within the total sample with regard to mean TTO utility versus

				mean SG utility value
Sharma et al. 2000(95)	USA	Patients with various ocular conditions	TTO	-
Sharma et al. 2002(96)	USA	AMD, DR and other ocular diseases including cataract, glaucoma, retinal detachment, non-diabetic oedema, amblyopia, vascular obstruction, corneal disease	TTO and SG	VF-14
Soubrane et al. 2007(97)	Canada, France, Germany, Spain, UK	Patients with bilateral subfoveal NV-AMD and controls	-	NEI-VFQ, EQ-5D, HADS anxiety and HADS depression
Stein et al. 2003 (98)	USA	AMD patients, general public and care providers with mean age of 75.1, 44.3 and 29 years respectively	TTO	-
Stein et al. 2013 (99)	Cost-utility model			
Yanagi et al. 2011(100)	Japan	Patients with bilateral exudative AMD with mean age of 75.9 years	TTO and SG	-

AMD age-related macular oedema; DR diabetic retinopathy; DME/DMO diabetic macular oedema; NPDR non-proliferative diabetic retinopathy; NV-AMD neovascular age-related macular oedema; TTO time trade-off; SG standard gamble

5.4.3.4 Summary

This HRQoL literature search did not identify any BRVO specific utilities suitable for inclusion in the model. Although the utilities available from Czoski-Murray et al. (2009)(77) are also not BRVO-specific, it was decided that these were the most appropriate for use in the submission. This approach would therefore ensure consistency with previous ophthalmology and BRVO appraisals ((66;68;78).

5.4.4 Health-related quality-of-life data used in cost-effectiveness analysis

5.4.4.1 Model approach

QALYs are derived by multiplying the time spent in a particular model health state by a utility value associated with that health state. Quality of life is a function of visual acuity in both eyes. Patients are assumed to have a constant HRQoL during their time in a health state, as such HRQoL is only affected by changes in BCVA and not the duration spent in a particular health state. HRQoL was also assumed to be constant over time with no adjustment made for the ageing of the population. This assumption seemed reasonable as it allowed all patients to have the same HRQoL gain from improved vision, regardless of age.

The model health states are defined by vision in both eyes and therefore health state utilities (and hence QALYs) account for which is the better-seeing and worse-seeing eye. This approach requires a total of 15 unique utility values to account for every possible combination of best-seeing eye and worse-seeing eye (Note – from a utility perspective the 2,1 health state is the same as the 1,2 health state) – see Table 76.

In Czoski-Murray et al. (2009)(77), three AMD vision states were produced by simulating the visual impairment associated with AMD through the use of custom-made contact lenses. Participants were randomly recruited from the healthy UK population. The TTO was anchored at full health and immediate death. After the insertion of each lens, participants undertook five activities of daily living and completed five VF-14 items, HUI3, and TTO of the new simulated vision state. Coefficients from Czoski-Murray et al. 2009(77) are reported in Table 74.

Table 74. Regression coefficient from Czoski-Murray et al (2009)(77)

	TTO values for simulated states regression coefficient
Constant	0.860
VA (LogMAR) ¥	-0.368

¥ logMAR values = log(1/Snellen fraction)

In line with the methodology outlined by Czoski-Murray et al. (2009)(77), coefficients reported in Table 75 will be applied to the log MAR derived from Snellen fractions and EDTRS midpoints.

Table 75. ETDRS intervals, Snellen fractions and logMAR values

ETDRS intervals	ETDRS midpoints	Snellen fractions§	logMAR values¥
Legally blind (<35)	17	0.035	1.46
Midpoint of 35-49	42	0.110	0.96
Midpoint of 50-64	57	0.219	0.66
Midpoint of 65-79	72	0.437	0.36
Best vision (80+)	90	1.000	0.00

§ Snellen fractions = 10^((<ETDRSi>-85)/50); where <ETDRSi> represents the ETDRS midpoint

¥ logMAR values = log(1/Snellen fraction)

The equation used to obtain utility values is reported below:

$$\text{Utility} = \text{Constant} + \text{CoeffVA logMAR} \times \text{logMARi}$$

In order to obtain utilities related to both eyes an adjustment was applied. Values describing the relationship between change in the WSE and utility relative to changes in utility from changes in the BSE were obtained using the following formula:

$$\Delta WSE = \Delta \text{Both eyes} \times (1/(1+1/y\%))$$

Where, y is the % of impact on utility for a change in the WSE compared to the BSE. This is set to 30% as has been done in previous submissions ((66;101)).

Table 76 reports the utility values associated with both eyes that has been inputted into the model.

Table 76. Utilities used at each model cycle based on both eyes

		Fellow eye				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**
Study eye	**VA1**	0.83	0.80	0.78	0.75	0.71
	VA2	0.80	0.70	0.67	0.65	0.61
	VA3	0.78	0.67	0.59	0.56	0.52
	VA4	0.75	0.65	0.56	0.48	0.44
	VA5	0.71	0.61	0.52	0.44	0.29

5.4.4.2 Adverse events

In addition to the health state utilities, disutilities were incorporated for specific adverse events. These reflect the negative impact of AEs on quality of life. Disutilities were weighted in the model according to the proportion of patients experiencing the event and were subtracted from the total QALYs, lowering the amount of QALYs accrued. Decrements associated to each adverse event are presented in Table 77.

A structured literature search was performed to identify a source for the disutility associated with IOP (see appendix **Error! Reference source not found.**). No sources for disutility were identified and therefore, to be consistent with previous submissions, ocular hypertension was not assumed to be associated with a utility decrement (66;101).

Table 77: Utility decrements due to adverse events

Adverse event	Disutility	Sources
Cataract disutility (normalised)	0.14	Brown et al 2007(102)
Ocular hypertension (IOP) disutility (normalised)	0.00	Assumption

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

5.5.1.1 Published resource use studies

A systematic literature search for resource use studies was performed in tandem with a search for economic evaluations. The search overview and methods and

process are described in section 5.1.1 and 5.1.2 respectively. The results of the search are reported in section 5.1.3.

Two studies were identified in the search reporting resource use, Fekrat et al. 2010(63) and Augustin et al. 2012(64). A full quality assessment on these studies based on the NICE guidance checklist is shown in appendix **Error! Reference source not found.** . The research question was well stated by both studies; Fekrat et al. 2010(63) included justification for the economic evaluation and the discussion around the importance of the research question. The methods for estimating quantities and unit costs were reported well in both studies, yet Fekrat et al. 2010(63) lacked some of the detail around inflation or currency conversion. Conclusions were included in the discussion with appropriate caveats.

5.5.1.1.1 Resource use included studies

Fekrat et al. 2010(63) and Augustin et al. 2012(64) are summarised in Table 78. The full data extraction is provided in appendix **Error! Reference source not found.**.

Fekrat et al. 2010(63) reported resource use in the US setting with a cost year of 2006. The main results reported were one year direct medical costs and one year resource use. Data for the study was collected over a five-year period (from 2001 through 2006). In BRVO patients the overall direct medical cost was estimated at $10,153. The resource use more commonly used by BRVO patients was reported as fluorescein angiography (45% of BRVO patients). Laser photocoagulation was found to be used in 16.6% of BRVO patients.

Augustin et al. 2012(64) used a retrospective chart review to determine resource utilisation and calculate health care costs associated with BRVO over a period of one year in France, Germany, and Italy. The main results reported were inpatient direct medical cost, outpatient direct medical cost (both over a 1 year time frame) and day admission cost. The results were split between resource use of patients receiving laser or injections. Overall, the direct medical costs for patients receiving an injection were lower than patients receiving laser across all country settings.

Table 78. Summary of resource use studies identified

Study	Analysis type	Study population of reported results	Country setting	Source of cost data	Input	Resource use
Fekrat et al. 2010(63)	Costing analysis based on retrospective cohort study	BRVO	US	BVOS (2006)	*One year direct medical costs:*	
					Overall direct medical cost	$10,153
					Indirect medical costs	$4,145
					Outpatient direct medical costs	$946
					Physician/carrier direct medical costs	$3,424
					One year resource use (% of BRVO patients):	
					Fluorescein angiography	45%
					Intravitreal injection	6.1%
					Laser photocoagulation	20.5%
					OCT	16.6%
					PRP	16%
					Vitrectomy	3.1%
Augustin et al. 2012(64)	Resource utilisation and cost analysis	BRVO	France	National public insurance tariffs and official drug price list (2005)	Inpatient direct medical costs (1 year): Laser/injection	€2,075.06
					Outpatient direct medical cost (1 year): Laser	€146.30 OR €98.10*
					Outpatient direct medical cost (1 year): Injection	€83.60
					Day admission: injection	€973.74
			Germany	German ophthalmologist fee scale, fee defined for privately insured	Inpatient direct medical costs (1 year): Laser/injection	€640.80
					Outpatient direct medical cost (1 year): Laser	€117.67 OR €41.22**

				patients, comparable services and pharmacy retail prices (2005)	Outpatient direct medical cost (1 year): Injection	€5.56**
			Italy	National tariffs and regional price list (2007)	Outpatient direct medical cost (1 year): Laser	€56.80
					Outpatient direct medical cost (1 year): Injection	€1,081.00
					Day admission: Laser	€1,032.40
					Day admission: Injection	€1,081.00

* Depending on procedure, ** Private practice.

5.5.1.2 Summary

The resource use studies identified in the economic search gave insight into the direct medical costs resource use of BRVO patients. However, Fekrat et al. 2010(63) and Augustin et al. 2012(64) are country specific and do not include resources from the UK. Therefore this resource use data could not be generalised to populate resource use inputs for the de novo analysis.

5.5.2 Intervention and comparators' costs and resource use

5.5.2.1 Overview of resource use and costs

The costs relevant to this evaluation are:

- costs of treatment (determined by the cost of each injection or laser procedure and the number of interventions),
- the cost of administration,
- the cost of monitoring combined with the frequency of monitoring, and
- cost of adverse events.
- cost of blindness

These resources and costs are outlined below.

The resource use systematic literature review did not identify any published sources to inform the resource use inputs of the model (see section 5.5.1.1). Consequently, to extend the data available from VIBRANT(25) a Physician Survey was conducted to source these inputs (see section 5.5.2.2.1 for a summary and appendix **Error! Reference source not found.** for more detail).

UK specific unit costs were collected for BRVO treatment (pharmacy cost, administration and specialist visits), monitoring visits, clinical tests and adverse events. The British National Formulary was used as the main source for the unit costs of each treatment option(103). Costs associated with treatment failures and adverse events were taken from the following UK sources:

- NHS Reference Costs (Department of Health, 2015(104))
- NCWC/NICE guidelines)

5.5.2.2 Resource use – treatment frequency

Three sources were used to inform the monitoring and treatment frequency inputs of the model i.e.1) the VIBRANT trial(25) 2) a Physician's survey, and 3) product SmPCs.

The number of treatments for each product used in the model are shown in Table 79 (first-line comparisons) and Table 81 (second-line comparisons). The source of each input is in each table. A description and justification for each input follows each table.

Table 79. Treatment frequency - Aflibercept as a first-line treatment option (Comparisons 1a, 1b, 1c)

	Efficacy Phase		Maintenance phase				Rest of Life phase
	0-6 months	6-12 months	Year 2	Year 3	Year 4	Year 5	Year 6+
Intervention pathway - Aflibercept followed by laser in treatment failures							
AFL only	9 (VIBRANT(25))		4.15 (Physician Survey)	2.61 (Physician Survey)	1.12 (Physician Survey)	0.58 (Physician Survey)	0 (Assumption)
AFL followed by LSR		3.0 AFL + 1 LSR (VIBRANT(25))	1.12 LSR (Physician Survey)	0.36 LSR (Physician Survey)	0.12 LSR (Physician Survey)	0.03 LSR (Physician Survey)	0 (Assumption)
Comparator pathway - Laser followed by ranibizumab in treatment failures: Comparison 1a							
LSR only	1.7 (VIBRANT(25))		1.12 (Physician Survey)	0.36 (Physician Survey)	0.12 (Physician Survey)	0.03 (Physician Survey)	0 (Assumption)
LSR followed by RAN		4.4 (assumed equal to AFL)	4.15 (Physician Survey)	2.61 (Physician Survey)	1.12 (Physician Survey)	0.58 (Physician Survey)	0 (Assumption)
Comparator pathway - Laser followed by dexamethasone in treatment failures: Comparison 1b							
LSR only	1.7 (VIBRANT(25))		1.12 (Physician Survey)	0.36 (Physician Survey)	0.12 (Physician Survey)	0.03 (Physician Survey)	0 (Assumption)
LSR followed by DEX		1 (SmPC)	1.69 (Physician Survey)	0.93 (Physician Survey)	0.21 (Physician Survey)	0.1 (Physician Survey)	0 (Assumption)
Comparator pathway - Laser followed by aflibercept in treatment failures: Comparison 1c							
LSR only	1.7 (VIBRANT(25))		1.12 (Physician Survey)	0.36 (Physician Survey)	0.12 (Physician Survey)	0.03 (Physician Survey)	0 (Assumption)
LSR followed by AFL		4.4 (VIBRANT(25))	4.15 (Physician Survey)	2.61 (Physician Survey)	1.12 (Physician Survey)	0.58 (Physician Survey)	0 (Assumption)

5.5.2.2.1 Clinical experts: Physician's Survey

A physician survey was developed with the objective of understanding how often patients with clinically significant BRVO who are treatment naïve require treatment and monitoring. The web-based survey was in the field between 24 February and 23 March 2015. 569 ophthalmologists were invited to participate. The survey was completed by 37 ophthalmologists (32 from England and 5 from Scotland). Physicians were asked for the average treatment frequency of aflibercept, laser photocoagulation, ranibizumab and dexamethasone (Table 80). A description of the survey and the results is provided in appendix **Error! Reference source not found.**. Results from the survey were used to inform resource use inputs of the model where inputs from VIBRANT(25) were not available.

Table 80. Physician survey – estimated average number of injections/laser procedures, per affected eye, per patient

	Year 1	Year 2	Year 3	Year 4	Year 5
Laser photocoagulation	2.00	1.12	0.36	0.12	0.03
Aflibercept	5.15	2.97	1.94	1.12	0.38
Ranibizumab	6.73	4.15	2.61	1.12	0.58
Dexamethasone	2.28	1.69	0.93	0.21	0.1

Intervention - Aflibercept followed by laser photocoagulation

Patients randomised to aflibercept in the VIBRANT study(25) received aflibercept for the first 6 months, with the possibility of switching treatment (adding laser photocoagulation) in the second 6 months if they met one of the rescue criteria.

For patients who remained on aflibercept alone for the first year it is assumed they have 9 injections. This is the mean number of treatments in the VIBRANT trial(25) for this arm. For years 2-5 results from the Physician's Survey were used in lieu of trial data. In the survey the results for aflibercept were lower than ranibizumab, for example, the results showed an average treatment frequency of 2.97 of aflibercept and 4.15 for ranibizumab in year 2 (Table 80). However, due to the similar posology of ranibizumab and aflibercept, it was assumed these inputs should be equal in the

model. Since there is experience with the use of ranibizumab in this condition the estimated rates for ranibizumab were also used for aflibercept.

For patients who switched to aflibercept + laser in the second 6 months of the efficacy phase, the VIBRANT trial(25) showed they received an average of 3.0 aflibercept injections and 1 laser treatment. For year 2-5 it was assumed they would only receive laser treatment because they had reached the failure criteria for aflibercept treatment in the efficacy phase. The frequency of laser treatment was taken from the Physician's Survey in lieu of clinical data.

All patients were assumed to have no further treatments after year 5.

Comparison 1a - Laser followed by ranibizumab

In this treatment pathway patients start treatment with laser and after six months can switch to ranibizumab if treatment with laser is not successful. For those patients who are successful on laser treatment the number of laser procedures in the first year is assumed to be equivalent to that seen in the VIBRANT trial(25) for patients who remained on laser photocoagulation treatment alone i.e. 1.7. In years 2-5 the number of laser procedures has been taken from the physician survey in the absence of trial data.

For patients who are unsuccessful on laser photocoagulation and who switch treatment to ranibizumab from 6 months, the frequency of treatment is assumed to be equivalent to aflibercept for patients switching to aflibercept in the VIBRANT study(25) (months 6-12) i.e. 4.4 injections. For years 2-5 ranibizumab injection frequency is taken from the physician survey.

Comparison 1b – Laser followed by dexamethasone

In this treatment pathway patients start treatment with laser and after six months can switch to dexamethasone if treatment with laser is not successful. For those patients who are successful on laser treatment the number of laser procedures in the first year is assumed to be equivalent to that seen in the VIBRANT trial(25) for patients who remained on laser photocoagulation treatment alone i.e. 1.7. In years 2-5 the

number of laser procedures has been taken from the physician survey in the absence of trial data.

For patients who switch to dexamethasone after 6 months, the frequency of treatment from 6-12 months is taken from the SmPC (Electronic Medicines Compendium, 2015(105)). The Physician's Survey estimated an average number of treatments of 2.28 in the first year, however since patients are only on dexamethasone from month 6 – 12 (6 months) if they switch treatment, one treatment was assumed as per the SmPC. From year 2 – year 5 the treatment frequency is sourced from the Physician's Survey.

Comparison 1c – Laser followed aflibcercept

All patients in this treatment pathway receive laser treatment for the first 6 months. Patients are eligible for switching treatment to aflibercept from 6 months.

For patients who are successful on laser photocoagulation and remain on this treatment the average number of procedures for the first year is taken from the VIBRANT study(25) i.e. 1.7. For years 2-5, in the absence of trial data, the frequency of laser photocoagulation is taken from the physician survey.

For patients who switch treatment to aflibercept after 6 months the number of injections in months 6-12 is taken from VIBRANT(25) i.e. 4.4. For years 2-5, in the absence of trial data, the frequency of aflibercept is taken from the physician survey and is assumed equal to ranibizumab as described above.

Table 81. Treatment frequency - Aflibercept as a second-line treatment option (Comparisons 2a, 2b)

	Efficacy Phase		Maintenance phase				Rest of Life phase
	0-6 months	**6-12 months**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6+**
Intervention pathway - Laser followed by aflibercept in treatment failures							
LSR	1.7 (VIBRANT(25))		1.12 (Physician Survey)	0.36 (Physician Survey)	0.12 (Physician Survey)	0.03 (Physician Survey)	0 (Assumption)
LSR followed by AFL		4.4 (VIBRANT(25))	4.15 (Physician Survey)	2.61 (Physician Survey)	1.12 (Physician Survey)	0.58 (Physician Survey)	0 (Assumption)
Comparator pathway - Laser followed by ranibizumab in treatment failures: Comparison 2a							
LSR	1.7 (VIBRANT(25))		1.12 (Physician Survey)	0.36 (Physician Survey)	0.12 (Physician Survey)	0.03 (Physician Survey)	0 (Assumption)
LSR followed by RAN		4.4 (assumed equal to AFL)	4.15 (Physician Survey)	2.61 (Physician Survey)	1.12 (Physician Survey)	0.58 (Physician Survey)	0 (Assumption)
Comparator pathway - Laser followed by dexamethasone in treatment failures: Comparison 2b							
LSR	1.7 (VIBRANT (25))		1.12 (Physician Survey)	0.36 (Physician Survey)	0.12 (Physician Survey)	0.03 (Physician Survey)	0 (Assumption)
LSR followed by DEX		1.0 (SmPC)	1.69 (Physician Survey)	0.93 (Physician Survey)	0.21 (Physician Survey)	0.1 (Physician Survey)	0 (Assumption)

Intervention – Laser followed by aflibercept

The frequency of treatment is as described for comparison 1c.

Comparison 2a - Laser followed by ranibizumab

The frequency of treatment is as described for comparison 1a.

Comparison 2b – Laser followed dexamethasone

The frequency of treatment is as described for comparison 1b.

5.5.2.3 Resource use - Monitoring visits

The frequency of monitoring visits was either assumed to equal the number of treatments or was sourced from the Physician's Survey. The model assumes each monitoring visit includes an eye test and an Optical Coherence Tomography (OCT). Monitoring visits are adjusted in the model to reflect that a treatment will be administered at each of these visits. For example, if the yearly treatment frequency is 4 and the yearly frequency of monitoring is 6, it is assumed 4 of the 6 monitoring visits cost will be covered by the treatment. Therefore, the yearly cost from monitoring would be the difference i.e. 2 visits.

The number of monitoring visits over the lifetime of the model and the data source is summarised in Table 83.

Monitoring visits in the first year for aflibercept and ranibizumab are assumed to equal the number of injections. This assumption was used as the number of monitoring visits scheduled in trial protocols would likely be higher than clinical practice. For dexamethasone the physician's survey was used as 1 visit (associated with 1 injection) was felt not to be representative of clinical practice. For laser in the first year the physician's survey was again used, as for dexamethasone, making monitoring visits equal to the number of treatments (i.e. a mean of 1.7 laser procedures) would be an underestimate compared to clinical practice.

Monitoring for all treatments in years 2-5 was taken from the physician survey. As for the number of injections estimated from the physician survey, the number of monitoring visits was estimated to be higher for ranibizumab. Using the same

rational as for injections monitoring was assumed to be the same for both treatments and the frequency for ranibizumab was used.

Table 82. Physician Survey – average number of monitoring visits, per affected eye, per patient

	Year 1	Year 2	Year 3	Year 4	Year 5
Laser photocoagulation	5.60	2.74	1.76	1.0	0.65
Aflibercept	5.40	4.49	3.40	2.17	1.09
Ranibizumab	7.47	5.62	4.09	2.44	1.35
Dexamethasone	5.20	3.87	3.00	1.70	0.93

Table 83. Monitoring frequency (aflibercept as a first-line treatment option)

	Efficacy Phase		Maintenance phase				Rest of Life phase
	0-6 months	**6-12 months**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6+**
Intervention pathway - Aflibercept followed by laser in treatment failures							
AFL alone	9 (Assumed equal to number of treatments)		5.6 (Physicians survey)	4.1 (Physicians survey)	2.4 (Physicians survey)	1.4 (Physicians survey)	0 (assumption)
AFL followed by LSR	na	3.0 (Assumed equal to no. of injections)	2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
Comparator pathway - Laser followed by ranibizumab in treatment failures: Comparison 1a							
LSR alone	5.6 (Physicians survey)		2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
LSR followed RAN	na	4.4 (Assumed equal to no. treatments)	5.6 (Physicians survey)	4.1 (Physicians survey)	2.4 (Physicians survey)	1.4 (Physicians survey)	0 (assumption)
Comparator pathway - Laser followed by dexamethasone in treatment failures: Comparison 1b							
LSR alone	5.6 (Physicians survey)		2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
LSR followed by DEX	na	3.0 (Physicians survey)	3.9 (Physicians survey)	3.0 (Physicians survey)	1.7 (Physicians survey)	0.9 (Physicians survey)	0 (assumption)
Comparator pathway - Laser followed by aflibercept in treatment failures: Comparison 1c							
LSR alone	5.6 (Physicians survey)		2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
LSR followed by AFL	na	4.4 (Assumed equal to no. treatments)	5.6 (Physicians survey)	4.1 (Physicians survey)	2.4 (Physicians survey)	1.4 (Physicians survey)	0 (assumption)

Table 84. Monitoring frequency (aflibercept as a second-line treatment option)

	Efficacy Phase		Maintenance phase				Rest of Life phase
	0-6 months	**6-12 months**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6+**
Intervention pathway - Laser followed by aflibercept in treatment failures							
LSR alone	5.6 (Physicians survey)		2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
LSR followed by AFL	na	4.4 (Assumed equal to no. treatments)	5.6 (Physicians survey)	4.1 (Physicians survey)	2.4 (Physicians survey)	1.4 (Physicians survey)	0 (assumption)
Comparator pathway - Laser followed by ranibizumab in treatment failures: Comparison 2a							
LSR alone	5.6 (Physicians survey)		2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
LSR followed RAN	na	4.4 (Assumed equal to no. treatments)	5.6 (Physicians survey)	4.1 (Physicians survey)	2.4 (Physicians survey)	1.4 (Physicians survey)	0 (assumption)
Comparator pathway - Laser followed by dexamethasone in treatment failures: Comparison 2b							
LSR alone	5.6 (Physicians survey)		2.7 (Physicians survey)	1.8 (Physicians survey)	1.0 (Physicians survey)	0.7 (Physicians survey)	0 (assumption)
LSR followed by DEX	na	3.0 (Physicians survey)	3.9 (Physicians survey)	3.0 (Physicians survey)	1.7 (Physicians survey)	0.9 (Physicians survey)	0 (assumption)

5.5.2.3.1 Fellow eye

The fellow eye, if affected by BRVO, follows the same treatment and monitoring frequencies as the study eye.

For bilateral patients it is assumed that patients will share monitoring visits in which both eyes will be examined 50% of the time. This assumption is tested in the sensitivity analyses.

5.5.2.4 Intervention and comparator costs

In the model, the cost of treatment is comprised of the drug acquisition cost, the cost of administration and the cost of monitoring.

Drug acquisition costs are shown in Table 85. These costs were sourced from the BNF for ranibizumab and dexamethasone. The submission uses the PAS price for aflibercept. There are no published sources providing detailed estimates of the cost of laser treatment per unit. Based on a previous NICE submission for aflibercept in DMO(66), the cost of laser was considered to be equivalent to a minor vitreous retinal procedure (reference BZ97A).

Table 85. Drug acquisition costs per patients

Drug	Drug cost (per patient)	Source
Aflibercept list	£816.00	BNF 2015(103)
Aflibercept PAS	[redacted]	Bayer
Laser	£111.00	BZ87A Minor Vitreous Retinal Procedures outpatient procedure, 19 years and over (Department of Health, 2014-15(104))
Ranibizumab	£742.17	BNF 2015(103)
Dexamethasone	£870.00	BNF 2015(103)

The general cost of an administration and a monitoring visit feed into the individual total administration cost for each treatment of the model. Table 86 shows the cost of administration is sourced from the NHS Reference Costs using the code for an ultrasound lasting less than 20 minutes without contrast, which has been used in previous submissions for back of the eye diseases ((66;101). The cost of a

monitoring visit is assumed to be the cost of a consultant led outpatient appointment in ophthalmology plus the administration cost which has been used in a previous submission(66).

Table 86. Unit costs; administration and monitoring

Resource	Cost (per patient)	Source (Department of Health, 2014-15(104))
Administration anti-VEGF	£53.96	RD40Z Ultrasound less than 20 minutes without contrast
Administration dexamethasone	£266.25	Weighted cost 75% BZ86B Day case, Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1, 25% BZ87A Outpatient, Minor Vitreous Retinal Procedures, 19 years and over
Monitoring visit	£150.07	Consultant led outpatient attendance service, code 130 + administration cost

These costs of administration and monitoring visit are used to calculate the treatment specific visit cost. The same administration cost is assumed for aflibercept and ranibizumab as they have the same method of administration. For laser, the administration cost is assumed to be equal to a monitoring visit. The administration cost of dexamethasone is higher than the other comparators to take into account the more complicated procedure. Costing guidance from the NHS for aflibercept in CRVO use a weighted administration cost of 75% day case minor retinal procedure, and 25% outpatient minor retinal procedure (National Institute of Health and Care Excellence, 2014(106)). In the 2014-15 NHS Reference Costs(104), the cost of a minor vitreous retinal procedure for day cases is more expensive than the intermediate procedure. Therefore, to be conservative and not overestimate the administration cost of dexamethasone, the day case intermediate vitreous retinal procedure cost was used.

5.5.3 Health-state unit costs and resource use

The cost applied at each health state is driven by the treatment arm with the appropriate treatment, administration and adverse event costs applied.

The only health state which is associated with an additional cost is for blindness in both eyes (VA5, VA5). In addition to the cost of treatment, administration and adverse events, an annual cost of £7,429 was added as the cost of blindness as

reported in McCrone et al. (2008)(107). This is consistent with the NICE assessment of ranibizumab in CNV for pathological myopia (National Institute for Health and Care Excellence, 2013(108)).

5.5.4 Adverse reaction unit costs and resource use

Total costs associated with the treatment of AEs were estimated based upon the unit costs associated with each AE and the proportion of patients experiencing each AE in the SE and FE.

Table 87 reports the unit cost per patient for each AE included in the model. These costs are only applied when the adverse event is observed.

Table 87. Unit costs of treating adverse events

Adverse event	Cost (per patient)	Source (Department of Health, 2014-15(104))
Cataract	£1,160.65	BZ34A Cataract Extraction and Lens Implant, with CC Score 4+ plus 3x consultant led outpatient attendance service code 130 (£872.31 + (3 x £96.11))
Ocular hypertension (IOP)	£3.57	NICE aflibercept in CRVO submission (National Institute for Health and Care Excellence, 2014(78))

5.5.5 Miscellaneous unit costs and resource use

There are no additional costs considered in the model.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Table 88 summarises the variables applied in the economic model.

Table 88. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age	65	52-78	5.3.1.1
Proportion female, %	0.45	0.36-0.54	5.3.1.1
Fellow eye involvement, %	0.061	0.049-0.073	5.3.2.3.4
Efficacy parameters			
RR vs aflibercept of gaining ≥15 letters			
Ranibizumab	0.93	0.38-2.31	0
Dexamethasone	0.34	0.12-0.96	
Long-term decline in vision (Rest of life phase/patients who have discontinued)			
Natural decline monthly rate BRVO eye	0.0017	0.00133-0.00200	5.3.2.3.3
Natural decline monthly rate unaffected eye	0.00167	0.00133-0.00200	
Mortality rates			
Background mortality	As per life tables	NA	5.3.1.2
RR of mortality (with poor vision)	1.23	1.16-1.31	
Monthly treatment discontinuation rates			
Aflibercept	0.00955	0.0076-0.0115	5.3.1.3
Ranibizumab	0.00955	0.0076-0.0115	
Dexamethasone	0.00955	0.0076-0.0115	
Laser treatment	0.00781	0.0025-0.0094	
Adverse event rates, % per month			
Aflibercept			
Cataract	0.00091	0.0007-0.0011	5.3.2.4
Ocular hypertension (IOP)	0.00091	0.0007-0.0011	
Ranibizumab			
Cataract	0.00091	0.0007-0.0011	5.3.2.4
Ocular hypertension (IOP)	0.00091	0.0007-0.0011	
Dexamethasone			
Cataract	0.00091	0.0007-0.0011	5.3.2.4

Ocular hypertension (IOP)	0.00091	0.0007-0.0011	
Laser treatment			
Cataract	0.0000	0.0000-0.0000	5.3.2.4
Ocular hypertension (IOP)	0.00090	0.0007-0.0011	
Mean number of injections/treatments (the mean number of treatments are presented in section 5.5.2.2.1)			
Mean number of monitoring visits (due to the number of pathways in the model, the mean number of monitoring visits are presented in section 5.5.2.3)			
Utility values (due to the number of health states utilities are presented in section 5.4.4.1)			
CI, confidence interval; RR, relative risk			

5.6.2 Assumptions

The key structural and input assumptions incorporated in the model are detailed with justification and associated sensitivity analyses in Table 89.

Table 89. Model assumptions summary

Assumption	Justification	Reference to section in submission	Sensitivity analysis
Structural			
It is assumed the maintenance phase lasts 4 years.	The incorporation of a maintenance phase is based on the Physician's Survey which showed Physician's would look to monitor patients and treat if required for up to 5 years.	Appendix **Error! Reference source not found.**	Scenario analyses were run for a maintenance phase of 2 and 3 years.
The treatment benefit accrued at the end of the efficacy phase is maintained with no diminished effect throughout the 4 years of the maintenance phase, unless a patient discontinues in which case there is a natural rate of decline in vision	Patients are monitored and treated at a frequency required to stabilise vision. This assumption has been the method used for previous back of the eye disease submissions to NICE and the SMC ((66;68;101).	5.3.2.3.2	None
It is assumed that during the maintenance phase patients remain on the treatment they ended the efficacy phase on. Patients who fail aflibercept in the aflibercept first-line arm of the model receive a laser treatment at week 36. During the maintenance phase it is assumed they will only receive laser treatment	Patients randomised to aflibercept who require rescue therapy with laser may still be given aflibercept for a short period of time if the patient is thought to be obtaining some benefit. However, based on expert opinion extra injections are expected to be very limited	5.3.2.3.2	None
It is assumed that eyes that are blind will not continue to be treated in the maintenance phase.	This assumption is based on treatment administered during the maintenance phase aims to maintain vision. Therefore, if a patient is blind, there would be no clinical benefit in continuing treatment.	5.3.2.3.2	None
The rest of the life phase is based on the assumption patient's vision declines at a steady rate over the remainder of their life.	This assumption is based on a source from the literature by (Van der pols, 2000(70)).	5.3.2.3.3	Rate of natural decline in the rest of life phase is tested in the one-way sensitivity analysis and probabilistic sensitivity analysis.

Inputs			
The starting distribution of the patients across the visual acuity scores were estimated from the full sample of VIBRANT patients, regardless of treatment arm, and are therefore assumed to be applicable to all patients.	This assumption was made to ensure the results were generalisable for all BRVO patients.	5.3.1.1	None
It is assumed each monitoring visit will include an eye test and an optical coherence test (OCT).	This assumption is based on previous submissions for back of the eye diseases.	5.5.2.3	None
For bilateral BRVO patients, it is assumed that 50% of patients will require only one monitoring visit in which both eyes will be examined.	This assumption is based on previous submissions for back of the eye diseases.	5.3.2.3.4	Sensitivity analyses were run on this input.
It is assumed only 50% of fellow eyes affected by BRVO are treated.	This assumption is based on previous submissions for back of the eye diseases.	5.3.2.3.4	Sensitivity analyses were run on this input.
Adverse event rates for ranibizumab and dexamethasone are assumed to be equivalent to aflibercept.	Aflibercept and ranibizumab have similar adverse event profiles in other back fo the eye conditions. The assumption of equivalent adverse event rates is conservative when aflibercept is compared to dexamethasone because dexamethasone is known to have a significant adverse event profile with a risk of cataracts that increases with the number of injections (Electronic Medicines Compendium, 2015(105))	5.3.2.4	Sensitivity analyses were run on these inputs.

5.7 Sensitivity analysis

In addition to the one-way and probabilistic analyses described below, the following scenario analyses were conducted:

- Equivalent efficacy between aflibercept and ranibizumab
- EQ5D utility estimates derived from the VIBRANT trial(25)
- The use of shift tables as source of efficacy data for the comparison of aflibercept first-line versus laser first-line (comparison 1c).

5.7.1 Deterministic sensitivity analysis

A one-way sensitivity analysis was conducted to examine the effect of a range of parameter values on the incremental costs, incremental outcomes and incremental cost-effectiveness ratio. The variables included in the analysis are descibed in Table 90.

Table 90. Variables included in the one-way sensitivity analysis

Parameter	Base case value	Lower value	Upper value	Reference
Starting age of cohort	65.00	52.00	78.00	95% CIs
% females	0.45	0.36	0.54	± 20% of the mean value
% bilateral involvement at baseline	0.061	0.05	0.07	± 20% of the mean value
Annual incidence of FEI	0.03	0.02	0.03	± 20% of the mean value
Proportion of fellow eye treated	0.50	0.40	0.60	± 20% of the mean value
FEI % of shared monitoring visits	0.50	0.40	0.60	± 20% of the mean value
% of shared injection/monitoring visits	1.00	0.80	1.00	± 20% of the mean value
Mortality				
RR of mortality associated with one eye blind	1.23	1.16	1.31	95% CIs
Costs				
Monitoring visit cost	150.07	120.06	180.08	± 20% of the mean value
Monthly cost of blindness	619.08	495.27	742.90	± 20% of the mean value
Administration cost (VEG-F)	204.03	163.22	224.84	± 20% of the mean value
Administration cost (dexamethasone)	266.25	213.00	319.50	± 20% of the mean value
Administration cost (laser)	150.07	120.06	180.08	± 20% of the mean value
Cataract cost	1160.65	928.52	1392.78	± 20% of the mean value
Ocular hypertension (IOP) cost	3.57	2.86	4.28	± 20% of the mean value
Efficacy				
OR dexamethasone gaining ≥15 letters	0.34	0.12	0.96	NMA 95% CrI
OR ranibizumab gaining ≥15 letters	0.93	0.38	2.31	NMA 95% CrI
Off treatment decline				
BRVO decline rate	0.0017	0.0013	0.0020	± 20% of the mean value

Unaffected eye decliner rate	0.0017	0.0013	0.0020	± 20% of the mean value
Discontinuation				
Aflibercept	0.00955	0.0076	0.0115	± 20% of the mean value
Ranibizumab	0.00955	0.0076	0.0115	± 20% of the mean value
Dexamethasone	0.00955	0.0076	0.0115	± 20% of the mean value
Laser	0.00781	0.0025	0.0094	± 20% of the mean value
Frequency of treatment				
Aflibercept 1st line year 1	9.00	7.20	10.80	± 20% of the mean value
Aflibercept 1st line year 2	4.15	3.32	4.98	± 20% of the mean value
Aflibercept 1st line year 3	2.61	2.09	3.13	± 20% of the mean value
Aflibercept 1st line year 4	1.12	0.90	1.34	± 20% of the mean value
Aflibercept 1st line year 5	0.58	0.46	0.70	± 20% of the mean value
Aflibercept + laser year 1 (Aflibercept injection)	3.00	2.40	3.60	± 20% of the mean value
Aflibercept + laser year 1 (Laser treatment)	1.00	0.80	1.20	± 20% of the mean value
Aflibercept + laser year 2 (laser treatment)	1.12	0.90	1.34	± 20% of the mean value
Aflibercept + laser year 3 (laser treatment)	0.36	0.29	0.43	± 20% of the mean value
Aflibercept + laser year 4 (laser treatment)	0.12	0.10	0.14	± 20% of the mean value
Aflibercept + laser year 5	0.03	0.024	0.036	± 20% of the mean value
Aflibercept 2nd line year 1	4.40	3.52	5.28	± 20% of the mean value
Aflibercept 2nd line year 2	4.15	3.32	4.98	± 20% of the mean value
Aflibercept 2nd line year 3	2.61	2.09	3.13	± 20% of the mean value
Aflibercept 2nd line year 4	1.12	0.90	1.34	± 20% of the mean value
Aflibercept 2nd line year 5	0.58	0.46	0.70	± 20% of the mean value
Ranibizumab 2nd line year 1	4.40	3.52	5.28	± 20% of the mean value
Ranibizumab 2nd line year 2	4.15	3.32	4.98	± 20% of the mean value

Ranibizumab 2nd line year 3	2.61	2.09	3.13	± 20% of the mean value
Ranibizumab 2nd line year 4	1.12	0.90	1.34	± 20% of the mean value
Ranibizumab 2nd line year 5	0.58	0.46	0.70	± 20% of the mean value
Laser 1st line year 1	1.70	1.36	2.04	± 20% of the mean value
Laser 1st line year 2	1.12	0.90	1.34	± 20% of the mean value
Laser 1st line year 3	0.36	0.29	0.43	± 20% of the mean value
Laser 1st line year 4	0.12	0.10	0.14	± 20% of the mean value
Laser 1st line year 5	0.03	0.024	0.036	± 20% of the mean value
Dexamethasone 2nd line year 1	1.00	0.80	1.20	± 20% of the mean value
Dexamethasone 2nd line year 2	1.69	1.35	2.03	± 20% of the mean value
Dexamethasone 2nd line year 3	0.93	0.74	1.12	± 20% of the mean value
Dexamethasone 2nd line year 4	0.21	0.17	0.25	± 20% of the mean value
Dexamethasone 2nd line year 5	0.10	0.08	0.12	± 20% of the mean value
Frequency of monitoring visits				
Aflibercept 1st line year 1	9.00	7.20	10.80	± 20% of the mean value
Aflibercept 1st line year 2	5.60	4.50	6.74	± 20% of the mean value
Aflibercept 1st line year 3	4.10	3.27	4.91	± 20% of the mean value
Aflibercept 1st line year 4	2.40	1.95	2.93	± 20% of the mean value
Aflibercept 1st line year 5	1.35	1.08	1.62	± 20% of the mean value
Aflibercept + laser year 1	3.00	2.40	3.60	± 20% of the mean value
Aflibercept + laser year 2	2.70	2.16	3.24	± 20% of the mean value
Aflibercept + laser year 3	1.80	1.41	2.11	± 20% of the mean value
Aflibercept + laser year 4	1.00	0.80	1.20	± 20% of the mean value
Aflibercept + laser year 5	0.70	0.56	0.84	± 20% of the mean value
Aflibercept 2nd line year 1	4.40	3.52	5.28	± 20% of the mean value
Aflibercept 2nd line year 2	5.60	4.48	6.72	± 20% of the mean value
Aflibercept 2nd line year 3	4.10	3.28	4.92	± 20% of the

				mean value
Aflibercept 2nd line year 4	2.40	1.92	2.88	± 20% of the mean value
Aflibercept 2nd line year 5	1.40	1.12	1.68	± 20% of the mean value
Ranibizumab 2nd line year 1	4.40	3.52	5.28	± 20% of the mean value
Ranibizumab 2nd line year 2	5.60	4.48	6.72	± 20% of the mean value
Ranibizumab 2nd line year 3	4.10	3.28	4.92	± 20% of the mean value
Ranibizumab 2nd line year 4	2.40	1.92	2.88	± 20% of the mean value
Ranibizumab 2nd line year 5	1.40	1.12	1.68	± 20% of the mean value
Laser 1st line year 1	5.60	4.48	6.72	± 20% of the mean value
Laser 1st line year 2	2.74	2.19	3.29	± 20% of the mean value
Laser 1st line year 3	1.76	1.41	2.11	± 20% of the mean value
Laser 1st line year 4	1.00	0.80	1.20	± 20% of the mean value
Laser 1st line year 5	0.65	0.52	0.78	± 20% of the mean value
Dexamethasone 2nd line year 1	3.00	2.40	3.60	± 20% of the mean value
Dexamethasone 2nd line year 2	3.90	3.10	4.64	± 20% of the mean value
Dexamethasone 2nd line year 3	3.00	2.40	3.60	± 20% of the mean value
Dexamethasone 2nd line year 4	1.70	1.36	2.04	± 20% of the mean value
Dexamethasone 2nd line year 5	0.90	0.72	1.08	± 20% of the mean value

In addition to the OWSA, the following scenario analyses were conducted:

Table 91: Variables included in the scenario analysis

Parameter	Base case value	Scenario value	Comment/Source
Time horizon	35 years	10 years	Assumption
Length of maintenance	4 years	3 years	Assumption
Length of maintenance	4 years	2 years	Assumption
Costs and benefits discount rate	3.5% both	0% both	Assumption
Costs and benefits discount rate	3.5% both	6% both	Assumption
Costs and benefits discount rate	3.5% both	6% costs; 1.5% benefits	Assumption

5.7.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning particular parametric distributions and repeatedly sampling mean parameter values. Sampling was based on point estimates used in the deterministic analysis and where standard errors were not avaliable, a default of 20% of the mean (point estimate) were used.

Each group of samples from all of the parameters included in the PSA generated an estimate for total costs and effects. A total of 1,000 different samples were taken from all distributions so that all values of a parameter are likely to have been present in the range of outputs.

Variables and statistical distributions used in the probabilistic sensitivity analyses are reported in Table 92.

The utilities are also included in the PSA and are varied using normal distributions and variance covariance matrices around the regression parameters.

Table 92. Variables included in the probabilistic sensitivity analysis

Input	Mean	Distribution type
% females	0.45	Beta (13, 16)
% bilateral involvement at baseline	0.07	Beta (23, 364)
Annual incidence of FEI	0.03	Beta (24, 950)
Proportion of fellow eye treated	0.50	Beta (12, 12)
FEI % of shared monitoring visits	0.55	Beta (11, 9)
% of shared injection/monitoring visits	1.00	Beta (-1, 0)
Mortality		
RR of mortality associated with one eye blind	1.23	Log-normal (1.23, 0.25)
Costs		
Monitoring visit cost	150.07	Gamma (25, 6)
Administration cost (VEG-F)	204.03	Gamma (25, 8)
Administration cost (dexamethasone)	266.25	Gamma (25, 11)
Administration cost (laser)	150.07	Gamma (25, 6)
Cataract cost	1160.65	Gamma (25, 46)
Ocular hypertension (IOP) cost	3.57	Gamma (25, 0.1)
Efficacy		
OR dexamethasone gaining ≥15 letters	0.34	Log-normal (0.34, 0.07)
OR ranibizumab gaining ≥15 letters	0.93	Log-normal (0.93, 0.19)
Off treatment decline		
BRVO decline rate	0.0017	Beta (25, 14949)
Unaffected eye decline rate	0.0017	Beta (25, 14949)
Discontinuation		
Aflibercept	0.00955	Beta (25, 2566)
Ranibizumab	0.00955	Beta (25, 2566)
Dexamethasone	0.00955	Beta (25, 2566)
Laser	0.00781	Beta (25, 3151)

Beta distribution (α, β) and gamma distribution (α, β) rounded to a whole number, lognormal distribution (μ, ʒ) rounded to 2 decimal places

5.8 Base-case results

A summary of the base-case cost-effectiveness results is in provided in Table 93. Aflibercept is a cost-effective treatment option when used as either a first or second-line treatment.

Table 93. Summary of the basecase cost-effectiveness results

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)	Incremental analysis
[A] Laser followed by dexamethasone (for treatment failures)	[redacted]	13.708	[redacted]	-	-	-	-	-
[B] Laser followed by aflibercept (for treatment failures)	[redacted]	13.709	[redacted]	[redacted]	0.001	[redacted]	11,792	11,792
[C] Laser followed by ranibizumab (for treatment failures)	[redacted]	13.709	[redacted]	[redacted]	0.001	[redacted]	28,513	Dominated
[D] Afibercept followed by laser (for treatment failures)	[redacted]	13.717	[redacted]	[redacted]	0.009	[redacted]	14,303	15,365
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

5.8.1 Aflibercept as a first-line treatment option

In the base case aflibercept as a first-line treatment option is compared to the current treatment pathway i.e. laser followed by ranibizumab in treatment failures (comparison 1a), laser followed by dexamethasone in treatment failures (comparison 1b) and, for completeness, laser followed by aflibercept in treatment failures (comparison 1c). Results are reported in terms of incremental cost, incremental QALYs, incremental LYs and incremental cost per QALY. Results are presented using the PAS price for aflibercept and the list price for ranibizumab and dexamethasone.

5.8.1.1 Aflibercept first-line vs laser followed by ranibizumab (comparison 1a)

Table 94 shows the results for this analysis. Aflibercept first-line is associated with higher costs in addition with marginal gains in LYs (incremental LYs: 0.0083) and a significant improvement in QALYs (incremental QALYs: [redacted]). These costs and QALYs result in an ICER of £8,939.

Table 94. Results: Comparison 1a - aflibercept first-line versus laser followed by ranibizumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL followed by LSR in treatment failures	[redacted]	13.717	[redacted]				
LSR followed by RAN in treatment failures	[redacted]	13.709	[redacted]	[redacted]	0.0083	[redacted]	8,939

5.8.1.2 Aflibercept first-line vs laser followed by dexamethasone (comparison 1b)

Table 95 shows the results for this analysis. Aflibercept first-line is associated with higher costs (incremental costs: [redacted]) in addition to a gain in LYs (incremental LYs: 0.0091) and QALYs (incremental QALYs: [redacted]). This resulted in an ICER of £14,303.

Table 95. Results: Comparison 1b - aflibercept first-line versus laser followed by dexamethasone

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL followed by LSR in treatment failures	[redacted]	13.717	[redacted]				
LSR followed by DEX in treatment failures	[redacted]	13.708	[redacted]	[redacted]	0.0091	[redacted]	14,303

5.8.1.3 Aflibercept first-line vs laser followed by aflibercept (comparison 1c)

Table 96 shows the results for this analysis. Aflibercept first-line is associated with higher costs (incremental costs: [redacted]), marginal gains in LYs (incremental LYs: 0.0082) however a significant improvement in QALYs (incremental QALYs: [redacted]) was observed. This resulted in an ICER of £15,365.

Table 96. Results: Comparison 1c - aflibercept first-line versus laser followed by aflibercept

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL followed by LSR in treatment failures	[redacted]	13.717	[redacted]				
LSR followed by AFL in treatment failures	[redacted]	13.709	[redacted]	[redacted]	0.0082	[redacted]	15,365

5.8.2 Aflibercept as a second-line treatment option

5.8.2.1 Laser followed by aflibercept versus laser followed by ranibizumab (comparison 2a)

Table 97 shows the results for laser followed by aflibercept versus laser followed by ranibizumab. The results of the base case analyses showed that laser followed by aflibercept is associated with lower cost (incremental cost: [redacted]) but also marginal gains in LYs (incremental LYs: 0.0001) and QALYs (incremental QALYs: [redacted]). This makes laser followed by aflibercept the dominant alternative.

Table 97. Results: Comparison 2a - laser followed by aflibercept versus laser followed by ranibizumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
LSR followed by AFL in treatment failures	[redacted]	13.709	[redacted]				
LSR followed by RAN in treatment failures	[redacted]	13.709	[redacted]	[redacted]	0.0001	[redacted]	Dominant

5.8.2.2 Laser followed by aflibercept versus laser followed by dexamethasone (Comparison 2b)

Table 98 shows the results of laser followed by aflibercept versus laser followed by dexamethasone. The results of the base case analyses showed that laser followed by aflibercept is associated with higher costs (incremental costs: [redacted]) in addition to a gain in LYs (incremental Lys: 0.0008) and QALYs (incremental QALYs: [redacted]). This results in an ICER of £11,792.

Table 98. Results: Comparison 2b - laser followed by aflibercept versus laser followed by dexamethasone

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
LSR followed by AFL in treatment failures	[redacted]	13.709	[redacted]				
LSR followed by DEX in treatment failures	[redacted]	13.708	[redacted]	[redacted]	0.0008	[redacted]	11,792

5.8.3 Clinical outcomes from the model

Table 99 - Table 102 show the proportion of the cohort in the health state over time for each state for each comparator in the first 5 years of the model.

Table 99. Markov trace: aflibercept first line followed by laser in aflibercept failures

Study eye	Fellow eye	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months				
1	1	0.3057	0.3012	0.2898	0.2784	0.2671	0.2559
1	2	0.1157	0.1181	0.1206	0.1225	0.1238	0.1247
1	3	0.0108	0.0123	0.0142	0.0160	0.0177	0.0193
1	4	0.0048	0.0050	0.0051	0.0052	0.0053	0.0054
1	5	0.0024	0.0025	0.0025	0.0026	0.0026	0.0026
2	1	0.3243	0.3077	0.2966	0.2861	0.2760	0.2662
2	2	0.1228	0.1206	0.1234	0.1259	0.1280	0.1297
2	3	0.0115	0.0125	0.0145	0.0164	0.0183	0.0201
2	4	0.0051	0.0051	0.0052	0.0053	0.0055	0.0056
2	5	0.0026	0.0026	0.0026	0.0027	0.0027	0.0028
3	1	0.0451	0.0455	0.0446	0.0442	0.0441	0.0443
3	2	0.0171	0.0178	0.0186	0.0194	0.0204	0.0216
3	3	0.0016	0.0019	0.0022	0.0025	0.0029	0.0033
3	4	0.0007	0.0008	0.0008	0.0008	0.0009	0.0009
3	5	0.0004	0.0004	0.0004	0.0004	0.0004	0.0005
4	1	0.0136	0.0190	0.0185	0.0181	0.0177	0.0174
4	2	0.0052	0.0074	0.0077	0.0079	0.0082	0.0085
4	3	0.0005	0.0008	0.0009	0.0010	0.0012	0.0013
4	4	0.0002	0.0003	0.0003	0.0003	0.0003	0.0004
4	5	0.0001	0.0002	0.0002	0.0002	0.0002	0.0002
5	1	0.0037	0.0056	0.0055	0.0054	0.0053	0.0053
5	2	0.0014	0.0022	0.0023	0.0024	0.0025	0.0026
5	3	0.0001	0.0002	0.0003	0.0003	0.0004	0.0004
5	4	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
5	5	0.0000	0.0000	0.0000	0.0001	0.0001	0.0001
DEATH		0.0047	0.0102	0.0231	0.0358	0.0483	0.0609

Table 100. Markov trace: Laser followed by aflibercept in laser failures

Study eye	Fellow eye	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months				
1	1	0.1017	0.1617	0.1552	0.1488	0.1425	0.1362
1	2	0.0385	0.0641	0.0657	0.0668	0.0677	0.0683
1	3	0.0042	0.0072	0.0085	0.0097	0.0108	0.0119
1	4	0.0017	0.0027	0.0027	0.0028	0.0028	0.0029
1	5	0.0008	0.0014	0.0015	0.0015	0.0015	0.0016
2	1	0.2990	0.3153	0.3028	0.2907	0.2789	0.2675
2	2	0.1132	0.1251	0.1281	0.1306	0.1326	0.1341
2	3	0.0123	0.0141	0.0166	0.0189	0.0212	0.0233
2	4	0.0049	0.0052	0.0053	0.0054	0.0056	0.0057
2	5	0.0025	0.0027	0.0028	0.0029	0.0030	0.0031
3	1	0.2023	0.1408	0.1358	0.1313	0.1272	0.1234
3	2	0.0766	0.0559	0.0574	0.0590	0.0605	0.0619
3	3	0.0083	0.0063	0.0074	0.0086	0.0097	0.0108
3	4	0.0033	0.0023	0.0024	0.0024	0.0025	0.0026
3	5	0.0017	0.0012	0.0013	0.0013	0.0014	0.0014
4	1	0.0477	0.0169	0.0166	0.0166	0.0167	0.0170
4	2	0.0181	0.0067	0.0070	0.0075	0.0079	0.0085
4	3	0.0020	0.0008	0.0009	0.0011	0.0013	0.0015
4	4	0.0008	0.0003	0.0003	0.0003	0.0003	0.0004
4	5	0.0004	0.0001	0.0002	0.0002	0.0002	0.0002
5	1	0.0383	0.0402	0.0386	0.0372	0.0358	0.0346
5	2	0.0145	0.0159	0.0163	0.0167	0.0170	0.0173
5	3	0.0016	0.0018	0.0021	0.0024	0.0027	0.0030
5	4	0.0006	0.0007	0.0007	0.0007	0.0007	0.0007
5	5	0.0003	0.0003	0.0004	0.0004	0.0004	0.0004
DEATH		0.0047	0.0104	0.0234	0.0362	0.0489	0.0616

Table 101. Markov trace: Laser followed by ranibizumab in laser failures

Study eye	Fellow eye	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months				
1	1	0.1017	0.1561	0.1499	0.1436	0.1375	0.1315
1	2	0.0385	0.0620	0.0634	0.0646	0.0654	0.0660
1	3	0.0042	0.0070	0.0082	0.0094	0.0105	0.0115
1	4	0.0017	0.0026	0.0026	0.0027	0.0027	0.0028
1	5	0.0008	0.0014	0.0014	0.0014	0.0015	0.0015
2	1	0.2990	0.3158	0.3033	0.2911	0.2792	0.2677
2	2	0.1132	0.1254	0.1284	0.1309	0.1329	0.1344
2	3	0.0123	0.0142	0.0167	0.0191	0.0213	0.0235
2	4	0.0049	0.0052	0.0053	0.0054	0.0056	0.0058
2	5	0.0025	0.0028	0.0028	0.0029	0.0030	0.0031
3	1	0.2023	0.1444	0.1393	0.1346	0.1304	0.1265
3	2	0.0766	0.0573	0.0590	0.0605	0.0620	0.0635
3	3	0.0083	0.0065	0.0077	0.0088	0.0100	0.0111
3	4	0.0033	0.0024	0.0024	0.0025	0.0026	0.0027
3	5	0.0017	0.0013	0.0013	0.0014	0.0014	0.0015
4	1	0.0477	0.0176	0.0174	0.0174	0.0175	0.0177
4	2	0.0181	0.0070	0.0074	0.0078	0.0083	0.0089
4	3	0.0020	0.0008	0.0010	0.0011	0.0013	0.0016
4	4	0.0008	0.0003	0.0003	0.0003	0.0003	0.0004
4	5	0.0004	0.0002	0.0002	0.0002	0.0002	0.0002
5	1	0.0383	0.0405	0.0390	0.0375	0.0362	0.0349
5	2	0.0145	0.0161	0.0165	0.0169	0.0172	0.0175
5	3	0.0016	0.0018	0.0021	0.0025	0.0028	0.0031
5	4	0.0006	0.0007	0.0007	0.0007	0.0007	0.0007
5	5	0.0003	0.0004	0.0004	0.0004	0.0004	0.0004
DEATH		0.0047	0.0104	0.0234	0.0362	0.0489	0.0616

Table 102. Markov trace: Laser followed by dexamethasone in laser failures

Study eye	Fellow eye	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months				
1	1	0.1017	0.1034	0.0991	0.0949	0.0907	0.0866
1	2	0.0385	0.0412	0.0422	0.0430	0.0436	0.0440
1	3	0.0042	0.0049	0.0058	0.0066	0.0074	0.0082
1	4	0.0017	0.0018	0.0018	0.0019	0.0019	0.0020
1	5	0.0008	0.0009	0.0009	0.0010	0.0010	0.0010
2	1	0.2990	0.3029	0.2904	0.2782	0.2663	0.2546
2	2	0.1132	0.1208	0.1237	0.1261	0.1280	0.1294
2	3	0.0123	0.0143	0.0169	0.0195	0.0219	0.0241
2	4	0.0049	0.0052	0.0053	0.0055	0.0056	0.0058
2	5	0.0025	0.0027	0.0028	0.0028	0.0029	0.0030
3	1	0.2023	0.1899	0.1827	0.1759	0.1696	0.1636
3	2	0.0766	0.0757	0.0778	0.0798	0.0815	0.0831
3	3	0.0083	0.0090	0.0107	0.0123	0.0139	0.0155
3	4	0.0033	0.0032	0.0033	0.0034	0.0036	0.0037
3	5	0.0017	0.0017	0.0017	0.0018	0.0019	0.0019
4	1	0.0477	0.0320	0.0312	0.0307	0.0304	0.0303
4	2	0.0181	0.0128	0.0133	0.0139	0.0146	0.0154
4	3	0.0020	0.0015	0.0018	0.0021	0.0025	0.0029
4	4	0.0008	0.0005	0.0006	0.0006	0.0006	0.0007
4	5	0.0004	0.0003	0.0003	0.0003	0.0003	0.0004
5	1	0.0383	0.0441	0.0424	0.0408	0.0393	0.0380
5	2	0.0145	0.0176	0.0181	0.0185	0.0189	0.0193
5	3	0.0016	0.0021	0.0025	0.0029	0.0032	0.0036
5	4	0.0006	0.0008	0.0008	0.0008	0.0008	0.0009
5	5	0.0003	0.0004	0.0004	0.0004	0.0004	0.0005
DEATH		0.0047	0.0104	0.0234	0.0363	0.0490	0.0616

The four tables below (Table 103 – Table 106) show the cumulative discounted QALYs for the four treatment arms under base case assumptions. A similar presentation format as above is provided where cumulative QALYs are shown for annual cycles from year 1 to 5.

Table 103. QALYs accrued over time: aflibercept first-line followed by laser in aflibercept failures

Study eye	Fellow eye	Undiscounted						Discounted					
		Year 1		Year 2	Year 3	Year 4	Year 5	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months					0-6 months	6-12 months				
1	1	0.1772	0.2957	0.2447	0.2352	0.2258	0.2166	0.1741	0.2907	0.2364	0.2273	0.2182	0.2092
1	2	0.0639	0.1101	0.0958	0.0975	0.0988	0.0996	0.0628	0.1083	0.0926	0.0942	0.0955	0.0963
1	3	0.0057	0.0107	0.0104	0.0118	0.0132	0.0145	0.0056	0.0105	0.0100	0.0114	0.0127	0.0140
1	4	0.0025	0.0043	0.0038	0.0038	0.0039	0.0040	0.0025	0.0043	0.0036	0.0037	0.0038	0.0039
1	5	0.0012	0.0021	0.0018	0.0018	0.0018	0.0019	0.0012	0.0020	0.0017	0.0018	0.0018	0.0018
2	1	0.3071	0.2914	0.2412	0.2326	0.2243	0.2165	0.3019	0.2864	0.2330	0.2247	0.2168	0.2091
2	2	0.0997	0.0985	0.0857	0.0875	0.0891	0.0904	0.0980	0.0968	0.0828	0.0846	0.0861	0.0873
2	3	0.0086	0.0094	0.0091	0.0104	0.0117	0.0129	0.0085	0.0093	0.0088	0.0101	0.0113	0.0125
2	4	0.0039	0.0038	0.0033	0.0034	0.0035	0.0036	0.0038	0.0038	0.0032	0.0033	0.0034	0.0035
2	5	0.0018	0.0018	0.0016	0.0016	0.0016	0.0017	0.0018	0.0018	0.0015	0.0015	0.0016	0.0016
3	1	0.1248	0.0411	0.0351	0.0346	0.0344	0.0344	0.1226	0.0404	0.0339	0.0334	0.0332	0.0333
3	2	0.0392	0.0136	0.0122	0.0128	0.0134	0.0141	0.0386	0.0134	0.0118	0.0123	0.0130	0.0136
3	3	0.0031	0.0012	0.0012	0.0014	0.0016	0.0019	0.0030	0.0012	0.0012	0.0014	0.0016	0.0018
3	4	0.0014	0.0005	0.0004	0.0005	0.0005	0.0005	0.0014	0.0005	0.0004	0.0004	0.0005	0.0005
3	5	0.0007	0.0002	0.0002	0.0002	0.0002	0.0002	0.0006	0.0002	0.0002	0.0002	0.0002	0.0002
4	1	0.0297	0.0148	0.0140	0.0137	0.0134	0.0131	0.0292	0.0145	0.0136	0.0132	0.0129	0.0127
4	2	0.0095	0.0050	0.0049	0.0051	0.0053	0.0054	0.0093	0.0049	0.0048	0.0049	0.0051	0.0053
4	3	0.0007	0.0004	0.0005	0.0006	0.0006	0.0007	0.0007	0.0004	0.0005	0.0005	0.0006	0.0007
4	4	0.0003	0.0002	0.0002	0.0002	0.0002	0.0002	0.0003	0.0002	0.0002	0.0002	0.0002	0.0002
4	5	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
5	1	0.0132	0.0041	0.0040	0.0039	0.0038	0.0038	0.0130	0.0041	0.0038	0.0037	0.0037	0.0036
5	2	0.0041	0.0014	0.0014	0.0014	0.0015	0.0015	0.0041	0.0014	0.0013	0.0014	0.0014	0.0015
5	3	0.0003	0.0001	0.0001	0.0002	0.0002	0.0002	0.0003	0.0001	0.0001	0.0002	0.0002	0.0002
5	4	0.0001	0.0000	0.0000	0.0000	0.0000	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0001
5	5	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 104. QALYs accrued over time: Laser followed by aflibercept in laser failures

Study eye	Fellow eye	Undiscounted						Discounted					
		Year 1		Year 2	Year 3	Year 4	Year 5	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months					0-6 months	6-12 months				
1	1	0.0538	0.1369	0.1312	0.1258	0.1206	0.1154	0.0528	0.1346	0.1267	0.1216	0.1165	0.1115
1	2	0.0194	0.0516	0.0520	0.0531	0.0539	0.0545	0.0190	0.0507	0.0503	0.0513	0.0521	0.0526
1	3	0.0020	0.0056	0.0063	0.0072	0.0081	0.0090	0.0019	0.0055	0.0061	0.0070	0.0079	0.0087
1	4	0.0008	0.0021	0.0020	0.0021	0.0021	0.0022	0.0008	0.0020	0.0020	0.0020	0.0020	0.0021
1	5	0.0004	0.0010	0.0010	0.0011	0.0011	0.0011	0.0004	0.0010	0.0010	0.0010	0.0010	0.0011
2	1	0.2679	0.2910	0.2465	0.2367	0.2272	0.2180	0.2633	0.2861	0.2382	0.2287	0.2195	0.2106
2	2	0.0867	0.0994	0.0888	0.0907	0.0922	0.0934	0.0853	0.0977	0.0858	0.0876	0.0891	0.0903
2	3	0.0083	0.0105	0.0105	0.0121	0.0137	0.0151	0.0081	0.0103	0.0102	0.0117	0.0132	0.0146
2	4	0.0035	0.0039	0.0034	0.0035	0.0036	0.0037	0.0034	0.0038	0.0033	0.0034	0.0035	0.0036
2	5	0.0017	0.0019	0.0017	0.0018	0.0018	0.0019	0.0016	0.0019	0.0017	0.0017	0.0018	0.0018
3	1	0.2340	0.1470	0.1075	0.1039	0.1006	0.0975	0.2300	0.1445	0.1039	0.1004	0.0972	0.0942
3	2	0.0741	0.0492	0.0380	0.0391	0.0401	0.0410	0.0728	0.0484	0.0367	0.0377	0.0387	0.0397
3	3	0.0064	0.0048	0.0041	0.0048	0.0055	0.0061	0.0063	0.0047	0.0040	0.0046	0.0053	0.0059
3	4	0.0027	0.0017	0.0013	0.0014	0.0014	0.0015	0.0026	0.0017	0.0013	0.0013	0.0014	0.0014
3	5	0.0013	0.0008	0.0007	0.0007	0.0007	0.0007	0.0012	0.0008	0.0006	0.0007	0.0007	0.0007
4	1	0.0471	0.0225	0.0125	0.0124	0.0125	0.0126	0.0463	0.0221	0.0121	0.0120	0.0121	0.0122
4	2	0.0151	0.0076	0.0045	0.0047	0.0050	0.0054	0.0148	0.0075	0.0043	0.0046	0.0049	0.0052
4	3	0.0013	0.0007	0.0005	0.0006	0.0007	0.0008	0.0013	0.0007	0.0005	0.0006	0.0007	0.0008
4	4	0.0005	0.0002	0.0001	0.0001	0.0002	0.0002	0.0005	0.0002	0.0001	0.0001	0.0002	0.0002
4	5	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001
5	1	0.0364	0.0331	0.0279	0.0268	0.0259	0.0249	0.0358	0.0325	0.0269	0.0259	0.0250	0.0241
5	2	0.0116	0.0111	0.0099	0.0101	0.0103	0.0105	0.0114	0.0109	0.0095	0.0098	0.0100	0.0101
5	3	0.0010	0.0010	0.0010	0.0012	0.0014	0.0015	0.0010	0.0010	0.0010	0.0012	0.0013	0.0015
5	4	0.0004	0.0003	0.0003	0.0003	0.0003	0.0003	0.0004	0.0003	0.0003	0.0003	0.0003	0.0003
5	5	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Table 105. QALYs accrued over time: Laser followed by ranibizumab in laser failures

Study eye	Fellow eye	Undiscounted						Discounted					
		Year 1		Year 2	Year 3	Year 4	Year 5	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months					0-6 months	6-12 months				
1	1	0.0538	0.1336	0.1272	0.1222	0.1172	0.1123	0.0528	0.1313	0.1229	0.1180	0.1132	0.1085
1	2	0.0194	0.0497	0.0496	0.0505	0.0511	0.0515	0.0190	0.0489	0.0479	0.0488	0.0493	0.0497
1	3	0.0020	0.0055	0.0062	0.0071	0.0080	0.0089	0.0019	0.0054	0.0060	0.0069	0.0078	0.0086
1	4	0.0008	0.0020	0.0020	0.0020	0.0021	0.0022	0.0008	0.0020	0.0019	0.0020	0.0020	0.0021
1	5	0.0004	0.0010	0.0010	0.0010	0.0011	0.0011	0.0004	0.0010	0.0010	0.0010	0.0010	0.0011
2	1	0.2679	0.2918	0.2480	0.2384	0.2291	0.2201	0.2633	0.2868	0.2396	0.2304	0.2214	0.2126
2	2	0.0867	0.0985	0.0878	0.0894	0.0906	0.0916	0.0853	0.0969	0.0849	0.0864	0.0876	0.0885
2	3	0.0083	0.0106	0.0107	0.0124	0.0140	0.0155	0.0081	0.0105	0.0104	0.0120	0.0135	0.0150
2	4	0.0035	0.0040	0.0035	0.0036	0.0037	0.0038	0.0034	0.0039	0.0034	0.0035	0.0036	0.0037
2	5	0.0017	0.0019	0.0017	0.0018	0.0019	0.0019	0.0016	0.0019	0.0017	0.0017	0.0018	0.0018
3	1	0.2340	0.1499	0.1108	0.1071	0.1038	0.1008	0.2300	0.1473	0.1071	0.1035	0.1003	0.0974
3	2	0.0741	0.0496	0.0385	0.0394	0.0403	0.0412	0.0728	0.0488	0.0372	0.0381	0.0390	0.0398
3	3	0.0064	0.0049	0.0043	0.0050	0.0057	0.0064	0.0063	0.0048	0.0042	0.0049	0.0055	0.0062
3	4	0.0027	0.0018	0.0014	0.0014	0.0015	0.0015	0.0026	0.0018	0.0013	0.0014	0.0014	0.0015
3	5	0.0013	0.0009	0.0007	0.0007	0.0007	0.0008	0.0012	0.0008	0.0007	0.0007	0.0007	0.0007
4	1	0.0471	0.0232	0.0132	0.0131	0.0131	0.0133	0.0463	0.0228	0.0127	0.0126	0.0127	0.0128
4	2	0.0151	0.0077	0.0046	0.0049	0.0051	0.0055	0.0148	0.0076	0.0045	0.0047	0.0050	0.0053
4	3	0.0013	0.0008	0.0005	0.0006	0.0007	0.0008	0.0013	0.0007	0.0005	0.0006	0.0007	0.0008
4	4	0.0005	0.0003	0.0002	0.0002	0.0002	0.0002	0.0005	0.0003	0.0001	0.0002	0.0002	0.0002
4	5	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001
5	1	0.0364	0.0334	0.0283	0.0272	0.0263	0.0254	0.0358	0.0328	0.0273	0.0263	0.0254	0.0245
5	2	0.0116	0.0111	0.0098	0.0100	0.0102	0.0104	0.0114	0.0109	0.0095	0.0097	0.0099	0.0100
5	3	0.0010	0.0011	0.0011	0.0012	0.0014	0.0016	0.0010	0.0011	0.0010	0.0012	0.0014	0.0015
5	4	0.0004	0.0004	0.0003	0.0003	0.0003	0.0003	0.0004	0.0003	0.0003	0.0003	0.0003	0.0003
5	5	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Table 106. QALYs accrued over time: Laser followed by dexamethasone in laser failures

Study eye	Fellow eye	Undiscounted						Discounted					
		Year 1		Year 2	Year 3	Year 4	Year 5	Year 1		Year 2	Year 3	Year 4	Year 5
		0-6 months	6-12 months					0-6 months	6-12 months				
1	1	0.0538	0.0991	0.0845	0.0812	0.0778	0.0746	0.0528	0.0974	0.0816	0.0784	0.0752	0.0721
1	2	0.0194	0.0369	0.0330	0.0335	0.0339	0.0342	0.0190	0.0362	0.0319	0.0324	0.0328	0.0330
1	3	0.0020	0.0041	0.0041	0.0047	0.0053	0.0059	0.0019	0.0040	0.0040	0.0046	0.0052	0.0057
1	4	0.0008	0.0015	0.0013	0.0014	0.0014	0.0014	0.0008	0.0015	0.0013	0.0013	0.0014	0.0014
1	5	0.0004	0.0007	0.0007	0.0007	0.0007	0.0007	0.0004	0.0007	0.0006	0.0007	0.0007	0.0007
2	1	0.2679	0.2838	0.2386	0.2293	0.2202	0.2113	0.2633	0.2789	0.2305	0.2215	0.2127	0.2041
2	2	0.0867	0.0958	0.0845	0.0860	0.0871	0.0879	0.0853	0.0942	0.0817	0.0831	0.0842	0.0849
2	3	0.0083	0.0104	0.0103	0.0119	0.0135	0.0149	0.0081	0.0102	0.0100	0.0115	0.0130	0.0144
2	4	0.0035	0.0039	0.0034	0.0035	0.0036	0.0037	0.0034	0.0038	0.0033	0.0033	0.0034	0.0035
2	5	0.0017	0.0019	0.0017	0.0017	0.0018	0.0018	0.0016	0.0018	0.0016	0.0017	0.0017	0.0018
3	1	0.2340	0.1779	0.1461	0.1410	0.1363	0.1318	0.2300	0.1749	0.1411	0.1362	0.1317	0.1274
3	2	0.0741	0.0590	0.0508	0.0519	0.0529	0.0538	0.0728	0.0580	0.0491	0.0501	0.0511	0.0520
3	3	0.0064	0.0059	0.0057	0.0066	0.0075	0.0084	0.0063	0.0058	0.0055	0.0064	0.0073	0.0081
3	4	0.0027	0.0021	0.0018	0.0019	0.0019	0.0020	0.0026	0.0021	0.0018	0.0018	0.0019	0.0020
3	5	0.0013	0.0010	0.0009	0.0009	0.0010	0.0010	0.0012	0.0010	0.0009	0.0009	0.0009	0.0010
4	1	0.0471	0.0329	0.0239	0.0234	0.0232	0.0231	0.0463	0.0323	0.0231	0.0227	0.0224	0.0223
4	2	0.0151	0.0110	0.0084	0.0087	0.0091	0.0095	0.0148	0.0108	0.0081	0.0084	0.0088	0.0092
4	3	0.0013	0.0011	0.0009	0.0011	0.0013	0.0015	0.0013	0.0011	0.0009	0.0011	0.0012	0.0014
4	4	0.0005	0.0004	0.0003	0.0003	0.0003	0.0003	0.0005	0.0004	0.0003	0.0003	0.0003	0.0003
4	5	0.0002	0.0002	0.0001	0.0001	0.0001	0.0002	0.0002	0.0002	0.0001	0.0001	0.0001	0.0002
5	1	0.0364	0.0353	0.0309	0.0298	0.0288	0.0278	0.0358	0.0347	0.0298	0.0288	0.0278	0.0269
5	2	0.0116	0.0117	0.0107	0.0110	0.0112	0.0114	0.0114	0.0115	0.0104	0.0106	0.0108	0.0110
5	3	0.0010	0.0011	0.0012	0.0014	0.0015	0.0017	0.0010	0.0011	0.0011	0.0013	0.0015	0.0017
5	4	0.0004	0.0004	0.0003	0.0003	0.0004	0.0004	0.0004	0.0004	0.0003	0.0003	0.0003	0.0004
5	5	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

5.8.4 Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregated undiscounted incremental clinical outcomes are reported by health states for each comparison in the tables below (Table 107 to Table 111). The summary of costs by health state is not presented as the model structure does not report disaggregated costs by health state.

Table 107. Summary of QALY gain by health state: aflibercept first-line vs laser followed by ranibizumab (Comparison 1a)

Study eye	Fellow eye	QALY intervention (aflibercept first-line)	QALY comparator (laser followed by RAN)	Increment	Absolute increment	% absolute increment
1	1	[redacted]	[redacted]	[redacted]	[redacted]	28.88%
1	2	[redacted]	[redacted]	[redacted]	[redacted]	16.08%
1	3	[redacted]	[redacted]	[redacted]	[redacted]	3.34%
1	4	[redacted]	[redacted]	[redacted]	[redacted]	0.91%
1	5	[redacted]	[redacted]	[redacted]	[redacted]	0.36%
2	1	[redacted]	[redacted]	[redacted]	[redacted]	2.44%
2	2	[redacted]	[redacted]	[redacted]	[redacted]	1.75%
2	3	[redacted]	[redacted]	[redacted]	[redacted]	0.07%
2	4	[redacted]	[redacted]	[redacted]	[redacted]	0.04%
2	5	[redacted]	[redacted]	[redacted]	[redacted]	0.02%
3	1	[redacted]	[redacted]	[redacted]	[redacted]	18.40%
3	2	[redacted]	[redacted]	[redacted]	[redacted]	8.92%
3	3	[redacted]	[redacted]	[redacted]	[redacted]	2.13%
3	4	[redacted]	[redacted]	[redacted]	[redacted]	0.53%
3	5	[redacted]	[redacted]	[redacted]	[redacted]	0.24%
4	1	[redacted]	[redacted]	[redacted]	[redacted]	2.16%
4	2	[redacted]	[redacted]	[redacted]	[redacted]	1.34%
4	3	[redacted]	[redacted]	[redacted]	[redacted]	0.44%
4	4	[redacted]	[redacted]	[redacted]	[redacted]	0.10%
4	5	[redacted]	[redacted]	[redacted]	[redacted]	0.04%
5	1	[redacted]	[redacted]	[redacted]	[redacted]	6.99%
5	2	[redacted]	[redacted]	[redacted]	[redacted]	3.65%
5	3	[redacted]	[redacted]	[redacted]	[redacted]	0.89%
5	4	[redacted]	[redacted]	[redacted]	[redacted]	0.20%
5	5	[redacted]	[redacted]	[redacted]	[redacted]	0.06%
Total		[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 108. Summary of QALY gain by health state: laser followed by aflibercept versus laser followed by ranibizumab

Study eye	Fellow eye	QALY intervention (laser followed by AFL)	QALY comparator (laser followed by RAN)	Increment	Absolute increment	% absolute increment
1	1	[redacted]	[redacted]	[redacted]	[redacted]	17.50%
1	2	[redacted]	[redacted]	[redacted]	[redacted]	18.91%
1	3	[redacted]	[redacted]	[redacted]	[redacted]	2.64%
1	4	[redacted]	[redacted]	[redacted]	[redacted]	0.34%
1	5	[redacted]	[redacted]	[redacted]	[redacted]	0.17%
2	1	[redacted]	[redacted]	[redacted]	[redacted]	9.74%
2	2	[redacted]	[redacted]	[redacted]	[redacted]	11.87%
2	3	[redacted]	[redacted]	[redacted]	[redacted]	0.71%
2	4	[redacted]	[redacted]	[redacted]	[redacted]	0.81%
2	5	[redacted]	[redacted]	[redacted]	[redacted]	0.32%
3	1	[redacted]	[redacted]	[redacted]	[redacted]	19.73%
3	2	[redacted]	[redacted]	[redacted]	[redacted]	1.11%
3	3	[redacted]	[redacted]	[redacted]	[redacted]	2.00%
3	4	[redacted]	[redacted]	[redacted]	[redacted]	0.84%
3	5	[redacted]	[redacted]	[redacted]	[redacted]	0.35%
4	1	[redacted]	[redacted]	[redacted]	[redacted]	6.02%
4	2	[redacted]	[redacted]	[redacted]	[redacted]	1.33%
4	3	[redacted]	[redacted]	[redacted]	[redacted]	0.70%
4	4	[redacted]	[redacted]	[redacted]	[redacted]	0.25%
4	5	[redacted]	[redacted]	[redacted]	[redacted]	0.11%
5	1	[redacted]	[redacted]	[redacted]	[redacted]	3.67%
5	2	[redacted]	[redacted]	[redacted]	[redacted]	0.26%
5	3	[redacted]	[redacted]	[redacted]	[redacted]	0.42%
5	4	[redacted]	[redacted]	[redacted]	[redacted]	0.17%
5	5	[redacted]	[redacted]	[redacted]	[redacted]	0.05%
Total		[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 109. Summary of QALY gain by health state: aflibercept first-line versus laser followed by aflibercept

Study eye	Fellow eye	QALY intervention (aflibercept first-line)	QALY comparator (laser followed by AFL)	Increment	Absolute increment	% absolute increment
1	1	[redacted]	[redacted]	[redacted]	[redacted]	29.13%
1	2	[redacted]	[redacted]	[redacted]	[redacted]	15.78%
1	3	[redacted]	[redacted]	[redacted]	[redacted]	3.34%
1	4	[redacted]	[redacted]	[redacted]	[redacted]	0.93%
1	5	[redacted]	[redacted]	[redacted]	[redacted]	0.36%
2	1	[redacted]	[redacted]	[redacted]	[redacted]	3.00%
2	2	[redacted]	[redacted]	[redacted]	[redacted]	1.25%
2	3	[redacted]	[redacted]	[redacted]	[redacted]	0.04%
2	4	[redacted]	[redacted]	[redacted]	[redacted]	0.08%
2	5	[redacted]	[redacted]	[redacted]	[redacted]	0.01%
3	1	[redacted]	[redacted]	[redacted]	[redacted]	18.14%
3	2	[redacted]	[redacted]	[redacted]	[redacted]	9.20%
3	3	[redacted]	[redacted]	[redacted]	[redacted]	2.11%
3	4	[redacted]	[redacted]	[redacted]	[redacted]	0.51%
3	5	[redacted]	[redacted]	[redacted]	[redacted]	0.23%
4	1	[redacted]	[redacted]	[redacted]	[redacted]	1.96%
4	2	[redacted]	[redacted]	[redacted]	[redacted]	1.32%
4	3	[redacted]	[redacted]	[redacted]	[redacted]	0.42%
4	4	[redacted]	[redacted]	[redacted]	[redacted]	0.10%
4	5	[redacted]	[redacted]	[redacted]	[redacted]	0.04%
5	1	[redacted]	[redacted]	[redacted]	[redacted]	7.07%
5	2	[redacted]	[redacted]	[redacted]	[redacted]	3.80%
5	3	[redacted]	[redacted]	[redacted]	[redacted]	0.90%
5	4	[redacted]	[redacted]	[redacted]	[redacted]	0.20%
5	5	[redacted]	[redacted]	[redacted]	[redacted]	0.06%
Total		[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 110. Summary of QALY gain by health state: aflibercept first-line versus laser followed by dexamethasone

Study eye	Fellow eye	QALY intervention (aflibercept first-line)	QALY comparator (laser followed by DEX)	Increment	Absolute increment	% absolute increment
1	1	[redacted]	[redacted]	[redacted]	[redacted]	26.91%
1	2	[redacted]	[redacted]	[redacted]	[redacted]	15.04%
1	3	[redacted]	[redacted]	[redacted]	[redacted]	3.31%
1	4	[redacted]	[redacted]	[redacted]	[redacted]	0.88%
1	5	[redacted]	[redacted]	[redacted]	[redacted]	0.36%
2	1	[redacted]	[redacted]	[redacted]	[redacted]	4.06%
2	2	[redacted]	[redacted]	[redacted]	[redacted]	2.55%
2	3	[redacted]	[redacted]	[redacted]	[redacted]	0.33%
2	4	[redacted]	[redacted]	[redacted]	[redacted]	0.13%
2	5	[redacted]	[redacted]	[redacted]	[redacted]	0.02%
3	1	[redacted]	[redacted]	[redacted]	[redacted]	18.14%
3	2	[redacted]	[redacted]	[redacted]	[redacted]	8.84%
3	3	[redacted]	[redacted]	[redacted]	[redacted]	2.07%
3	4	[redacted]	[redacted]	[redacted]	[redacted]	0.52%
3	5	[redacted]	[redacted]	[redacted]	[redacted]	0.23%
4	1	[redacted]	[redacted]	[redacted]	[redacted]	3.89%
4	2	[redacted]	[redacted]	[redacted]	[redacted]	2.23%
4	3	[redacted]	[redacted]	[redacted]	[redacted]	0.63%
4	4	[redacted]	[redacted]	[redacted]	[redacted]	0.15%
4	5	[redacted]	[redacted]	[redacted]	[redacted]	0.06%
5	1	[redacted]	[redacted]	[redacted]	[redacted]	5.67%
5	2	[redacted]	[redacted]	[redacted]	[redacted]	3.01%
5	3	[redacted]	[redacted]	[redacted]	[redacted]	0.75%
5	4	[redacted]	[redacted]	[redacted]	[redacted]	0.17%
5	5	[redacted]	[redacted]	[redacted]	[redacted]	0.05%
Total		[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 111. Summary of QALY gain by health state: laser followed by aflibercept versus laser followed by dexamethasone

Study eye	Fellow eye	QALY intervention (laser followed by AFL)	QALY comparator (laser followed by DEX)	Increment	Absolute increment	% absolute increment
1	1	[redacted]	[redacted]	[redacted]	[redacted]	22.39%
1	2	[redacted]	[redacted]	[redacted]	[redacted]	13.52%
1	3	[redacted]	[redacted]	[redacted]	[redacted]	3.24%
1	4	[redacted]	[redacted]	[redacted]	[redacted]	0.79%
1	5	[redacted]	[redacted]	[redacted]	[redacted]	0.34%
2	1	[redacted]	[redacted]	[redacted]	[redacted]	6.20%
2	2	[redacted]	[redacted]	[redacted]	[redacted]	5.17%
2	3	[redacted]	[redacted]	[redacted]	[redacted]	1.07%
2	4	[redacted]	[redacted]	[redacted]	[redacted]	0.22%
2	5	[redacted]	[redacted]	[redacted]	[redacted]	0.09%
3	1	[redacted]	[redacted]	[redacted]	[redacted]	18.08%
3	2	[redacted]	[redacted]	[redacted]	[redacted]	8.10%
3	3	[redacted]	[redacted]	[redacted]	[redacted]	1.98%
3	4	[redacted]	[redacted]	[redacted]	[redacted]	0.52%
3	5	[redacted]	[redacted]	[redacted]	[redacted]	0.22%
4	1	[redacted]	[redacted]	[redacted]	[redacted]	7.80%
4	2	[redacted]	[redacted]	[redacted]	[redacted]	4.05%
4	3	[redacted]	[redacted]	[redacted]	[redacted]	1.04%
4	4	[redacted]	[redacted]	[redacted]	[redacted]	0.25%
4	5	[redacted]	[redacted]	[redacted]	[redacted]	0.10%
5	1	[redacted]	[redacted]	[redacted]	[redacted]	2.83%
5	2	[redacted]	[redacted]	[redacted]	[redacted]	1.42%
5	3	[redacted]	[redacted]	[redacted]	[redacted]	0.43%
5	4	[redacted]	[redacted]	[redacted]	[redacted]	0.11%
5	5	[redacted]	[redacted]	[redacted]	[redacted]	0.03%
Total		[redacted]	[redacted]	[redacted]	[redacted]	100%

A summary of predicted resource use by category of cost for each comparison is reported in the tables below (Table 112 to Table 116).

Table 112. Summary of predicted resource use by category of cost: aflibercept first-line versus laser followed by ranibizumab

Health state	Costs intervention (aflibercept first-line)	Costs comparator (laser followed by RAN)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	88%
Administration and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	10%
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	1%
Blindness costs	[redacted]	[redacted]	[redacted]	[redacted]	1%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 113. Summary of predicted resource use by category of cost: laser followed by aflibercept versus laser followed by ranibizumab

Health state	Costs intervention (laser followed by AFL)	Costs comparator (laser followed by RAN)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	100%
Administration and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Blindness costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 114. Summary of predicted resource use by category of cost: aflibercept first-line versus laser followed by aflibercept

Health state	Costs intervention (aflibercept first-line)	Costs comparator (laser followed by AFL)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	92%
Administration and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	7%
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Blindness costs	[redacted]	[redacted]	[redacted]	[redacted]	1%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 115. Summary of predicted resource use by category of cost: aflibercept first-line versus laser followed by dexamethasone

Health state	Costs intervention (aflibercept first-line)	Costs comparator (laser followed by DEX)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	90%
Administration and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	9%
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Blindness costs	[redacted]	[redacted]	[redacted]	[redacted]	1%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 116. Summary of predicted resource use by category of cost: laser followed by aflibercept versus laser followed by dexamethasone

Health state	Costs intervention (laser followed by AFL)	Costs comparator (laser followed by DEX)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	[redacted]	[redacted]	120%
Administration and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	19%
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	0%
Blindness costs	[redacted]	[redacted]	[redacted]	[redacted]	1%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

5.9 Sensitivity analyses

5.9.1 Deterministic sensitivity analysis

Deterministic sensitivity analyses were run for the following comparisons:

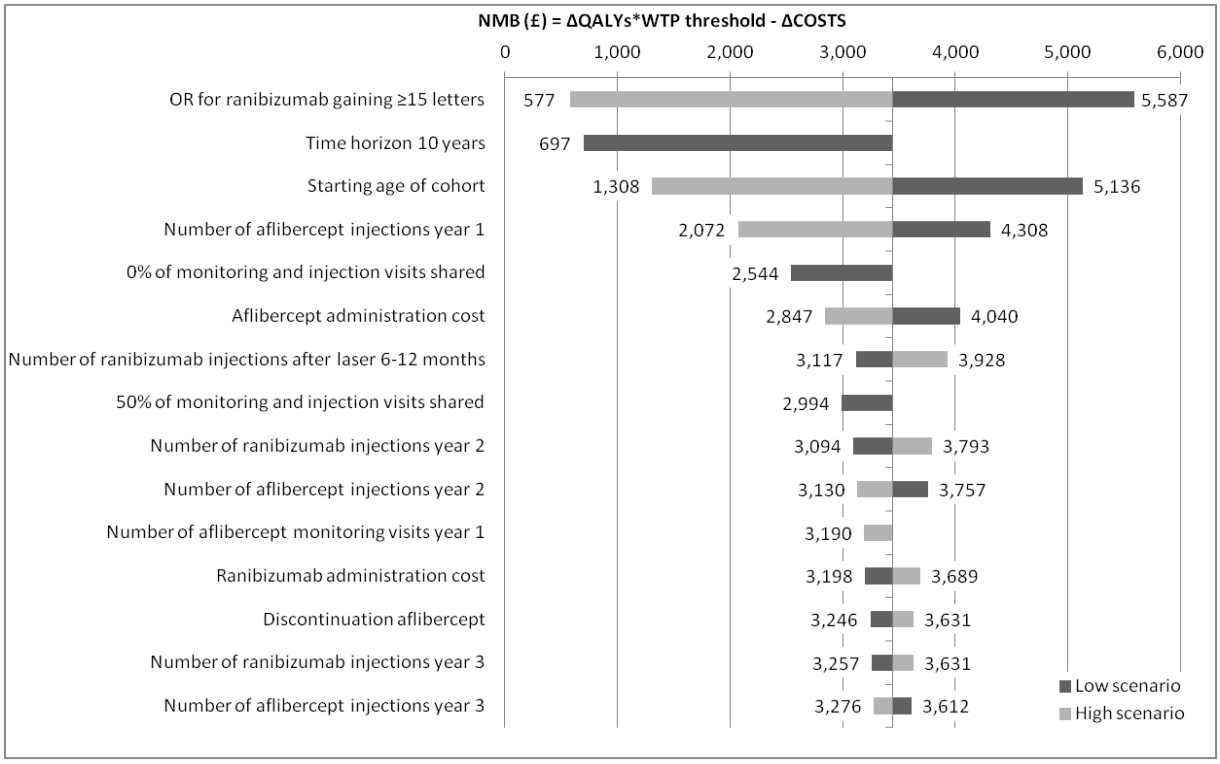
- Comparison 1a - Aflibercept first- line versus laser followed by ranibizumab
- Comparison 1b - Aflibercept first- line versus laser followed by dexamethasone
- Comparison 1c - Aflibercept first- line versus laser followed by aflibercept
- Comparison 2a - Laser followed by aflibercept versus laser followed by ranibizumab
- Comparison 2b - Laser followed by aflibercept versus laser followed by dexamethasone

Overall there were 94 sensitivity and scenario analyses conducted for the base-case. A tornado plot for the top 15 most sensitive parameters based on the net monetary benefit (NMB) measured at a willingness to pay of £20,000 per QALY was used to illustrate the results of the analysis. Note the tornado diagram reports both the OWSA and the scenario analysis; this is why for several parameters only one bar showing either the results of the “low” or “high” variation of a scenario can be seen.

5.9.1.1 Aflibercept first-line versus laser followed by ranibizumab (Comparison 1a)

Figure 51 displays the tornado plot for aflibercept first-line versus laser follow by ranibizumab. Aflibercept first-line remained cost-effective in all the sensitivity and scenario analyses. The key drivers of this comparison were the shorter time horizon (10 years), the relative efficacy associated with ranibizumab and starting age of the cohort. The shorter time horizon resulted in aflibercept being less cost-effective than in the base case as the incremental QALY benefit was reduced. The starting age of the cohort is a driver as a younger cohort accrued QALYs for a longer period of time relative to an older cohort.

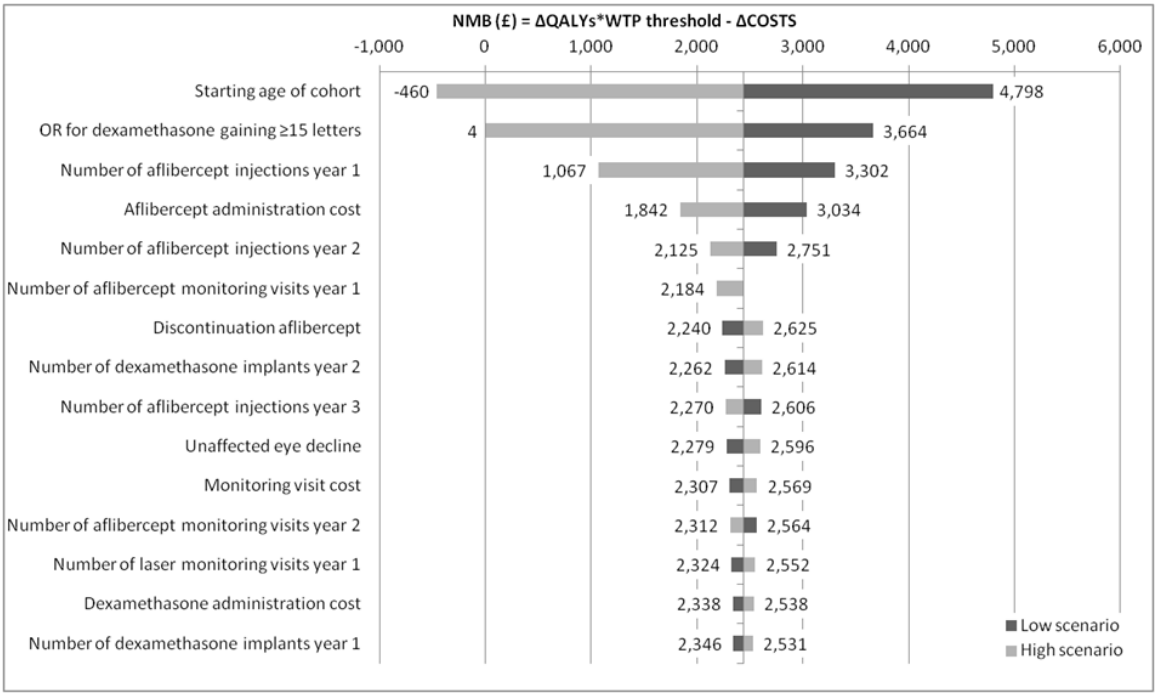
Figure 51: Tornado plot: Comparison 1a - aflibercept first-line versus laser followed by ranibizumab



5.9.1.2 Aflibercept first-line versus laser followed by dexamethasone (comparison 1b)

Figure 52 displays the tornado plot for aflibercept first-line versus laser followed by dexamethasone. Aflibercept first-line is the cost-effective option except where an older population is considered. The key drivers of this analysis are the starting age of the cohort, relative efficacy associated with dexamethasone and the number of aflibercept injections in the first year.

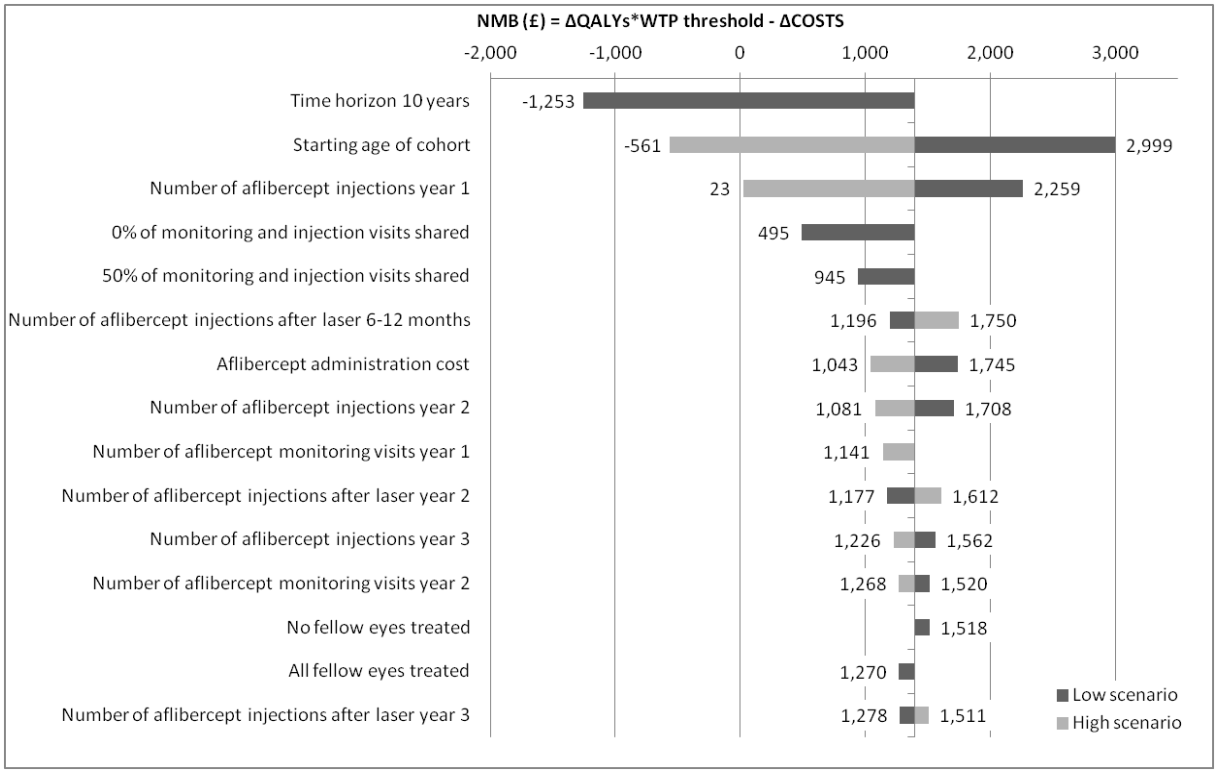
Figure 52. Tornado plot: comparison 1b - aflibercept first-line versus laser followed by dexamethasone.



5.9.1.3 Aflibercept first-line versus laser followed by aflibercept (comparison 1c)

Figure 53 displays the tornado plot for aflibercept first-line versus laser followed by aflibercept. Aflibercept first-line remains cost-effective (£20K per QALY threshold) with the exception of when a shorter time horizon and older population is assumed in the model. In addition to the above variables, another key driver is represented by the number of aflibercept injections in the first year associated with aflibercept used at the first-line position i.e. a greater number of injections increases the costs of aflibercept and reduces the cost-effectiveness.

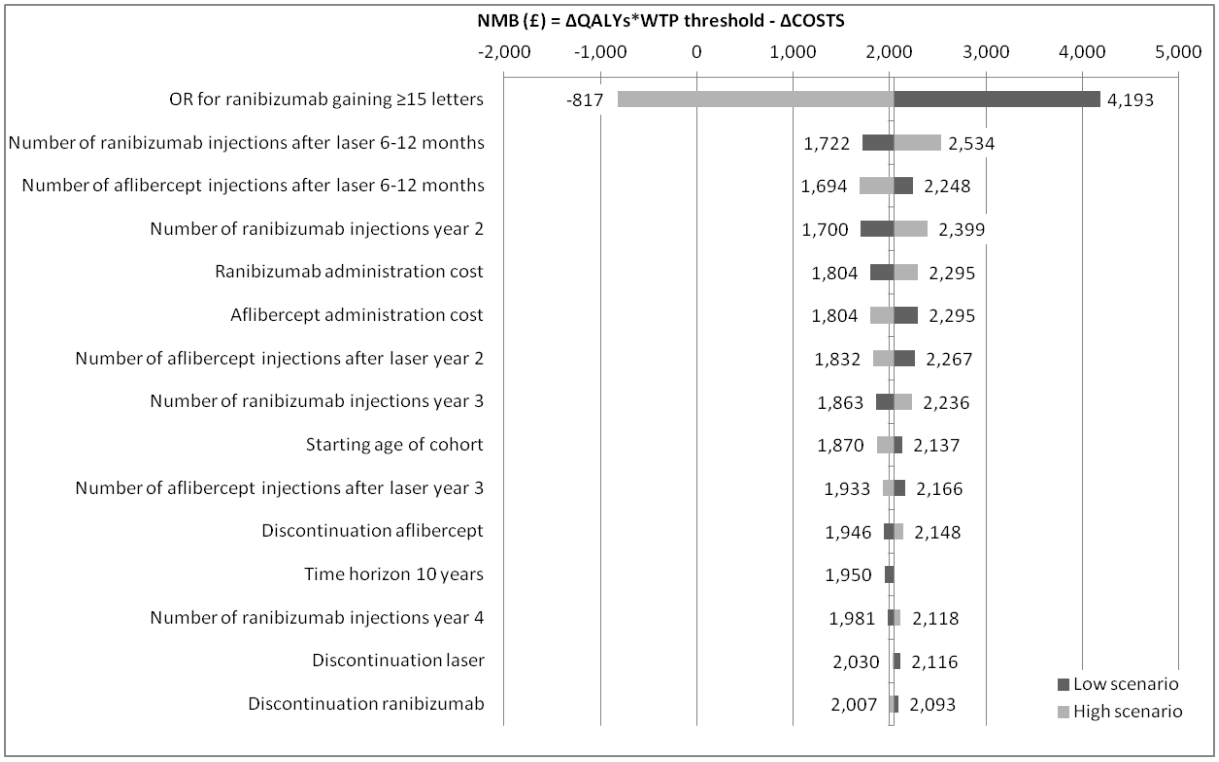
Figure 53. Tornado plot: comparison 1c - aflibercept first-line versus laser followed by aflibercept



5.9.1.4 Laser followed by aflibercept line versus laser followed by ranibizumab (comparison 2a)

Figure 54 displays the tornado plot for laser followed by aflibercept line versus laser followed by ranibizumab. Laser followed by aflibercept is cost-effective with the exception of when a high scenario for the relative efficacy of ranibizumab (i.e. ranibizumab has a greater odds of achieving a 15 or greater letter gain versus aflibercept) is considered. The key drivers of this comparison were the relative efficacy associated with ranibizumab, and the number of injections (which increases/decreases costs) for both aflibercept and ranibizumab and administration costs.

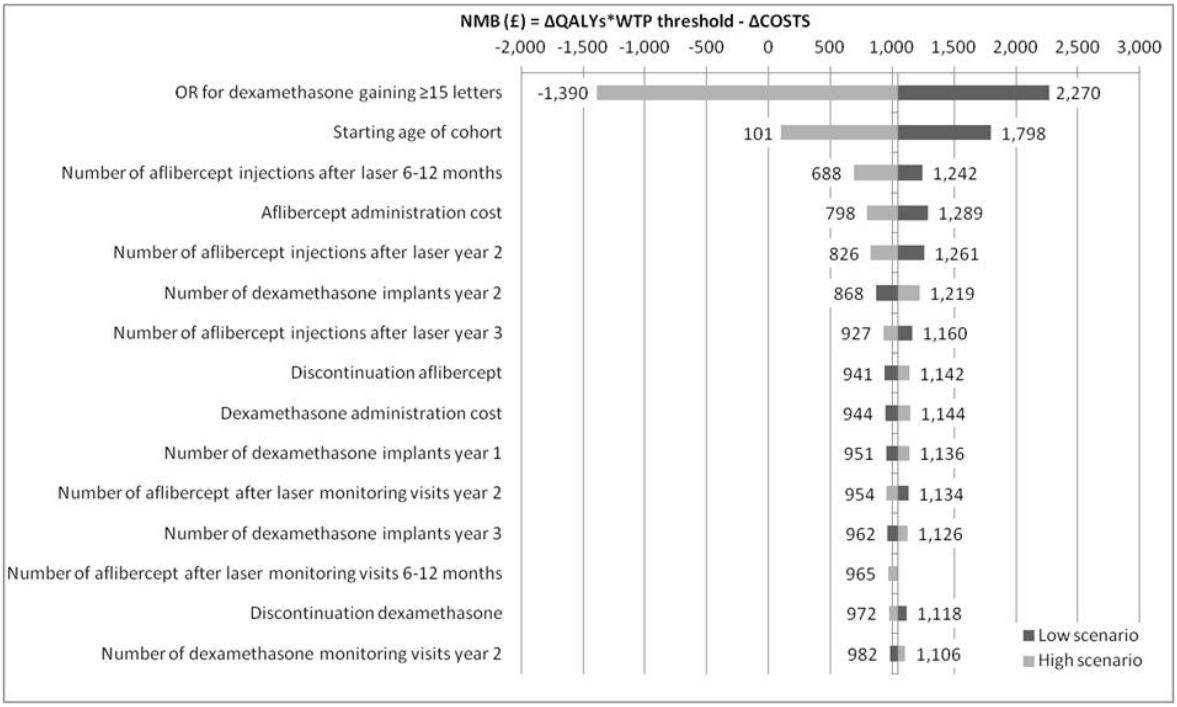
Figure 54. Tornado plot: Comparison 2a – laser followed by aflibercept versus laser followed by ranibizumab



5.9.1.5 Laser followed by aflibercept versus laser followed by dexamethasone (comparison 2b)

Figure 55 displays the tornado plot for laser followed by aflibercept versus laser followed by dexamethasone. Similar to the above comparison, laser followed by aflibercept is not the cost effective alternative only when a high scenario for the relative efficacy of dexamethasone is considered. The key drivers of this analysis are the relative efficacy associated with dexamethasone and the starting age of the cohort.

Figure 55: Tornado plot: comparison 2b - laser followed by aflibercept versus laser followed by dexamethasone.



5.9.2 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis was run with 1,000 simulations.

PSA outputs are represented graphically by:

1. Plotting incremental cost and QALY pairs on the cost effectiveness plane (CE scatter plot)

2. Presenting the likelihood of aflibercept being cost-effective at a range of willingness-to-pay (WTP) thresholds.

Probabilistic sensitivity analyses were run for each of the five comparisons.

A summary of the probability of being cost-effective for each comparison is shown in Table 117. Aflibercept was associated with a high probability of being cost-effective as a first-line treatment and also a second-line treatment. When laser followed by aflibercept is compared to laser followed by ranibizumab, the former is associated to a probability of 100% to be cost effective at a WTP equal to 0. This is justified by the fact that aflibercept is the dominant alternative in this comparison.

Table 117. Summary of the probability of being cost-effective for each comparison

	Probability of being cost-effective		
	WTP = £0	**WTP = £20,000**	**WTP = £30,000**
Aflibercept as a first-line treatment option			
Aflibercept first-line versus laser followed by ranibizumab (comparison 1a)	0%	99.2%	100%
Aflibercept first-line versus laser followed by dexamethasone (comparison 1b)	0%	99.4%	100%
Aflibercept first-line versus laser followed by aflibercept (comparison 1c)	0%	98.9%	100%
Aflibercept as a second-line treatment option			
Laser followed by aflibercept versus laser followed by ranibizumab (comparison 2a)	100%	90.6%	84.7%
Laser followed by aflibercept versus laser followed by dexamethasone (comparison 2b)	0%	99.1%	100%

A graphical representation, CE scatter plot and Cost-Effectiveness acceptability curve, for each of the comparison is reported in sections below (5.9.2.1-5.9.2.5).

5.9.2.1 Aflibercept first-line versus laser followed by ranibizumab (comparison 1a)

Figure 56 shows the cost-effectiveness plane for aflibercept first-line versus laser followed by ranibizumab.

Figure 56. Scatterplot: comparison 1a - aflibercept first-line versus laser followed by ranibizumab

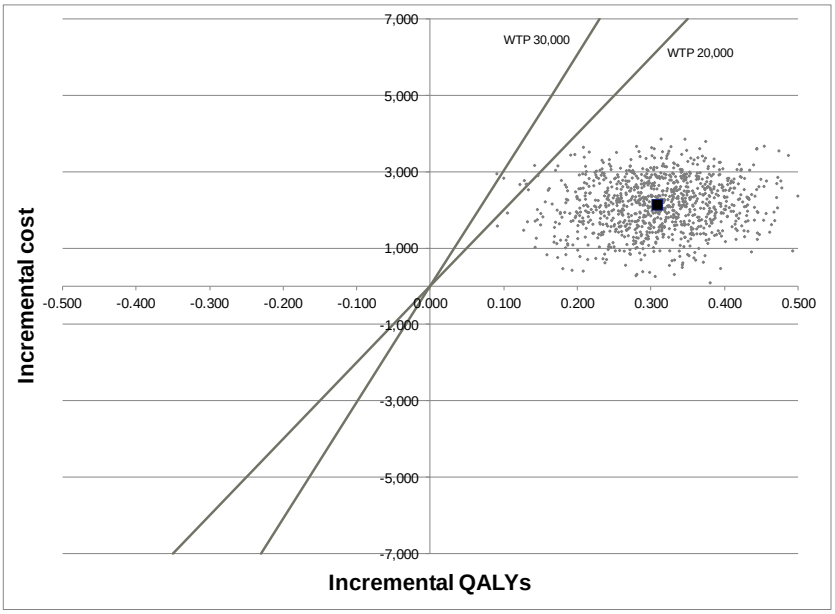
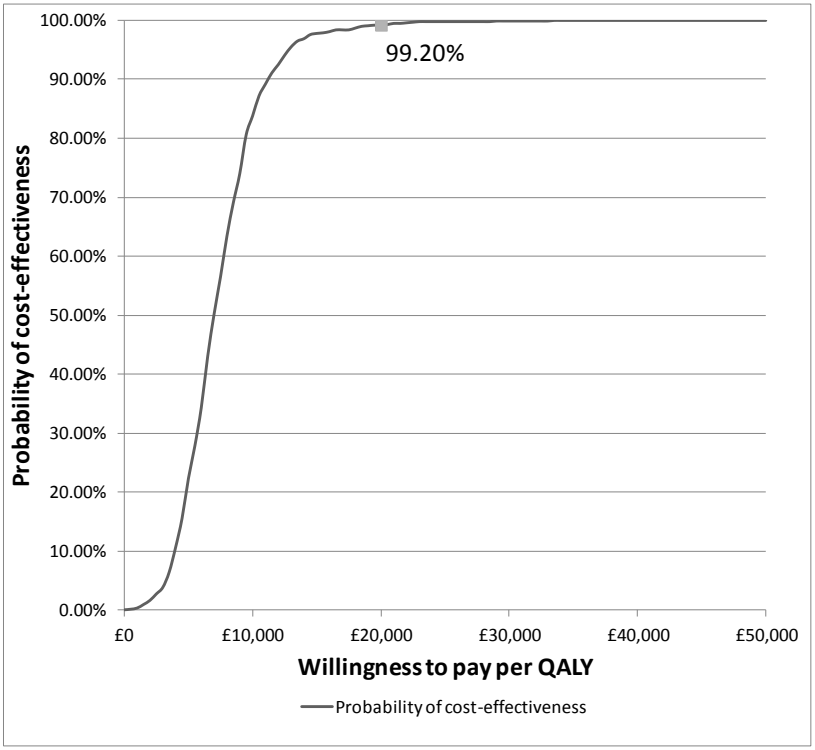


Figure 57. CEAC: comparison 1a - aflibercept first-line versus laser followed by ranibizumab



5.9.2.2 Aflibercept first-line versus laser followed by dexamethasone (comparison 1b)

Figure 58 shows the cost-effectiveness plane for aflibercept first-line versus laser followed by dexamethasone.

Figure 58. Scatterplot: comparison 1b - aflibercept first-line versus laser followed by dexamethasone

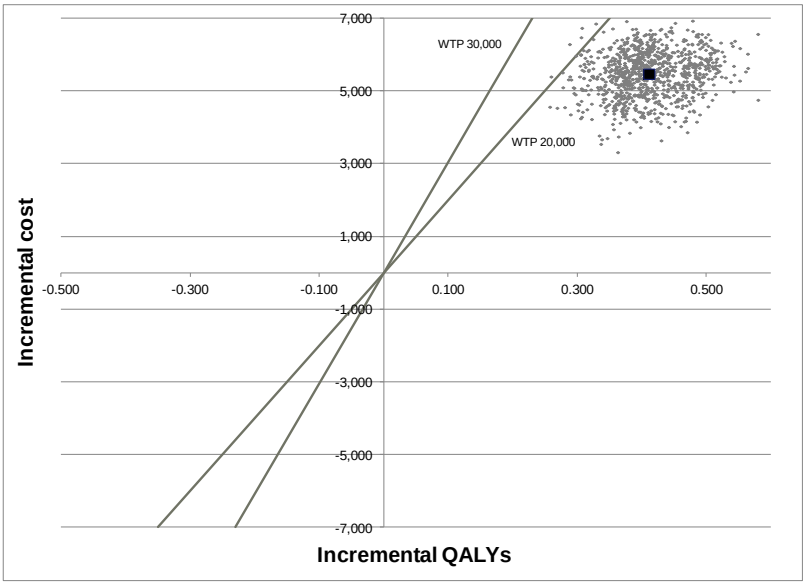
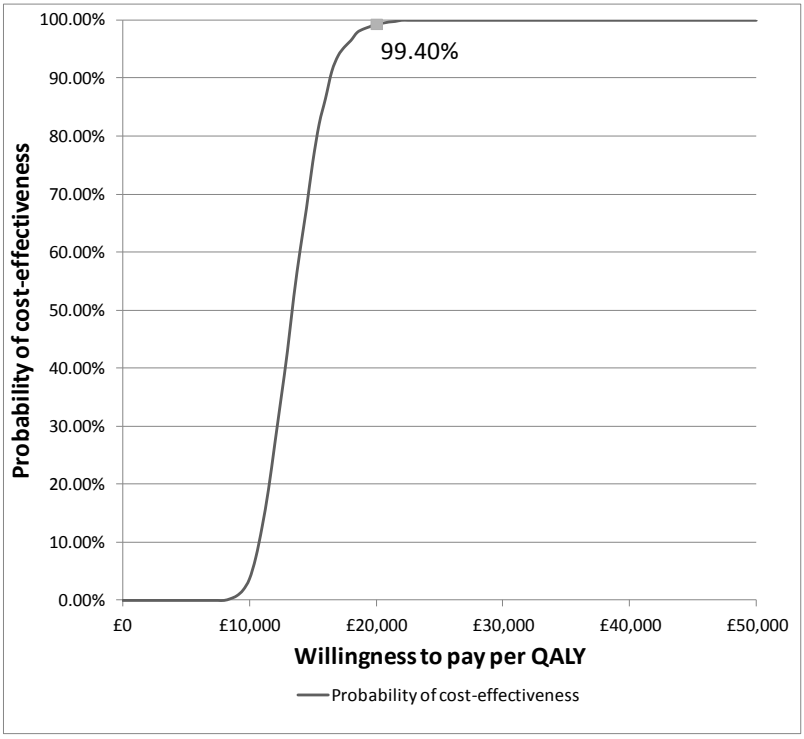


Figure 59. CEAC: comparison 1b - aflibercept first-line versus laser followed by dexamethasone



5.9.2.3 Aflibercept first-line versus laser followed by aflibercept (comparison 1c)

Figure 60 shows the cost-effectiveness plane for aflibercept first-line versus laser followed by aflibercept.

Figure 60. Scatterplot: comparison 1c - aflibercept first-line versus laser followed by aflibercept

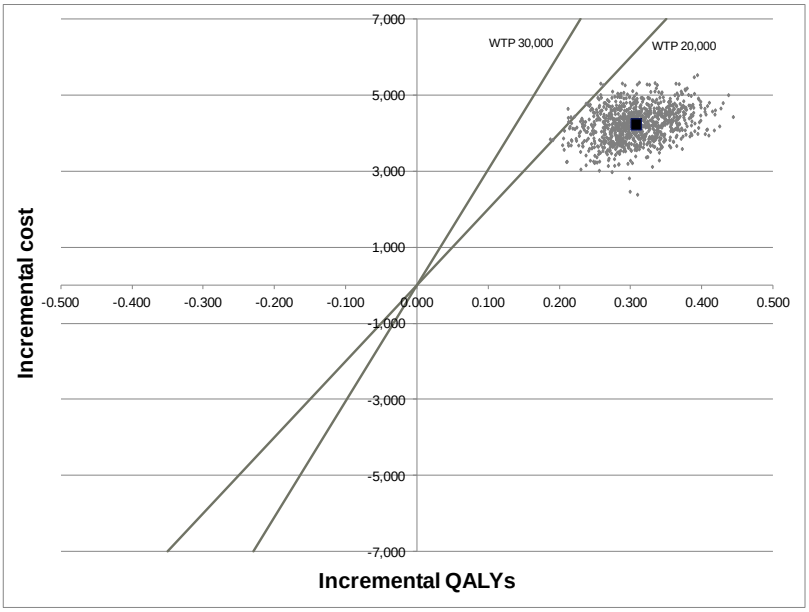
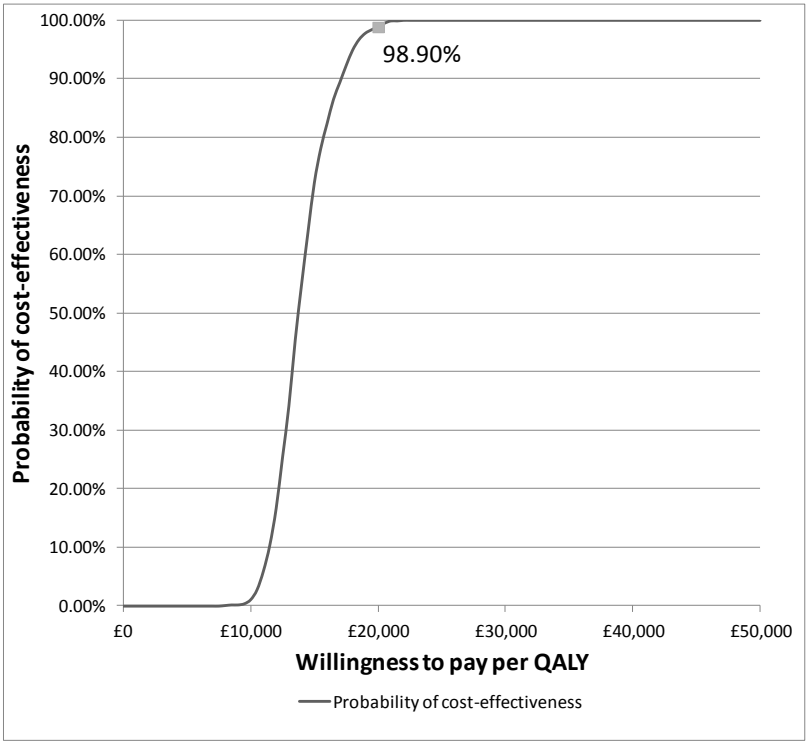


Figure 61. CEAC: comparison 1c - aflibercept first-line versus laser followed by aflibercept



5.9.2.4 Laser followed by aflibercept versus laser followed by ranibizumab (comparison 2a)

Figure 62 shows the cost-effectiveness plane for laser followed by aflibercept versus laser followed by ranibizumab.

Figure 62. Scatterplot: comparison 2a - laser followed by aflibercept versus laser followed by ranibizumab

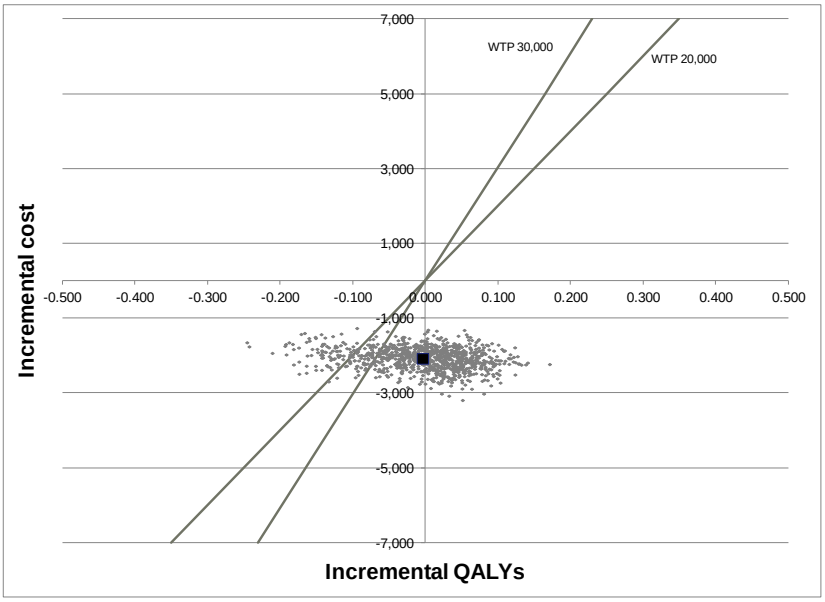
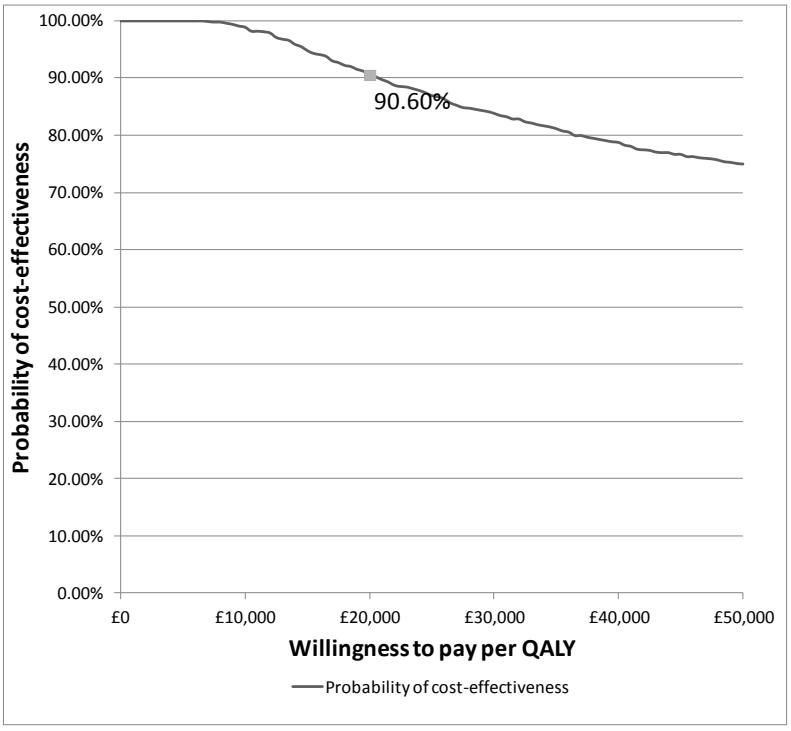


Figure 63. CEAC: comparison 2a - laser followed by aflibercept versus laser followed by ranibizumab



5.9.2.5 Laser followed by aflibercept versus laser followed by dexamethasone (comparison 2b)

Figure 64 shows the cost-effectiveness plane for laser followed by aflibercept versus laser followed by dexamethasone.

Figure 64. Scatterplot: comparison 2b - laser followed by aflibercept versus laser followed dexamethasone

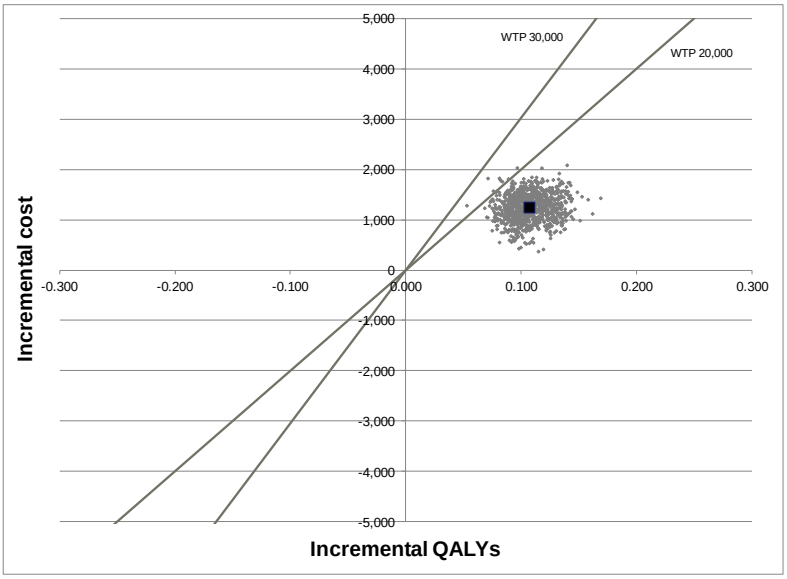


Figure 65. CEAC: comparison 2b - laser followed by aflibercept versus laser followed dexamethasone

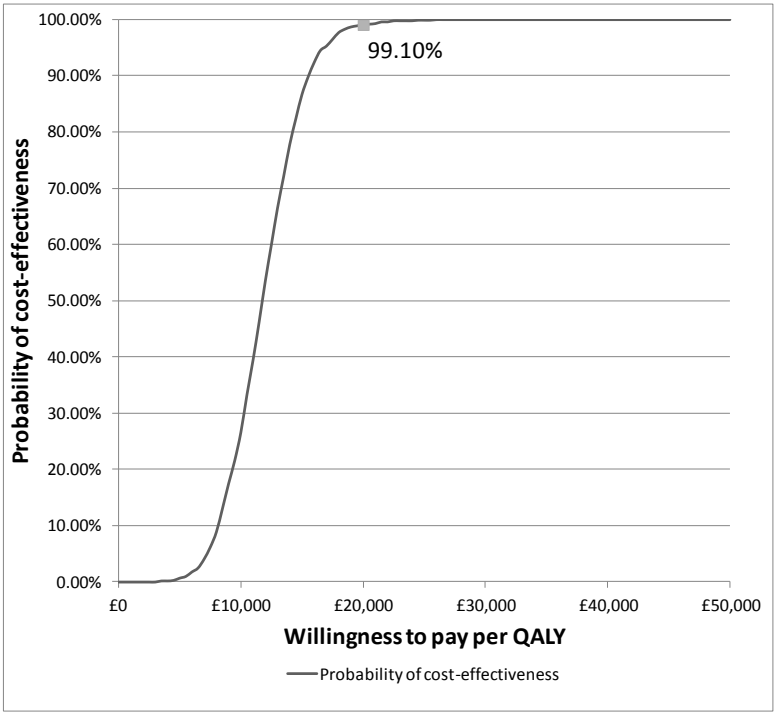
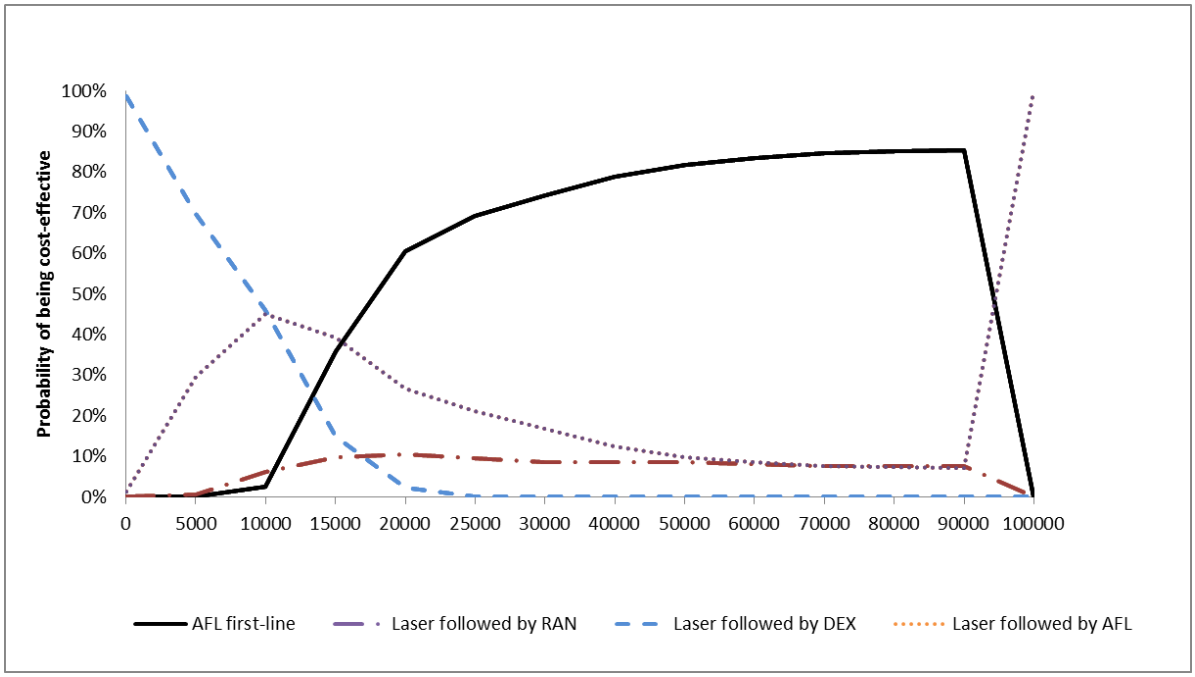


Figure 66 shows the cost-effectiveness frontier for the four treatment pathways that form the basis of the five cost-effectiveness comparisons. For a willingness to pay of £20,000 per QALY the use of aflibercept as a first-line treatment has the greatest probability of being most cost-effective.

Figure 66. Cost-effectiveness frontier



5.9.3 Scenario analysis

Four scenario analyses were conducted:

- Equivalent efficacy between aflibercept and ranibizumab
- Efficacy based on the NMA results where excluded trials were included in the evidence network (for comparisons against ranibizumab i.e. 1a & 2a)
- EQ5D estimates from VIBRANT trial were used for the health state utility values
- The use of shift tables as source of efficacy data for the transition probabilities (only done for comparison 1c using data from the VIBRANT trial).

5.9.3.1 Scenario analysis - Equivalent efficacy between aflibercept and ranibizumab (comparisons 1a, 2a)

In the base case deterministic analyses different efficacy values derived from the network metaanalysis were applied to aflibercept and ranibizumab (Table 55). In this scenario the same efficacy was applied to aflibercept and ranibizumab. Consequently, all the inputs between the two treatments were assumed to be equivalent except for the costs associated with the injections. Results for the two comparisons (1a, 2a) where aflibercept and ranibizumab are included are reported separately below.

Aflibercept first-line versus laser followed by ranibizumab (comparison 1a)

In this scenario analysis aflibercept first-line is associated with an additional cost of £ [redacted] and higher QALYs (incremental QALYs: [redacted]) giving an ICER of £9,259.

Table 118: Results: comparison 1a - aflibercept first-line versus laser followed by ranibizumab (equivalent efficacy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL followed by LSR in treatment failures	[redacted]	13.717	[redacted]				
LSR followed by RAN in treatment failures	[redacted]	13.709	[redacted]	[redacted]	0.0082	[redacted]	9,259

Laser followed by aflibercept versus laser followed by ranibizumab (comparison 2a)

When laser followed by aflibercept is compared to laser followed by ranibizumab the model shows that aflibercept is associated with a reduction in cost of £[redacted]. This confirms that when equal efficacy between aflibercept and ranibizumab is assumed laser followed by aflibercept is a cost saving option.

Table 119: Results: comparison 2a - Laser followed by aflibercept versus laser followed by ranibizumab (equivalent efficacy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
LSR followed by AFL	[redacted]	13.709	[redacted]				
LSR followed by RAN	[redacted]	13.709	[redacted]	[redacted]	0.0000	[redacted]	Cost saving

5.9.3.2 Scenario analysis: all trials included in network meta-analysis (comparison 1a, 2a)

In these two scenario analyses a median OR of 1.08 and credible interval of 0.45-1.45 (for achieving a ≥15 letter increase) was used for ranibizumab.

Aflibercept first-line versus laser followed by ranibizumab (comparison 1a)

Deterministic results are shown in Table 120. Aflibercept first-line is associated with a higher QALY gain (incremental [redacted]) as well as a higher cost (incremental £[redacted]) resulting in an ICER of £9,632, below the NICE £20,000 per QALY WTP threshold.

Table 120. Results: comparison 1a – aflibercept first-line versus laser followed by ranibizumab (all trials included in NMA)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.717	[redacted]				
LSR followed by RAN	[redacted]	13.709	[redacted]	[redacted]	0.0082	[redacted]	9,632

Figure 57 shows the cost-effectiveness plane for aflibercept 1st line vs ranibizumab after laser. The large majority of iterations are in the north-east quadrant and below the willingness-to-pay threshold of £20,000. Figure 2 shows the probability aflibercept 1st line is cost-effective at the WTP threshold of £20,000 is 97.2%.

Figure 67. Scatterplot: comparison 1a - aflibercept first-line versus laser followed by ranibizumab (all trials included in NMA)

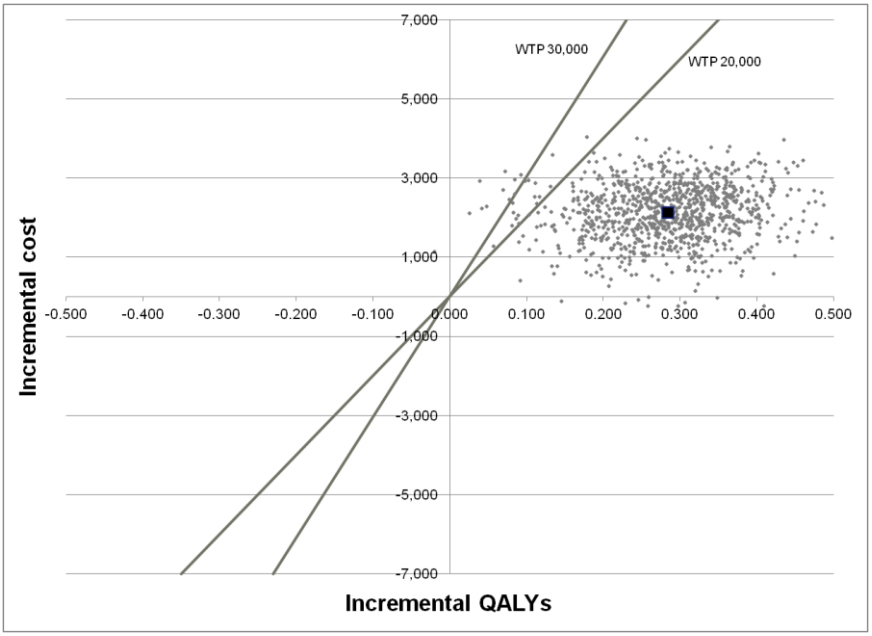
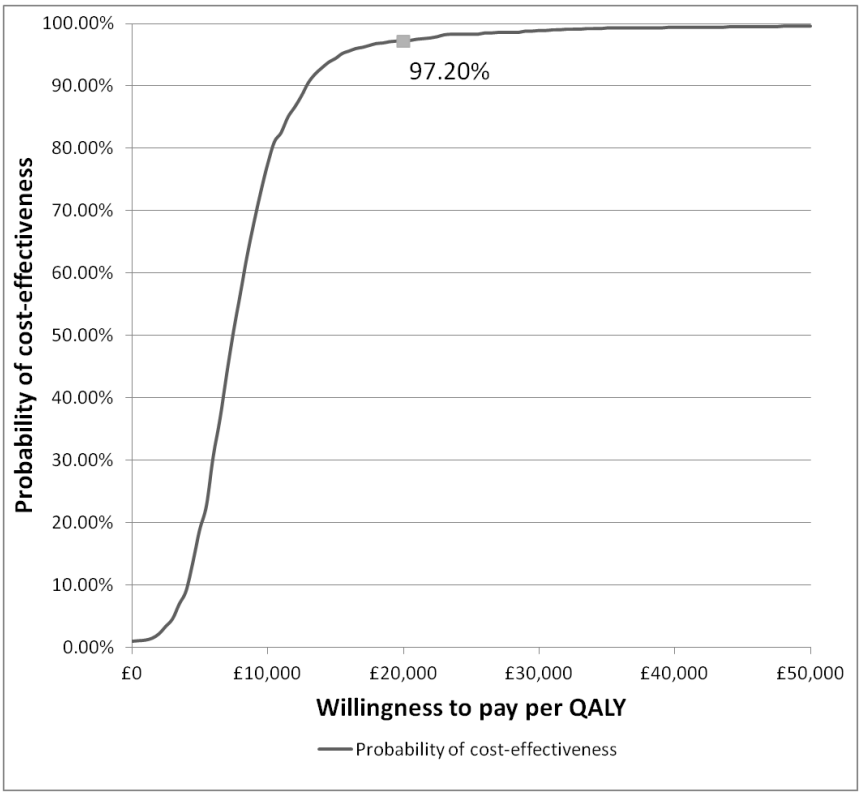


Figure 68. CEAC: comparison 1a – aflibercept first-line versus laser followed by ranibizumab (all trials included in NMA)



Laser followed by aflibercept versus laser followed by ranibizumab (comparison 2a)

The deterministic results are shown in Table 121. Laser followed by aflibercept is associated with a lower cost (incremental -£[redacted]) as well as a reduced QALY gain (incremental [redacted]) resulting in an ICER of £158,853.

Table 121. Results: comparison 2a – laser followed by aflibercept versus laser followed by ranibizumab (all trials included in NMA)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
LSR followed by AFL	[redacted]	13.709	[redacted]				
LSR followed by RAN	[redacted]	13.709	[redacted]	[redacted]	-0.0001	[redacted]	158,853*

*result lies in the southwest quadrant of the cost-effectiveness plane

Figure 69 shows the cost-effectiveness plane for laser followed by aflibercept versus laser followed by ranibizumab. The iterations are spread across the south-east and south-west quadrants. Figure 4 shows the probability aflibercept after laser is cost-effective compared to ranibizumab after laser is 84.9% at a WTP threshold of £20,000 per QALY.

Figure 69. Scatterplot: comparison 2a – laser followed by aflibercept versus laser followed by ranibizumab (all trials included in NMA)

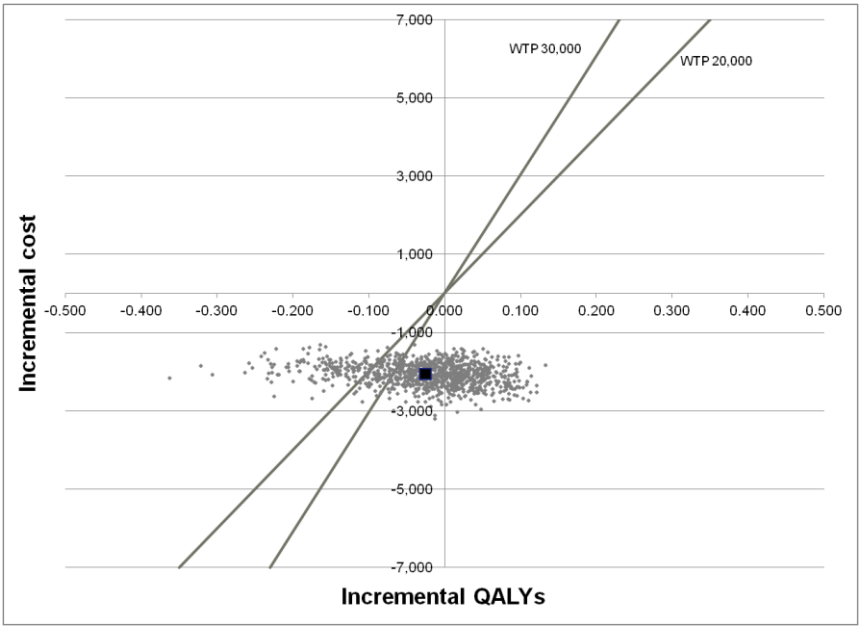
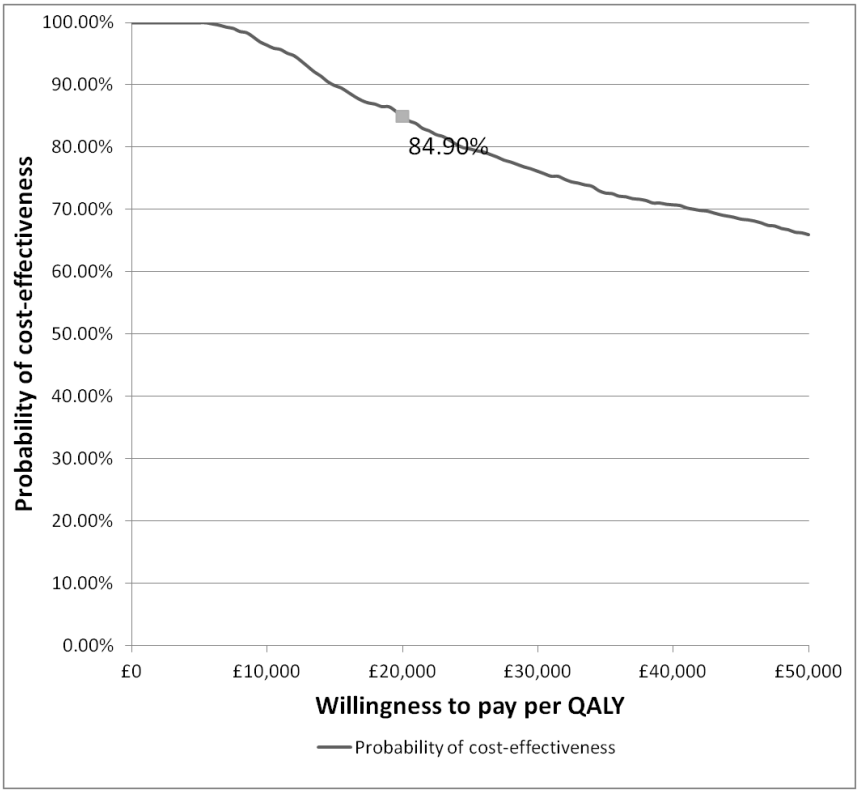


Figure 70. CEAC: comparison 2a – laser followed by aflibercept versus laser followed by ranibizumab (all trials included in NMA)



5.9.3.3 Scenario analysis: EQ5D estimates from VIBRANT trial

This scenario was performed using the utility values from the integrated VIBRANT trial analysis which were derived using the EQ-5D instrument. Descriptive statistics and regression analyses were used to estimate mean utility values for health states as well as the relationship between visual acuity and utility. Full details on how utility values were obtained are reported in appendix **Error! Reference source not found.**. Utility values elicited through TTO methods have reported a large range between best and worst utility values, suggesting that EQ-5D may not be responsive to disease severity in this condition.

Utility values used in this scenario are reported in Table 122.

Table 122: Vision state utility values from VIBRANT

Lines		Best-seeing eye				
		VA1 (90)	VA2 (72.5)	VA3 (57.5)	VA4 (42.5)	VA5 (17.5)
Worst-seeing eye	VA1 (90)	0.9003				
	VA2 (72.5)	0.8774	0.8403			
	VA3 (57.5)	0.8578	0.8207	0.7889		
	VA4 (42.5)	0.8382	0.8011	0.7693	0.7375	
	VA5 (17.5)	0.8054	0.7684	0.7366	0.7048	0.6518

Results for each comparison are reported in separated sections below.

Aflibercept first-line versus laser followed by ranibizumab (comparison 1a)

Table 123: Results: comparison 1a - aflibercept first-line versus laser followed by ranibizumab (EQ5D utility values)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL followed by LSR	[redacted]	13.717	[redacted]				
LSR followed by RAN	[redacted]	13.709	[redacted]	[redacted]	0.0083	[redacted]	14,848

Aflibercept first-line versus laser followed by dexamethasone (comparison 1b)

Table 124: Results: comparison 1b - aflibercept first-line versus laser followed by dexamethasone (EQ5D utility values)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.717	[redacted]				
LSR followed by DEX	[redacted]	13.708	[redacted]	[redacted]	0.0091	[redacted]	23,971

Aflibercept first-line versus laser followed by aflibercept (comparison 1c)

Table 125: Results: comparison 1c - Aflibercept first-line versus laser followed by aflibercept (EQ5D utility values)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.717	[redacted]				
LSR followed by AFL	[redacted]	13.709	[redacted]	[redacted]	0.0082	[redacted]	25,471

Laser followed by aflibercept versus laser followed by ranibizumab (comparison 2a)

Table 126: Results: comparison 2a - Laser followed by aflibercept versus laser followed by ranibizumab (EQ5D utility values)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
LSR followed by AFL	[redacted]	13.709	[redacted]				
LSR followed by RAN	[redacted]	13.709	[redacted]	[redacted]	0.0001	[redacted]	Cost saving

Laser followed by aflibercept vs laser followed by dexamethasone (comparison 2b)

Table 127: Results: comparison 2b - laser followed by aflibercept versus laser followed by dexamethasone (EQ5D utility values)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
LSR followed by AFL	[redacted]	13.709	[redacted]				
LSR followed by DEX	[redacted]	13.708	[redacted]	[redacted]	0.0008	[redacted]	20,289

5.9.3.4 Scenario analysis – transition tables based on shift tables (comparison 1c)

The availability of patient level data from the VIBRANT trial allowed for a comparison of the transition matrices generated using shift tables and transition matrices generated using the MSM package. The actual distribution of patients between health states (shift tables) was used to inform the transitions in the model for this analysis. The results of this scenario are presented in Table 128.

Table 128: Results: comparison 1c - aflibercept first-line versus laser followed by aflibercept (shift tables)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.716	[redacted]				
LSR followed by AFL	[redacted]	13.712	[redacted]	[redacted]	0.0043	[redacted]	17,976

5.9.4 Summary of sensitivity analyses results

A comprehensive set of sensitivity and scenario analyses were completed. The incremental cost per QALY for aflibercept remained below £20,000 in all but the following instances:

- Higher starting age of the cohort (Aflibercept first-line versus laser followed by dexamethasone or aflibercept: comparisons 1b and 1c)
- A 10-year time horizon (aflibercept first-line versus laser followed by aflibercept: comparison 1c)
- Better efficacy for ranibizumab or dexamethasone relative to aflibercept (laser followed by aflibercept versus laser followed by ranibizumab or dexamethasone: comparisons 2a and 2b)
- EQ-5D utility values (comparisons 1b, 1c, 2b)

The main drivers of cost-effectiveness were the starting age of the cohort, time horizon and the relative efficacy of aflibercept versus the comparators.

5.10 Subgroup analysis

As per the scope, subgroup analyses were performed according to BCVA. The two subgroups considered were determined by the stratification of BCVA at baseline in the VIBRANT trial i.e.

- BCVA 24-34 letters
- BCVA 35-73 letters

The analysis was performed for comparison 1c (aflibercept first-line versus laser followed by aflibercept) using data from the VIBRANT study. The number of patients in the 24-34 letter group was small (n=13) and consequently the MSM package could not be used to determine the transition probabilities. For this analysis transition probabilities are based on shift tables. The results for both subgroups are shown in Table 129 and Table 130.

Table 129. Subgroup analysis results: BCVA 24-34 letters – Comparison 1c (aflibercept first-line versus laser followed by aflibercept)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.698	[redacted]				
LSR followed by AFL	[redacted]	13.646	[redacted]	[redacted]	0.0515	[redacted]	5,569

Table 130. Subgroup analysis results: BCVA 35-73 letters – comparison 1c (aflibercept first-line versus laser followed by aflibercept)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13,716	[redacted]				
LSR followed by AFL	[redacted]	13,715	[redacted]	[redacted]	0.0005	[redacted]	22,814

5.11 Validation

5.11.1 Validation of de novo cost-effectiveness analysis

5.11.1.1 Expert opinion

Clinical experts were consulted during the model development to ensure key assumptions (e.g. around model structure and disease progression) underlying the model were appropriate. In addition, a Physician survey was conducted to estimate values for resource use inputs (appendix **Error! Reference source not found.**). Unit cost values were aligned with those used in previous HTA submissions in ophthalmic indications.

5.11.1.2 Quality control

A check of internal validity was performed to ensure that outputs were logical and accurate within the framework set by the model. This was ensured by quality control of the model by the model developers, and a model audit performed by an experienced health economist outside of the team of developers in which extreme value scenarios were tested to cross check that the model behaved logically.

5.11.1.3 Clinical outcomes

As described in section 5.3.2.3, transition probabilities between the VA health states were derived using the MSM package, using trial data to calculate the most likely, or 'averaged', transitions for patients. The proportion of patients occupying the different VA health states at the 6-month timepoint as predicted by the model were compared to the results from the trial data. As can be seen from Figure 71 and Figure 72, the model estimates were closely aligned to those from the trial.

Figure 71. Proportion of patients in each VA health state – laser group

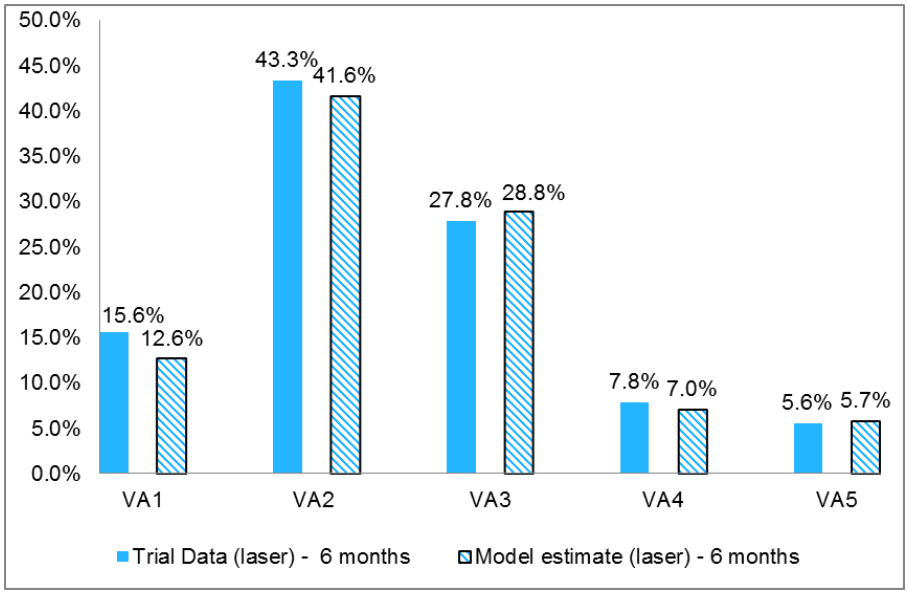
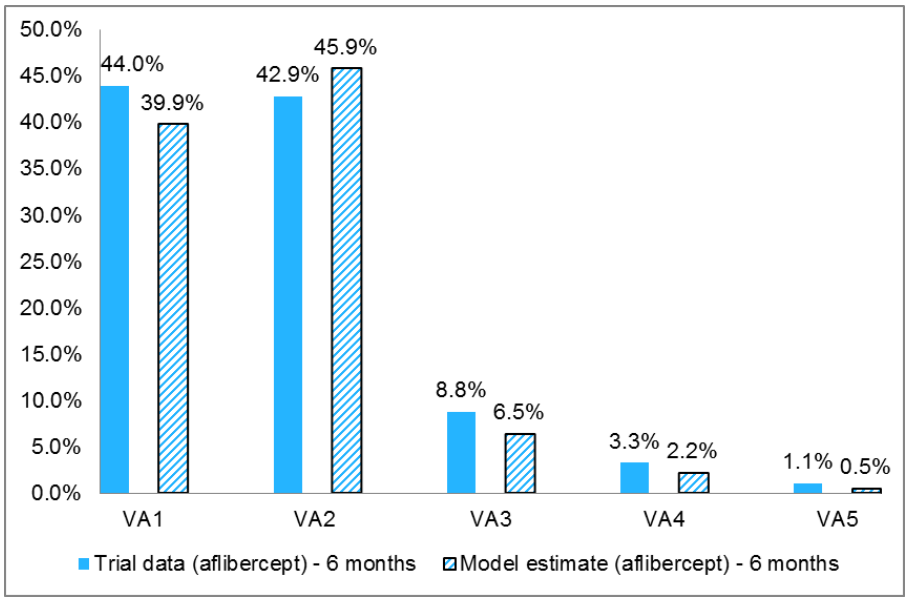


Figure 72. Proportion of patients in each VA health state – aflibercept group



5.12 Interpretation and conclusions of economic evidence

The economic evaluation is relevant to all groups of patients who could receive aflibercept as identified in the decision problem. The cohort modelled is the patient population from the VIBRANT trial. These patients had vision loss due to macular oedema secondary to BRVO and therefore the results of this trial match the licensed indication and are generalisable to patients in England and Wales.

The main strengths of the analysis are that both eyes are considered. In addition, the VIBRANT trial is well designed to inform the cost and efficacy of aflibercept if used as a first or second-line treatment. The model takes into account the costs and effects of first and second-line treatment which is a strength in comparison to other models in this disease area. Another strength is that the resource use estimates are based on a large UK based physician survey designed specifically to capture inputs relevant for the *de novo* model presented.

A weakness in the model is that the indirect comparison versus ranibizumab and dexamethasone is based on a low number of trials which leads to results with wide confidence intervals.

The economic results show that aflibercept is a cost-effective use of NHS resources when used in the current position recommended by NICE for newer treatments i.e. second-line. The results also show that aflibercept is cost-effective when used as a first-line alternative to laser photocoagulation. First-line use of aflibercept is associated with higher costs but is also associated with better patient outcomes. Overall, the results demonstrate that at a cost per QALY threshold of £20K, the most cost-effective use of aflibercept is as a first-line treatment.

6 Assessment of factors relevant to the NHS and other parties

6.1 Patients eligible for treatment

The population eligible for treatment comprises patients with visual impairment due to macular oedema secondary to BRVO.

In order to estimate a projected eligible BRVO population from year 2015 to 2019, the following parameters have been considered:

- Total projected England and Wales population ≥43 years of age from 2015 to 2019

  A population age of ≥43 years was used in the model to be consistent with previous submissions. The ONS reports the aging distribution of 16-64 years and ≥65 years as 64% and 18% respectively. For the population in 2015 a calculation was performed, making the assumption that the percentage of people in each age group has an equal distribution, assuming that 35.27% of the population reported as 16-64 years were aged 16-42 years. Therefore, 46.73% of the total population was assumed to be ≥43 years. A fixed annual growth rate index of 0.81% for subsequent years, calculated using projection data from the ONS using a weighted average across England and Wales was applied.

- Annual incidence rate of BRVO

  The annual incidence rate of BRVO was taken from the ranibizumab NICE submission for treatment visual impairment caused by MO secondary to retinal vein occlusion. The prevalence of BRVO was sourced from Laouri et al. (2011).

- Fellow eye involvement

  Bilateral involvement is low in BRVO. The same value used in the economic model was used in the budget impact sourced from the Physican Survey (i.e. 6.1%). For consistency with the economic model it is assumed that 50% of fellow eyes are treated.

- Proportion of patients with MO secondary to BRVO and proportion with visual impairment

  These values were sourced from the ranibizumab NICE submission costing template.

- Eligible BRVO population

  The eligible BRVO population was calculated for the study eye and fellow eye using the BRVO incidence rate and fellow eye involvement. The proportion of patients with MO following BRVO and the proportion of patients with visual impairment are then applied to calculate a BRVO number of eyes treated.

The input parameters and estimated eligible patients are shown in Table 131 and Table 132, respectively.

Table 131. Parameters from estimation of eligible patients

Parameter	Estimated Value	Reference
General population ≥43 years	26,829,733	Adjustment made to ONS total population
Annual population growth	0.81%	ONS
Annual incidence rate BRVO	0.12%	Ranibizumab NICE submission costing template
Fellow eye involvement	6.1%	Physician survey
% fellow eyes treated	50%	Assumption
Proportion of patients with MO following BRVO	50%	Ranibizumab NICE submission costing template
Proportion of patients with visual impairment	90%	Ranibizumab NICE submission costing template

Table 132. Forecast of number of eligible cases

	Year 1	Year 2	Year 3	Year 4	Year 5
Study eye prevalence	0	32,196	64,653	97,373	130,359
Study eye incidence per year	32,196	32,457	32,720	32,986	33,253
Prevalence of fellow eye involvement	0	982	1,972	2,970	3,976
Incidence of fellow eye involvement	982	990	998	1,006	1,014
Total prevalence	0	33,178	66,625	100,343	134,335
Total incidence of BRVO	33,178	33,447	33,718	33,992	34,268
Number of eyes with MO (50%)	16,589	16,723	16,859	16,996	17,134
Number of eyes with visual impairment (90%)	14,930	15,051	15,173	15,296	15,420
Incident BRVO number of eyes treated	**14,930**	**15,051**	**15,173**	**15,296**	**15,420**
Total eyes treated	**14,930**	**29,981**	**45,032**	**60,083**	**75,134**

6.2 Assumptions

This model focuses on injectable therapies i.e. ranibizumab and dexamethasone. However it is ranibizumab that is most likely to be displaced by aflibercept as it is from the same class. It is assumed that the decision to use dexamethasone will be unaffected by the recommendation of a second anti-VEGF treatment. The number of injections per year for each treatment is the same as used in the cost-effectiveness model (see section 5.5). Prevalent patients (prior to year 1) are not considered as the treatment of these patients is assumed to not change.

6.3 Market Shares

It is assumed that uptake of aflibercept will displace a portion of the ranibizumab market share and that by year 2 the market shares of aflibercept and ranibizumab in BRVO will be the same. The dexamethasone market share is assumed to remain stable across the 5 years of the budget impact model. The year 1 market shares are from a market research survey (May – August 2015) conducted by a 3rd party company (data on file). The assumed market share projections in the world without and world with aflibercept are shown in Table 133 and Table 134.

Table 133. Projected market shares: world without aflibercept

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept	0%	0%	0%	0%	0%
Ranibizumab	75%	75%	75%	75%	75%
Dexamethasone	25%	25%	25%	25%	25%

Table 134. Projected market shares: world with aflibercept

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept	18.5%	37.5%	37.5%	37.5%	37.5%
Ranibizumab	56.5%	37.5%	37.5%	37.5%	37.5%
Dexamethasone	25.0%	25.0%	25.0%	25.0%	25.0%

6.4 Additional costs

In addition to technology costs, the following additional costs were modeled in the cost-effectiveness analysis and were therefore also incorporated into the budget impact analysis:

- Cost of treatment administration,
- Cost of follow-up monitoring.

6.5 Unit costs

Unit costs are the same as in the cost-effectiveness analysis. The costs of treatment (technology and administration costs) and monitoring costs were combined with rates of occurrence reported in section 5.5. Rates used in the budget impact analysis cover the treatment and maintenance duration in the base case cost-effectiveness analysis (5 years).

6.6 Resource saving estimates

No resources saving estimates were observed.

6.7 Budget impact results

The total budget impact across the 5 years of the analysis is shown in Table 135. These results are for the PAS price of aflibercept and list prices for ranibizumab and dexamethasone.

Table 135. Budget impact results

Budget impact in a world without aflibercept (£)					
	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact in a world with aflibercept (£)					
	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact (£)					
	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Admin and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As expected, a negative net budget impact was observed in all years following the launch of aflibercept given the lower total costs associated with aflibercept compared to ranibizumab. The administration and monitoring costs have a 0% change because of the assumption of equivalence between ranibizumab and aflibercept for number of injections and monitoring, as well as the assumption the dexamethasone shares remain stable across all five years.

6.8 Other opportunities for resource saving

No other opportunities for resource saving were observed.

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Single technology appraisal

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

Dear [redacted],

The Evidence Review Group, Aberdeen Health Technology Assessment Group, and the technical team at NICE have looked at the submission received on 2nd February 2016 from Bayer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **12pm on Thursday 10 March 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Henry Edwards, Technical Lead (henry.edwards@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk).

Yours sincerely

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On behalf of Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Table 139 (page 229 of the company submission) states that the Campochiaro 2008 paper was excluded from the systematic review of clinical effectiveness because "pooled results (BRVO and CRVO)" were reported. However, Figure 5 on page 797 of the Campochiaro paper provides separate results for the branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) groups for median change from baseline in visual acuity (VA) and it appears to fulfil the eligibility criteria for the search strategy listed in Table 6 (page 46 of the company submission).

Please clarify the reason(s) for excluding the Campochiaro 2008 paper from the systematic review of clinical effectiveness.

A2. Mortality has not been specified as an outcome in the eligibility criteria for the search strategy for the review of clinical effectiveness (Table 6, page 46 of the company submission). Please clarify if mortality was used as an outcome in the search strategy.

A3. The eligibility criteria for the search strategy for the systematic review of clinical effectiveness (table 6, page 46 of the company submission) states "recent systematic reviews and meta-analyses" as an inclusion criteria. Please provide a definition of the term "recent".

A4. The company submission states that the subgroups were determined by the stratification of best corrected visual acuity (BCVA) at baseline in VIBRANT (page 268 of the company submission). However, further clarification is not provided. Please clarify how the BCVA subgroups 24-34 letters and 35-73 letters were determined.

A5. Please specify by treatment arm, what number of study eyes in VIBRANT had a BCVA better or equal to that of the fellow eye at:

a. baseline
b. at 24 weeks/6 months pre cross over
c. at end of trial

A6. **Priority Question:** The network meta-analyses inputs provided in Table 37 (page 114 of the company submission) only report percentages and means. Further details

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are provided in Appendix 7, however, there appear to be some discrepancies between the data in Table 37 and Appendix 7 (an error may have occurred where the lines for BRIGHTER and COMRADE-B in Table 37 may have been swapped over). In addition, the source of the data in Table 37 and/or Appendix 7 is unclear. Data for BRIGHTER and COMRADE-B appear to be sourced from the poster by Regnier and Bezlyak (2014), although BCVA data for BRIGHTER appears to be sourced from the abstract by Mones (2015). It is also not clear how the standard errors for the BRIGHTER and COMRADE-B studies have been estimated in Appendix 7. The method used does not appear to be consistent with the methods described in section 16.1.3.2 of the Cochrane Handbook for Systematic Reviews referenced on page 115 of the company submission.

Please provide a revised version of Table 37 confirming the full data used in the network meta-analyses (e.g., numerator and denominator for proportion gaining >15 letters and mean, standard deviation [SD] and number [n] for mean BCVA change from baseline). Please clarify that the references used to obtain the data are correct and provide any assumptions that may have been used to impute data if data was unavailable from the literature.

Section B: Clarification on cost-effectiveness data

B1.

a. **Priority Question:** Please provide the following patient count data separately for all patients in (a) the study eyes of the aflibercept treatment arm of VIBRANT and (b) the study eyes of the laser treatment arm of VIBRANT separately for:

- T0= baseline to T1= 24 weeks / 6 months pre cross over
- T0= 6 months to T1= 1 year among those remaining on their original treatment
- T0= 6 months to T1= 1 year among those crossing over

These data can be presented within an Excel spreadsheet.

		BCVA T_1				
		VA1	**VA2**	**VA3**	**VA4**	**VS5**
BCVA T_0	**VA1**	n=???	n=???	n=???	n=???	n=???
	VA2	n=???	n=???	n=???	n=???	n=???
	VA3	n=???	n=???	n=???	n=???	n=???
	VA4	n=???	n=???	n=???	n=???	n=???
	VA5	n=???	n=???	n=???	n=???	n=???

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b. Please provide the data specified in B1a, separately for the subgroups with a baseline (1) BCVA in VA1, (2) BCVA in VA2, (3) BCVA in VA3, (4) BCVA in VA4 and (5) BCVA in VA5.

B2. **Priority Question:** Please provide the patient numbers that underlie the following cells D85:H98, U91:Y98, D103:D116 and U109:Y116 of the Shift_Tables worksheet for the patient subgroups with a baseline for their study eye of a (1) BCVA in VA1, (2) BCVA in VA2, (3) BCVA in VA3 and (4) BCVA in VA4. These data can be presented within an Excel spreadsheet.

B3. **Priority Question:** Please provide the following treatment administration count by those who did not cross over and those who did cross over by 4 week treatment cycles during the VIBRANT trial in each treatment arm.

Example table of results

	Aflibercept treatment arm				**Laser treatment arm**			
	No cross over		Crossed over		No cross over		Crossed over	
N admin of	Aflib.	Laser	Aflib.	Laser	Aflib.	Laser	Aflib.	Laser
Cycle 1	n=???	n.a.	n=???	n=???	n.a.	n=???	n=???	n=???
Cycle 2	n=???	n.a.	n=???	n=???	n.a.	n=???	n=???	n=???
etc…	n=???	n.a.	n=???	n=???	n.a.	n=???	n=???	n=???

B4. **Priority Question**: Please provide the following anonymised patient level data at baseline assessment and at each EQ-5D collection point thereafter for the VIBRANT trial:

a. the BCVA in the study eye (SE BCVA)
b. the BCVA in the non-study eye (NSE BCVA)
c. the EQ-5D value assessed by the UK social tariff.

Please record missing data should be recorded as "..". There is no requirement for the patient level data to be grouped by trial arm or ordered in any particular way. These data can be provided within an Excel spreadsheet.

	Baseline assessment			**1st EQ-5D assessment**			**Etc…**
	SE BCVA	NSE BCVA	EQ-5D	SE BCVA	NSE BCVA	EQ-5D	Etc…
Patient 1	???	???	???	???	???	???	Etc…
Patient 2	???	???	???	???	???	???	Etc…
etc…	???	???	???	???	???	???	Etc…

B5. Please list all the variables of interest that were initially tested using OLS regression models in the EQ-5D analysis.

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B6. Has the company undertaken or commissioned any repeated measures analysis of the VIBRANT EQ-5D data? If so, please provide the results of this.

B7. Please present the VIVID/VISTA EQ-5D OLS regression coefficients that were used by the company in its submission for the appraisal of aflibercept for treating diabetic macular oedema (technology appraisal guidance 346 [TA 346]) and which have been redacted from Table 27 of the ERG report for TA 346.

B8. Page 188 of the company submission states '….NICE guidance stating that EQ-5D is not sufficiently sensitive to changes in visual acuity…'. Please provide a reference for the NICE guidance, and page reference(s), that states that the EQ-5D is not sufficiently sensitive to changes in visual acuity.

B9. Please provide the following data:

a. The patient/event counts that would underlie the 24 week pre-cross over corollary of the patient numbers that underlie Table 71 (adverse event rates, page 188 of the company submission).

b. The patient numbers underlying Table 71 (1year) split by crossover status.

c. Clarify whether these data are patient count data; i.e. the number of patients experiencing at least one event, or event count data.

	24 weeks	**1 year**
Aflibercept pre-cross over Cataract IOP	 n=??? n=???	 n=??? n=???
Aflibercept cross over Cataract IOP	 n.a. n.a.	 n=??? n=???
Laser pre-cross over Cataract IOP	 n=??? n=???	 n=??? n=???
Laser cross over Cataract IOP	 n.a. n.a.	 n=??? n=???

B10. The clinical data in the SHIFT_TABLES worksheet and the Transistion_MX worksheet do not appear to have been implemented probabilistically. Please clarify whether they have been implemented probabilistically. If the clinical data have been implemented probabilistically, please highlight where in the model this has been implemented.

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B11. Please clarify how the respondents for the resource use survey (referenced in section 5.5.2.2.1, of the company submission) were identified. Please provide a copy of the online resource use questionnaire or access to the online survey.

B12. Section 5.5.2.1 (page 203 of the company submission) states that some of the costs associated with treatment failures and adverse events were taken from NCWC/NICE. Please provide the specific unit costs and reference(s) for each of the unit costs drawn from NCWC/NICE guidelines.

B13. The patient count data in the Shift_Tables worksheet suggests a denominator for laser of 90. The discontinuation data in the Tx_Inputs worksheet suggests a denominator of 92. Please clarify which data are correct.

B14. The patient count data in cells U70:Y77 of the Shift_Tables worksheet suggests 53, 62, 64, 64, 66, 66, 67, 67 patients having crossed over in the laser treatment arm for cycles 6 to 13 respectively. Given the 90 patients in the laser treatment arm this suggests cross over percentages of 58.9% and given rounding of 10%, 2%, 0%, 2%, 0% and 2%. While the CBH worksheet suggests percentages of 58.9% and given rounding of 10%, 2%, 0%, 2%, 1% and 0%. Please clarify which worksheet is correct.

B15. For 2nd line laser there is a 0.0025% probability of patients in VA1 transitioning to VA5. Given the trial patient numbers, it is unclear how the transition probability was estimated. Please clarify how this transition probability was calculated and the calculation used.

B16. The submission states that there are no efficacy data for aflibercept for the maintenance phase. Please clarify whether a literature search has been undertaken to identify any follow-up studies for any treatment for BRVO or CRVO which might support the assumption of stable vision for 5 years during maintenance. If follow-up studies for other treatments for BRVO or CRVO have been identified, please clarify whether these studies support the assumption of stable vision for 5 years during maintenance.

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Single technology appraisal

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

Dear [redacted],

The Evidence Review Group, Aberdeen Health Technology Assessment Group, and the technical team at NICE have looked at the response to the points for clarification received on 10th March 2016 from Bayer. In general they felt that most points for clarification were responded to well. However, the ERG would like further clarification that will aid their review of your submission (see questions listed at end of letter).

Given that the clarification response deadline has passed, NICE understands that this is an additional request that Bayer may not be able to respond to it. Please can you confirm whether you are able to respond to this additional request by the end of the day.

If you are able to provide a response to the ERG additional clarification request, the deadline for your response is **9:00am, Tuesday 29 March 2016**.

Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Henry Edwards, Technical Lead (henry.edwards@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk).

Yours sincerely

Joanne Holden

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Technical Adviser – Appraisals

On behalf of Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Further clarification on cost-effectiveness data

Could you provide the results of Table 7 and Table 8 of the response to clarification (response to question B6) for each of the eight model types listed in Appendix 13 on page 497 of the company submission, that is, in model types:

a. OLS
b. OLS model including interaction terms (between BCVA, BSE and WSE)
c. OLS model including squared variables
d. Fixed effects model
e. Random effects model
f. Tobit model (assuming utility is censored at values above 1)
g. TPM using logit and OLS regression
h. TPM using logit and OLS with logarithmic utility decrements

Can the analysis be presented for each model type based upon (i) the Linear BCVA model and (ii) the Logarithmic BCVA model, together with their associated R^2 and $\bar{R}^2$.

Could you also provide explanatory information to help interpret the analyses that were undertaken (similar to that found in the company response to question B6) which outlines that the random effects model included the subject as the random intercept. Alternatively, if an internal report has already been prepared on this work could you provide a copy of this.

Could you provide scatter plots of:

i. changes in EQ-5D utility against the changes in BCVA(BSE)
j. changes in EQ-5D utility against the changes in BCVA (WSE) .

For each patient, the data to be plotted would be the changes from baseline, based upon the longest period from baseline for which data exists for that patient; i.e. if a patient has some missing data in their end of trial measurement set then the last set of complete measurements before the end of trial should be used to calculate their changes from baseline.

Could you provide six additional OLS analyses based upon changes in the EQ-5D quality of life and changes in the BCVA as defined above could be conducted:

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k. Change in EQ-5D utility on intercept, against change in BSE BCVA and change in WSE BCVA
l. Change inEQ-5D utility on against change in BSE BCVA and change in WSE BCVA
m. Change inEQ-5D utility on intercept, against change in Ln BSE BCVA and change in Ln WSE BCVA
n. Change inEQ-5D utility on change in Ln BSE BCVA and change in Ln WSE BCVA
o. Change inEQ-5D utility on intercept, (change in BSE BCVA)^2 and (change in WSE BCVA)^2
p. Change in EQ-5D utility on (change in BSE BCVA)^2 and (change in WSE BCVA)^2

For part *o* and *p*, where change in BSE BCVA < 0 the (change in BSE BCVA)^2 should be transformed by multiplying by -1, and likewise for the change in WSE BCVA.

Section A: Clarification on effectiveness data

A1.Table 139 (page 229 of the company submission) states that the Campochiaro 2008 paper was excluded from the systematic review of clinical effectiveness because "pooled results (BRVO and CRVO)" were reported. However, Figure 5 on page 797 of the Campochiaro paper provides separate results for the branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) groups for median change from baseline in visual acuity (VA) and it appears to fulfil the eligibility criteria for the search strategy listed in Table 6 (page 46 of the company submission).

A broad systematic literature review was conducted to locate studies which provided data on the clinical efficacy of aflibercept and of comparator treatments for use in an indirect treatment comparison. As you highlight, data was presented separately in the Campochiaro 2008 paper for BRVO and CRVO and therefore this paper should not have been excluded on this basis. However, the study did not meet the inclusion criteria as it was uncontrolled and open-label and therefore, albeit for different reasons, the exclusion of the paper was correct.

A2. Mortality has not been specified as an outcome in the eligibility criteria for the search strategy for the review of clinical effectiveness (Table 6, page 46 of the company submission). Please clarify if mortality was used as an outcome in the search strategy.

In order to identify studies relevant to the decision problem broad searches were conducted at the level of drug, disease area and study type, thus ensuring no studies of interest were missed. Each citation identified from the search was then assessed for appropriateness. It was at the point of citation review that inclusion/exclusion criteria were applied. The omission of 'mortality' from table 6 was an error for which we apologise. Please note that specific searches were also conducted to locate studies investigating an association between BRVO and mortality risk (Submission appendix 11).

A3. The eligibility criteria for the search strategy for the systematic review of clinical effectiveness (table 6, page 46 of the company submission) states "recent systematic reviews and meta-analyses" as an inclusion criteria. Please provide a definition of the term "recent".

Please ignore the word "recent". No data limits were applied and all systematic reviews and meta-analyses were captured in the SLR.

A4. The company submission states that the subgroups were determined by the stratification of best corrected visual acuity (BCVA) at baseline in VIBRANT (page 268 of the company submission). However, further clarification is not provided. Please clarify how the BCVA subgroups 24-34 letters and 35-73 letters were determined.

In the VIBRANT study, the protocol specified that randomisation was stratified according to baseline BCVA i.e. >20/200 [≤34 letters] and ≤20/200 [≥35 letters]). The inclusion criteria of the VIBRANT study in terms of BCVA was 73 to 24 letters (see Table 10 of the submission).

Combining the stratification and inclusion criteria results in the BCVA subgroups that were assessed in the cost-effectiveness analysis:

- BCVA 24-34 letters
- BCVA 35-73 letters

A5. Please specify by treatment arm, what number of study eyes in VIBRANT had a BCVA better or equal to that of the fellow eye at:

a. baseline

b. at 24 weeks/6 months pre cross over

c. at end of trial

Please note that VIBRANT was not a 'cross-over' study. Patients in the trial were able to switch treatments according to pre-defined criteria (see Tables 11 & 12 of the submission). Patients on aflibercept who met these criteria were able to have a laser treatment at week 36. Patients in the laser arm were able to switch to aflibercept from week 24 if the criterion for switching was met. In the answers which follow we have changed the terminology from 'cross-over' to 'switch' to better reflect the design of the VIBRANT study.

In VIBRANT, the study eye (at baseline) was the worse-seeing eye in approximately 98% of patients. Table 1 shows the number of eyes that had a BCVA better or equal to that of the fellow-eye at various timepoints in the trial.

Table 1. Number of 'study eyes' with better BCVA than the 'fellow eye'

	Aflibercept arm	Laser arm
Baseline	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

A6. <u>Priority Question</u>: The network meta-analyses inputs provided in Table 37 (page 114 of the company submission) only report percentages and means. Further details are provided in Appendix 7, however, there appear to be some discrepancies between the data in Table 37 and Appendix 7 (an error may have occurred where the lines for BRIGHTER and COMRADE-B in Table 37 may have been swapped over). In addition, the source of the data in Table 37 and/or Appendix 7 is unclear. Data for BRIGHTER and COMRADE-B appear to be sourced from the poster by Regnier and Bezlyak (2014), although BCVA data for BRIGHTER appears to be sourced from the abstract by Mones (2015). It is also not clear how the standard errors for the BRIGHTER and COMRADE-B studies have been estimated in Appendix 7. The method used does not appear to be consistent with the methods described in section 16.1.3.2 of the Cochrane Handbook for Systematic Reviews referenced on page 115 of the company submission.

Please provide a revised version of Table 37 confirming the full data used in the network meta-analyses (e.g., numerator and denominator for proportion gaining >15 letters and mean, standard deviation [SD] and number [n] for mean BCVA change from baseline). Please clarify that the references used to obtain the data are correct and provide any assumptions that may have been used to impute data if data was unavailable from the literature.

Apologies for the error in table 37 of the submission where BRIGHTER and COMRADE-B have indeed been swapped over in error. In addition the figures in table 37 which relate to the BRIGHTER study are wrongly reported. We can confirm that these errors are isolated to this table and that the data used in the indirect treatment comparison are for the appropriate studies (Appendix 7 of the submission).

Please find below a revised version of table 37 confirming the full data used in the network meta-analyses (e.g., numerator and denominator for proportion gaining >15 letters and mean, standard deviation [SD] and number [n] for mean BCVA change from baseline) together with the data source for each figure.

Calculation of standard errors

Where standard deviation was available (VIBRANT, BRAVO, Pichi 2014 and Tan 2014) the following formula was used to calculate the SE:

$$SE = \frac{SD}{\sqrt{n}}$$

Where only the confidence intervals were available (RABAMES) the following formula was used to calculate the SE:

$$SE = (UCI - LCI)/3.92$$

In COMRADE-B and BRIGHTER there was no SD reported and no further information was available to calculate the SE. The method detailed in the Cochrane Handbook 16.3.1.2 was not used because there was not enough information reported in the abstract and poster for COMRADE-B and BRIGHTER. In order to apply the formula reported in the Cochrane handbook a standard deviation needs to be reported for the baseline and final values. The studies included in the NMA only reported the standard deviation for the mean change in BCVA from baseline. In lieu of this information, only a weighted average SD could be calculated based on the studies identified in the literature review. This was then applied to the first formula detailed above to calculate the SE.

$$\frac{\sum_{i=1}^{n}(SD_i\ N_i)}{\sum_{i=1}^{N}(N_i)}$$

n = number of arms across all trials
N = number of patients per arm

The SD calculations were performed in excel before implementing in Winbugs. A check on this calculation has identified that the weighted SD for the nine studies identified in the literature search should be 12.37 and not 11.07. This difference does not affect the indirect comparison regarding the proportion of patients gaining 15 or more letters from baseline, the results of which were used in the economic model. However, the difference has a very small (i.e. a fraction of a letter) impact on the indirect comparison concerning the number of letters gained from baseline - Table 2.

Table 2. Indirect comparison – change in BCVA from baseline

Comparison	Mean	Median	2.5% CrI	97.5% CrI
Ranibizumab vs aflibercept fixed effects				
Submitted results	-2.68	-2.68	-7.43	2.05
New SD results	-2.57	-2.60	-7.46	2.41
Ranibizumab vs aflibercept random effects				
Submitted results	-2.56	-2.59	-12.25	7.41
New SD results	-2.51	-2.50	-12.27	7.28
Dexamethasone vs aflibercept fixed effects				
Submitted results	-10.59	-10.59	-16.08	-5.10
New SD results	-10.47	-10.49	-16.22	-4.59
Dexamethasone vs aflibercept random effects				
Submitted results	-10.46	-10.51	-22.25	1.54
New SD results	-10.39	-10.37	-22.27	1.51

Table 3. Revised table 37 from the submission

Study	Treatment arm	Proportion of patients gaining ≥15 letters	Mean BCVA change from baseline	Source of data/Comments
Base case				
VIBRANT	Aflibercept	n= 91, r=48 52.7%	μ= 17.00 SD= 11.88 n= 91	VIBRANT CSR SE was calculated using the SD and n from the CSR using the formula detailed in section 7.7.3.2 from the Cochrane Handbook.
	Laser	n=90, r=24 26.7%	μ= 6.90 SD= 12.91 n= 90	
BRAVO	Ranibizumab 0.3mg	n=134, r=74 55.2%	μ= 16.60 SD= 11 n= 134	Peer-reviewed publication (Campochiaro et al., 2010) SE was calculated using the SD and n from the publication using the formula detailed in section 7.7.3.2 from the Cochrane Handbook.
	Ranibizumab 0.5mg	n=131, r=80 61.1%	μ= 18.30 SD= 13.2 n= 131	
	Sham + Laser	n=132, r=38 28.8%	μ= 7.30 SD= 13 n= 132	
BRIGHTER	Ranibizumab 0.5mg	n=142, r=71 50%	μ= 13.05 SD= NR n= 142	Mean BCVA change from baseline: Abstract (Mones, 2015) A weighted average was taken between the ischemic and non-ischemic groups in the trial reported in the abstract. SD was not reported. Proportion of patients gaining ≥15 letters: Poster (Regnier et al., 2014)
	Ranibizumab 0.5mg + Laser	n=143, r=69 48%	μ= 12.84 SD= NR n= 143	
	Laser	n=69, r=18 26%	μ= 5.55 SD= NR n= 69	

COMRADE-B	Ranibizumab 0.5mg	n=124, r=76 61.3%	μ= 17.00 SD= NR n= 124	Poster (Regnier et al., 2014) SD was not reported.
	Dexamethasone	n=117, r=43 36.8	μ= 9.10 SD= NR n= 117	
Included in sensitivity analyses				
Azad, 2012	Ranibizumab 0.5mg + Laser	n=10, r=3 30.0%	μ= 12.25 SD= NR n= 10	Peer-reviewed publication (Azad et al., 2012) SD was not reported.
	Ranibizumab 0.5mg + Laser	n=10, r=4 40%	μ= 12.70 SD= NR n= 10	
	Laser	n=10, r=1 10%	μ= 4.85 SD= NR n= 10	
Parodi, 2008	Laser	n=16, r=6 37.5%	μ= 9.25 SD= NR n= 16	Peer-reviewed publication (Parodi et al., 2008) SE was calculated using the SD and n reported in the publication.
	Observation	n=15, r=0.5 3.3%	μ= -6.50 SD= NR n= 15	
Pichi, 2014	Dexamethasone	NR	μ= 8.80 SD= 7.3 n= 25	Peer-reviewed publication (Pichi et al., 2014) SE was calculated using the SD and n reported in the publication.
	Dexamethasone + Laser	NR	μ= 9.50 SD= 7.95 n= 25	

Tan, 2014	Ranibizumab 0.5mg	n=15, r=8 53.3%	μ= 12.50 SD= 19.3 n=15	Peer-reviewed publication (Tan et al., 2014) SE was calculated using the SD and n reported in the publication.
	Sham + Laser	n=21, r=4 19.0%	μ= -1.60 SD= 18.2 n= 21	
RABAMES	Ranibizumab 0.5mg	n=10, r=7 70%	μ= 17.00 SD= NR n= 10	Peer-reviewed publication (Pielen et al., 2015) SD was not reported. SE was calculated using the confidence intervals reported in the publication.
	Ranibizumab 0.5mg + Laser	n=10, r=7 70%	μ= 6.00 SD= NR n= 10	
	Laser	n=10, r=2 20%	μ= 2.00 SD= NR n= 10	

Section B: Clarification on cost-effectiveness data

As notified to NICE on the 2 February the list price used for ranibizumab in the submitted cost-effectiveness model was £742.17 per vial. The price should be £742 per vial to reflect a change in NHS list price for ranibizumab. The table below shows the submitted basecase ICERs and the corrected basecase ICERS using the current ranibizumab NHS list price.

All cost-effectiveness results presented in this section use the PAS price for aflibercept and the NHS list prices for comparator treatments.

Table 4. Basecase cost-effectiveness results

Comparison	ICERS (RAN price = £742.17)	ICERs (RAN price = £742)
1a: Aflibercept 1st line versus laser followed by ranibizumab for treatment failures	£8,939	£8,943
1b: Aflibercept 1st line versus laser followed by dexamethasone for treatment failures	£14,303	£14,303
1c: Aflibercept 1st line versus laser followed by aflibercept	£15,365	£15,365
2a: Laser followed by aflibercept for treatment failures versus laser followed by ranibizumab in treatment failures	Dominant	Dominant
2b: Laser followed by aflibercept for treatment failures versus laser followed by dexamethasone in treatment failures	£11,792	£11,792

B1a. Priority Question: Please provide the following patient count data separately for all patients in (a) the study eyes of the aflibercept treatment arm of VIBRANT and (b) the study eyes of the laser treatment arm of VIBRANT separately for:

i. T0= baseline to T1= 24 weeks / 6 months pre cross over

ii. T0= 6 months to T1= 1 year among those remaining on their original treatment

iii. T0= 6 months to T1= 1 year among those crossing over

These data can be presented within an Excel spreadsheet.

		BCVA T_1				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**
BCVA T_0	**VA1**	n=???	n=???	n=???	n=???	n=???
	VA2	n=???	n=???	n=???	n=???	n=???
	VA3	n=???	n=???	n=???	n=???	n=???
	VA4	n=???	n=???	n=???	n=???	n=???
	VA5	n=???	n=???	n=???	n=???	n=???

b. Please provide the data specified in B1a, separately for the subgroups with a baseline (1) BCVA in VA1, (2) BCVA in VA2, (3) BCVA in VA3, (4) BCVA in VA4 and (5) BCVA in VA5.

Please find the tables requested in worksheet 'Question B1' of the attached Excel file (EYL_BRVO_ID844_ClarificationQuestions).

For B1b the question has been interpreted that baseline refers to the visual acuity of patients at the beginning of the trial. For example, for VA2 in the aflibercept arm there were 31 patients at baseline. 28 patients who initiated treatment with aflibercept remained on treatment and three switched to laser. For the 28 who were in VA2 for aflibercept at baseline and remained on the same treatment during the whole trial, at six months there were 18 patients in VA1 and 10 in VA2. At 12 months there were 18 patients in VA1, 9 patients in VA2 and 1 patient in VA3.

B2. Priority Question: Please provide the patient numbers that underlie the following cells D85:H98, U91:Y98, D103:D116 and U109:Y116 of the Shift_Tables worksheet for the patient subgroups with a baseline for their study eye of a (1) BCVA in VA1, (2) BCVA in VA2, (3) BCVA in VA3 and (4) BCVA in VA4. These data can be presented within an Excel spreadsheet.

Please find the tables requested in worksheet 'Question B2' of the attached Excel file (EYL_BRVO_ID844_ClarificationQuestions)

B3. Priority Question: Please provide the following treatment administration count by those who did not cross over and those who did cross over by 4 week treatment cycles during the VIBRANT trial in each treatment arm.

Example table of results

	Aflibercept treatment arm				**Laser treatment arm**			
	No cross over		Crossed over		No cross over		Crossed over	
N admin of	Aflib.	Laser	Aflib.	Laser	Aflib.	Laser	Aflib.	Laser
Cycle 1	n=???	n.a.	n=???	n=???	n.a.	n=???	n=???	n=???
Cycle 2	n=???	n.a.	n=???	n=???	n.a.	n=???	n=???	n=???
etc…	n=???	n.a.	n=???	n=???	n.a.	n=???	n=???	n=???

As per question A5, the VIBRANT trial was not a crossover study. Patients could change treatment from the 6-month timepoint dependent of pre-specified criteria. Please see the treatment schedule for the study in Figure 1.

- Irrespective of individual response to treatment, patients randomised to aflibercept received aflibercept every 4 weeks until week 24 and then every 8 weeks thereafter. Patients could receive laser at week 36 if they met the criteria for rescue treatment (see section 4.3.3.4 of the submission).

- Patients randomised to laser received laser at baseline and then at weeks 12, 16, or 20 if required (see table 12 of the submission). From week 24, if the criteria for rescue treatment was reached aflibercept was given every 4 weeks until the end of the study.

Figure 1. Treatment schedule in the VIBRANT study

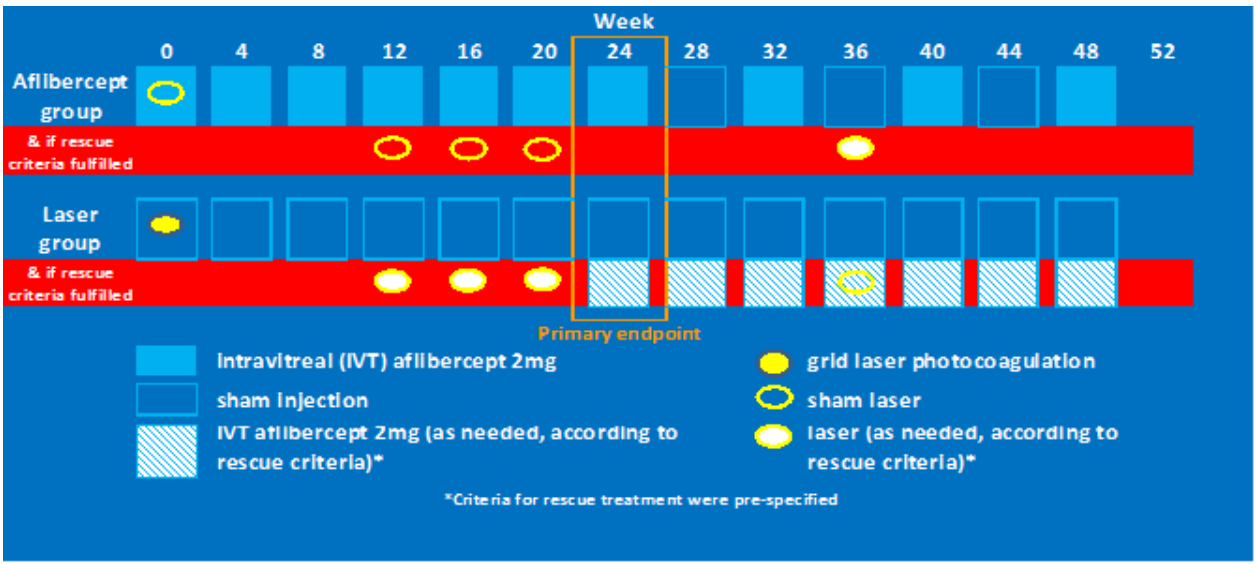

Table 3 is a simplified version of the example table suggested. This table aligns to the study design and provides the treatments received for each randomised treatment group per model cycle.

Table 5. Treatment received in each randomised treatment arm (full analysis set)

	Aflibercept arm (N=91)		Laser arm (N=90)	
N admin of	**Aflibercept (n)**	**Laser (n)**	**Aflibercept (n)**	**Laser (n)**
Week 0	91			90
Week 4				
Week 8				
Week 12				
Week 16				
Week 20				
Week 24				
Week 28				
Week 32				
Week 36		9		
Week 40				
Week 44				
Week 48				

B4. Priority Question: Please provide the following anonymised patient level data at baseline assessment and at each EQ-5D collection point thereafter for the VIBRANT trial:

a. ***the BCVA in the study eye (SE BCVA)***

b. ***the BCVA in the non-study eye (NSE BCVA)***

c. ***the EQ-5D value assessed by the UK social tariff.***

Please record missing data should be recorded as "..". There is no requirement for the patient level data to be grouped by trial arm or ordered in any particular way. These data can be provided within an Excel spreadsheet.

	Baseline assessment			**1st EQ-5D assessment**			**Etc…**
	SE BCVA	NSE BCVA	EQ-5D	SE BCVA	NSE BCVA	EQ-5D	Etc…
Patient 1	???	???	???	???	???	???	Etc…
Patient 2	???	???	???	???	???	???	Etc…
etc…	???	???	???	???	???	???	Etc…

If specific analyses are required please let us know so that these can be provided. However, we are unable to provide patient level data as it is against Bayer policy to disclose this information.

B5. Please list all the variables of interest that were initially tested using OLS regression models in the EQ-5D analysis.

Please see Table 6.

Table 6. Variables tested initially using OLS regression models

Group	Parameter
Patient characteristics	Age
	Sex
	BMI
	Race: Asian
	Race: Black
	Race: White
	Race: Hawaiian / Pacific Islander
Clinical characteristics	BCVA (Best seeing eye)
	BCVA (Worst seeing eye)
	Ln[(BCVA (Best seeing eye)]
	Ln[BCVA (Worst seeing eye)]
	Duration of BRVO
	Central retinal thickness
	Intraocular pressure
	Perfused disease

B6. Has the company undertaken or commissioned any repeated measures analysis of the VIBRANT EQ-5D data? If so, please provide the results of this.

Repeated measures were considered using a random effects model with subject as the random intercept. The random effects model provided similar results to the OLS model (table 206 in the submission), however the OLS model was preferred for several reasons:

1. While the coefficients in the random effects model were similar to those of the OLS model none were significant whereas two coefficients were significant in the OLS model. This implies that there were no significant predictors of quality of life in the dataset (including BCVA in BSE and WSE) when the random effects model is used
2. The R^2 of the OLS model was superior (0.04 vs 0.03) and therefore the OLS model explains a greater proportion of the variance in the dataset than the random effects model
3. The additional complexity of the random effects model is not justified given the above two points

The model specification for the random effects repeated measures model is provided in Table 7.

Table 7.

	Coefficient	Standard error	Z	P>|z|	[95% Conf. Interval]	
Age	-0.0007	0.0012	-0.64	0.52	-0.0030	0.0015
BCVA (BSE)	0.0018	0.0012	1.53	0.13	-0.0005	0.0041
BCVA (WSE)	0.0007	0.0005	1.46	0.15	-0.0003	0.0017
Constant	0.7070	0.1390	5.09	0.00	0.4346	0.9795
Sigma u	0.1488					
Sigma e	0.1195					
Rho	0.6081					

On receipt of this question we have taken the step of estimating the utilities (using the repeated measures results) for the visual acuity health states used in the model. In addition these utilities have then been used to estimate cost-effectiveness for the different treatment comparisons. The predicted utilities, based on an age of 65 years, are in Table 8. Cost-effectiveness results are in Table 9.

The results of this analysis provide a narrower range of utility values for the health states in comparison to the OLS estimates showing a reduced impact of decreased vision on quality of life. As expected, this reduction of the impact of vision on quality of life leads to an increase in the ICERs for the different treatment comparisons. However, EQ5D is recognised as not being appropriate in the context of vision and therefore the results presented in the basecase using Czoski-Murray utility values are more relevant for decision-making.

Table 8. Utility values estimated using the repeated measures EQ5D coefficients

		BCVA (BSE)				
		90.0	**72.5**	**57.5**	**42.5**	**17.5**
BCVA (WSE)	**90.0**	0.8865				
	72.5	0.8743	0.8428			
	57.5	0.8638	0.8323	0.8053		
	42.5	0.8533	0.8218	0.7948	0.7678	
	17.5	0.8358	0.8043	0.7773	0.7503	0.7053

Table 9. Cost effectiveness results using repeated measure utility values

	EQ5D (OLS model estimates as per submission)*	EQ5D (Random effect model repeated measures)
Comparison 1a	£14,854	£23,090
Comparison 1b	£23,971	£37,337
Comparison 1c	£25,471	£39,604
Comparison 2a	Dominant	Dominant
Comparison 2b	£20,289	£31,741

*RAN list price of £742

B7. Please present the VIVID/VISTA EQ-5D OLS regression coefficients that were used by the company in its submission for the appraisal of aflibercept for treating diabetic macular oedema (technology appraisal guidance 346 [TA 346]) and which have been redacted from Table 27 of the ERG report for TA 346.

Please find the information requested in Table 10.

Table 10. VIVID/VISTA Eq-5D OLS regression (table 27 of redacted ERG report)

	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]

B8. Page 188 of the company submission states '….NICE guidance stating that EQ-5D is not sufficiently sensitive to changes in visual acuity…'. Please provide a reference for the NICE guidance, and page reference(s), that states that the EQ-5D is not sufficiently sensitive to changes in visual acuity.

- Technical Support Document No.8 states that evidence the EQ-5D is probably not appropriate for assessing the impact of hearing loss, some specific forms of visual impairment, and schizophrenia (Technical Support Document No.8 page 22).

- Non-EQ-5D derived utility values have been accepted in previous back of the eye conditions e.g.TA346, FAD section 4.10; TA283, FAD - section 4.15. In TA346 the committee "concluded that the Czoski-Murray et al utility values, although not ideal, were an acceptable basis for its decision-making"

- A NICEQol project, funded by the MRC and NIHR, was conducted to determine whether commonly used generic-preference based measures of health care are appropriate for key conditions. The review found that EQ-5D performs well in studies of cancer and skin conditions; however is likely to be inappropriate for studies of hearing disorders and some visual impairment (http://www.brunel.ac.uk/herg/news/ne_356313 -page vi)

B9. Please provide the following data:

a. The patient/event counts that would underlie the 24 week pre-cross over corollary of the patient numbers that underlie Table 71 (adverse event rates, page 188 of the company submission).

b. The patient numbers underlying Table 71 (1year) split by crossover status.

c. Clarify whether these data are patient count data; i.e. the number of patients experiencing at least one event, or event count data.

	24 weeks	1 year
Aflibercept pre-switch over Cataract IOP	 n=??? n=???	 n=??? n=???
Aflibercept switch Cataract IOP	 n.a. n.a.	 n=??? n=???
Laser pre-switch over Cataract IOP	 n=??? n=???	 n=??? n=???
Laser post-switch Cataract IOP	 n.a. n.a.	 n=??? n=???

The monthly rate for aflibercept in table 71 is based on 1 event each of cataract and IOP in the aflibercept group. Both events occurred during the first 24 weeks of the study.

The Clark paper (reference 25 from the submission) reports an event of IOP between weeks 24 and 52 of the study, however this event was described as mild. The approach to adverse events was not to include mild or transient events and therefore table 71 is incorrect and should have a monthly rate of zero for this event for laser. The model has been updated accordingly and the results are reported in Table 11. As can be seen the model results are minimally affected. This is because IOP was associated with no disutility in the model and because the event has very low costs (see table 87 of the submission).

Table 11. Revised cost-effectiveness results after correcting the adverse event rate for laser photocoagulation

Comparison	Submission ICER	Corrected IOP laser rate ICER
1a: Aflibercept 1st line versus laser followed by ranibizumab for treatment failures	£8,943	£9,099
1b: Aflibercept 1st line versus laser followed by dexamethasone for treatment failures	£14,303	£14,484
1c: Aflibercept 1st line versus laser followed by aflibercept	£15,365	£15,644
2a: Laser followed by aflibercept for treatment failures versus laser followed by ranibizumab in treatment failures	Dominant	Dominant
2b: Laser followed by aflibercept for treatment failures versus laser followed by dexamethasone in treatment failures	£11,792	£11,792

B10. The clinical data in the SHIFT_TABLES worksheet and the Transistion_MX worksheet do not appear to have been implemented probabilistically. Please clarify whether they have been implemented probabilistically. If the clinical data have been implemented probabilistically, please highlight where in the model this has been implemented.

The transition matrices from the MSM package used in the base case, and the shift tables used in a scenario analysis, have not been implemented probabilistically. In terms of the MSM package we are not aware of any methods to test the transition matrices for aflibercept and laser probabilistically. Regarding the shift tables, they are based on counts of real observations from patient level data, for which there is no uncertainty. In addition, it would not be possible to implement the shift tables probabilistically due to the transitions being interrelated i.e. changing the transitions from one VA health-state to another has a knock-on effect to every other transition between every other VA health state. For example, if more patients move from VA2 to VA1 then adjustments would need to be made to the transitions between VA2 and healthstates VA3 to VA5 in order for transitions to sum to 1.

The base case transition matrices for ranibizumab and dexamethasone are derived by applying the odds ratio (OR) from the NMA to the transition matrices for aflibercept (see section 5.3.2.3.1 of the submission for a description of the methodology). These transition matrices have been tested probabilistically using the credible intervals for the OR obtained from the NMA (see Tx_Input tab in the cost-effectiveness model, cells L19:O19 and L28:O28). This results in more/less favourable transition matrices for the comparator treatments relative to aflibercept.

B11. Please clarify how the respondents for the resource use survey (referenced in section 5.5.2.2.1, of the company submission) were identified. Please provide a copy of the online resource use questionnaire or access to the online survey.

Please find attached a copy of the questionnaire.

In total 569 ophthalmologists were invited to participate in the survey. These ophthalmologists were from a database held by 'Medical Radar', the external agency conducting the survey. Other than passing the screening criteria no other 'selection' criteria were applied. The screening criteria were utilitised to ensure ophthalmologists suitably experienced in the management of BRVO completed the survey.

B12. Section 5.5.2.1 (page 203 of the company submission) states that some of the costs associated with treatment failures and adverse events were taken from NCWC/NICE. Please provide the specific unit costs and reference(s) for each of the unit costs drawn from NCWC/NICE guidelines.

The costs associated with treatment failures and adverse events, and the references, are detailed in Table 12 and Table 13 below (Table 86 and Table 87 in the submission).

The only health state which is associated with an additional cost is for blindness in both eyes (VA5, VA5) (detailed in section 5.5.3 in the submission). In addition to the cost of treatment, administration and adverse events, an annual cost of £7,429 was added as the cost of blindness as reported in McCrone et al. (2008). This is consistent with the NICE assessment of ranibizumab in CNV for pathological myopia (National Institute for Health and Care Excellence, 2013).

Table 12. Unit costs; administration and monitoring

Resource	Cost (per patient)	Source (Department of Health, 2014-15)
Administration anti-VEGF	£53.96	RD40Z Ultrasound less than 20 minutes without contrast
Administration dexamethasone	£266.25	Weighted cost 75% BZ86B Day case, Intermediate Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1, 25% BZ87A Outpatient, Minor Vitreous Retinal Procedures, 19 years and over
Monitoring visit	£150.07	Consultant led outpatient attendance service, code 130 + administration cost

Table 13. Unit costs of treating adverse events

Adverse event	Cost (per patient)	Source (Department of Health, 2014-15)
Cataract	£1,160.65	BZ34A Cataract Extraction and Lens Implant, with CC Score 4+ plus 3x consultant led outpatient attendance service code 130 (£872.31 + (3 x £96.11))
Ocular hypertension (IOP)	£3.57	NICE aflibercept in CRVO submission (National Institute for Health and Care Excellence, 2014)

B13. The patient count data in the Shift_Tables worksheet suggests a denominator for laser of 90. The discontinuation data in the Tx_Inputs worksheet suggests a denominator of 92. Please clarify which data are correct.

The denominator in the Shift_Tables tab is correct at 90 patients. When this is corrected in the Tx_Inputs tab for discontinuation and AEs, the effect on the ICER is minimal (see Table 14.

Table 14. Cost-effectiveness results: corrected denominator

Comparison	Submission ICER	Corrected laser denominator ICER
1a: Aflibercept 1st line versus laser followed by ranibizumab for treatment failures	£8,943	£8,956
1b: Aflibercept 1st line versus laser followed by dexamethasone for treatment failures	£14,303	£14,304
1c: Aflibercept 1st line versus laser followed by aflibercept	£15,365	£15,365
2a: Laser followed by aflibercept for treatment failures versus laser followed by ranibizumab in treatment failures	Dominant	Dominant
2b: Laser followed by aflibercept for treatment failures versus laser followed by dexamethasone in treatment failures	£11,792	£11,792

B14. The patient count data in cells U70:Y77 of the Shift_Tables worksheet suggests 53, 62, 64, 64, 66, 66, 67, 67 patients having crossed over in the laser treatment arm for cycles 6 to 13 respectively. Given the 90 patients in the laser treatment arm this suggests cross over percentages of 58.9% and given rounding of 10%, 2%, 0%, 2%, 0% and 2%. While the CBH worksheet suggests percentages of 58.9% and given rounding of 10%, 2%, 0%, 2%, 1% and 0%. Please clarify which worksheet is correct.

The percentages in the CBH worksheet (58.9%, 10%, 2%, 0%, 2%, 1% and 0%) are not linked to any cells in the model and should be removed.

The patient count data in cells U70:Y77 of the Shift_Tables worksheet are correct and are the values currently used in the model for the implementation of the switching strategy as observed in the VIBRANT trial.

B15. For 2nd line laser there is a 0.0025% probability of patients in VA1 transitioning to VA5. Given the trial patient numbers, it is unclear how the transition probability was estimated. Please clarify how this transition probability was calculated and the calculation used.

Transition probabilities were derived using the MSM package in R. As described in the submission dossier (section 5.3.2.3.1), this package allows a general multi-state model to be fitted to longitudinal data to model transition intensities. This method makes use of all available data and does not discard observations at intermediate time points. In this specific case the transitions of patients from the VIBRANT trial were converted to the 4 weekly cycles used in the model. Therefore, the 0.0025% does not represent the transition of a patient from the beginning to the end (6 months to 12 months in this case), instead it represents the average patient's transition over 6 time points. In summary it represents the expected transition over a 4-week time period. For example, if a patient moves from VA1 to VA5 for 2 cycles and then transitions back, a small probability of moving from VA1 to VA5 will be captured by the MSM package. All the calculations were conducted in R and therefore cannot be summarised.

B16. The submission states that there are no efficacy data for aflibercept for the maintenance phase. Please clarify whether a literature search has been undertaken to identify any follow-up studies for any treatment for BRVO or CRVO which might support the assumption of stable vision for 5 years during maintenance. If follow-up studies for other treatments for BRVO or CRVO have been identified, please clarify whether these studies support the assumption of stable vision for 5 years during maintenance.

A specific literature search for follow-up studies for any treatment in CRVO and BRVO has not been conducted. However, the RCO guidelines summarise the experience in BRVO and are supportive of the assumption of stable vision for the 4 year maintenance phase. In these guidelines it is stated that the "natural history of MO due to BRVO indicates that MO may resolve or reduce over time". As MO is responsible for the vision loss it is reasonable to assume that on its resolution vision would be stable. The guidelines summarise the longer-term experience of ranibizumab in BRVO with the evidence coming from follow-up of patients enrolled in the BRAVO study. The outcomes at 49 months (bolded text below) compare favourably to the results at 12 months i.e. 18.3 BCVA letter gain versus baseline (Brown et al 2011) and support the assumption of maintained vision used in the model.

> *"Further to BRAVO the open label extension of the HORIZON trial looked at 304 previous BRAVO patients with MO secondary to BRVO to assess the long term safety and efficacy of ranibizumab treatment. Patients entered the trial after one year in BRAVO and were enrolled for a further 12 months in HORIZON. Patients were seen at least every three months and given an intravitreal ranibizumab 0.5 mg if pre-specified retreatment criteria met. Patients were eligible to receive an intravitreal*

injection of 0.5 mg ranibizumab if visual acuity was less than or equal to 20/40 or center subfield thickness was ≥250 µm. Patients with BRVO were eligible for rescue grid laser therapy if BCVA was ≤20/40 (6/12) caused by MO. The mean change from baseline BCVA at 12 months was 0.9 in the sham/0.5mg, -2.3 in the 0.3/0.5mg ranibizumab and -0.7 in the 0.5mg groups respectively. There were no new adverse events identified. As such the long term administration of ranibizumab in a prn regimen was well tolerated and efficacious in patients with MO secondary to BRVO. ***The more recent RETAIN Study included 34 patients with BRVO in a prospective follow-up of a subset of patients from two phase three trials of ranibizumab in RVO. Over a mean follow-up of 49.0 months, 17 of 34 BRVO eyes (50%) had resolution of their oedema (defined as no intraretinal fluid for six months or more after the last injection). The last injection was given within two years of treatment initiation in 76%. The mean number of injections required in unresolved patients in year four was 3.2. In eyes where the oedema had resolved, a mean improvement in BCVA of 25.9 letters was achieved versus 17.1 letters (p= 0.09) in eyes with unresolved oedema.*** *This shows that the long-term outcomes of BRVO eyes treated with ranibizumab was excellent, although about half of them required continuing treatment."*

Sensitivity analyses were conducted in the original submission whereby the 4-year maintenance phase (basecase) was reduced to 3 and 2 years (table 91 of the submission). This change was not one of the top 15 drives of cost-effectiveness (figures 51-55 of the submission). As the model was relatively insensitive to reducing the maintenance period the actual figures for these scenario analyses were not presented. However, in response to this question the results are tabulated below. When a shorter duration of maintenance is used the ICER improves in the majority of the comparisons.

Table 15. Scenario analysis using different duration of maintenance

Comparison	Submission ICER	2 year maintenance	3 year maintenance
1a: Aflibercept 1st line versus laser followed by ranibizumab for treatment failures	£8,943	£9,069	£9,015
1b: Aflibercept 1st line versus laser followed by dexamethasone for treatment failures	£14,303	£13,498	£14,099
1c: Aflibercept 1st line versus laser followed by aflibercept	£15,365	£15,002	£15,313
2a: Laser followed by aflibercept for treatment failures versus laser followed by ranibizumab in treatment failures	Dominant	Dominant	Dominant
2b: Laser followed by aflibercept for treatment failures versus laser followed by dexamethasone in treatment failures	£11,792	£9,965	£11,238

Consolidated results

Two questions (B9 & B13) highlighted errors in the model. For completeness, Table 16 provides the results when the corrections for each question are combined.

Table 16. Consolidated cost-effectiveness results

Comparison	Submission ICER (RAN price £742)	Corrected ICER
Aflibercept 1st line versus laser followed by ranibizumab	£8,943	£9,116
Aflibercept 1st line versus laser followed by dexamethasone	£14,303	£14,489
Aflibercept 1st line versus laser followed by aflibercept	£15,365	£15,649
Laser followed by aflibercept versus laser followed by ranibizumab	Aflibercept dominates	Aflibercept dominates
Laser followed by aflibercept versus laser followed by dexamethasone	£11,792	£11,792

EYLEA – ID844: Additional Clarification questions (30 March 2016)

Please find below the responses to the additional clarification questions. We have not been able to conduct all of the additional analyses requested in the short timeframe given.

Could you provide the results of Table 7 and Table 8 of the response to clarification (response to question B6) for each of the eight model types listed in Appendix 13 on page 497 of the company submission, that is, in model types:

a. **OLS**
b. **OLS model including interaction terms (between BCVA, BSE and WSE)**
c. **OLS model including squared variables**
d. **Fixed effects model**
e. **Random effects model**
f. **Tobit model (assuming utility is censored at values above 1)**
g. **TPM using logit and OLS regression**
h. **TPM using logit and OLS with logarithmic utility decrements**

Can the analysis be presented for each model type based upon (i) the Linear BCVA model and (ii) the Logarithmic BCVA model, together with their associated R^2 and $\overline{R}^2$.

Could you also provide explanatory information to help interpret the analyses that were undertaken (similar to that found in the company response to question B6) which outlines that the random effects model included the subject as the random intercept. Alternatively, if an internal report has already been prepared on this work could you provide a copy of this.

Table 7

A technical report providing some of the information requested above is attached as a separate file (EYL_BRVO_ID844_EQ5DTechnicalReport_AIC). Where the requested information was not available from this report additional analyses have been conducted. These are provided in a separate excel file (EYL_BRVO_ID844_ClarificationQus_2ndset_AIC).

Table 8

Tables corresponding to Table 8 from the first set of clarification questions are in the separate excel file for models a – e. Estimating utilities from models f – h is much more complex and has not been possible in the time provided. However, the fitted Tobit and TPMs did not give

plausible results (for example the estimated TPMs resulted in negative coefficients for BCVA variables).

Figure 1 provides a summary of the information provided in the excel file. For each EQ-5D model (a-e), the figure shows:

1) the utility difference between perfect vision in both eyes and blindness in both eyes

2) the utility difference between perfect vision in both eyes and 'perfect vision in one eye and blindness in the other'

The narrow ranges between these health states, coupled with the very low R^2 values (maximum of 5%), confirms that EQ-5D is not sensitive to changes in visual acuity. These results are in keeping with the findings of the NICEQoL project, funded by the MRC and NIHR (Longworth L et al, 2014). One of the objectives of the research was to determine whether the EQ-5D was appropriate in visual disorders. The project showed that most studies using EQ-5D found little or no difference between groups defined by clinical measures of visual impairment.

Non-EQ-5D derived utility values have been accepted in previous back of the eye conditions e.g.TA346, FAD section 4.10; TA283, FAD - section 4.15. In TA346 the committee "concluded that the Czoski-Murray et al utility values, although not ideal, were an acceptable basis for its decision-making".

Reference

Longworth L, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess 2014;18(9).

Figure 1. Summary of the utility ranges for different vision-related health states

[Academic/commercial in confidence information removed]

Could you provide scatter plots of:

a) **changes in EQ-5D utility against the changes in BCVA(BSE)**

b) **changes in EQ-5D utility against the changes in BCVA (WSE) .**

For each patient, the data to be plotted would be the changes from baseline, based upon the longest period from baseline for which data exists for that patient; i.e. if a patient has some missing data in their end of trial measurement set then the last set of complete measurements before the end of trial should be used to calculate their changes from baseline.

Provided in a separate excel file (EYL_BRVO_ID844_ClarificationQus_2ndset_AIC).

Could you provide six additional OLS analyses based upon changes in the EQ-5D quality of life and changes in the BCVA as defined above could be conducted:

a) **Change in EQ-5D utility on intercept, against change in BSE BCVA and change in WSE BCVA**

b) **Change inEQ-5D utility on against change in BSE BCVA and change in WSE BCVA**

c) **Change inEQ-5D utility on intercept, against change in Ln BSE BCVA and change in Ln WSE BCVA**

d) **Change inEQ-5D utility on change in Ln BSE BCVA and change in Ln WSE BCVA**

e) **Change inEQ-5D utility on intercept, (change in BSE BCVA)^2 and (change in WSE BCVA)^2**

f) **Change in EQ-5D utility on (change in BSE BCVA)^2 and (change in WSE BCVA)^2**

For part *o* and *p*, where change in BSE BCVA < 0 the (change in BSE BCVA)^2 should be transformed by multiplying by -1, and likewise for the change in WSE BCVA.

We apologise but we have not been able to conduct these additional analyses in the time provided.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Aflibercept for treating visual impairment caused by macular oedema in branch retinal vein occlusion

1. About you and your organisation

Please note: this is a joint response from Royal National Institute of Blind People (RNIB) and Macular Society.

Your name: [redacted]
Name of your organisation: RNIB
Your position in the organisation: [redacted]
Brief description of the organisation: RNIB is the UK's leading charity offering information, support and advice to almost two million people with sight loss. We have over 13,000 members throughout the UK and 80 per cent of our Trustees are blind or partially sighted. We encourage members to get involved in our work and regularly consult them on matters relating to Government policy and ideas for change.

Name: [redacted]
Name of your organisation: [redacted]
Your position in the organisation: [redacted] at Macular Society
Brief description of the organisation: Macular Society is the specialist UK charity for people living with macular conditions. We are the largest patient member organisation in the eye care sector with nearly 16,000 members. We offer a range of support and information services to people with central vision loss, as well as their families and carers. We provide information for health professionals, campaign for better services, sponsor research and raise awareness of macular degeneration and its prevention.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

a) Patient experience

Macular Odema (MO) secondary to Branch Retinal Vein Occulsion (BRVO) damages central vision which is responsible for the perception of detail and colour vision. Patients report symptoms which range from initial blurriness to complete central vision loss- which they describe as 'large black shadow' or 'opaque patch' in the middle of their eye.

Sight loss as result of MO secondary to BRVO can have a negative impact on every-day living and quality of life; some of these examples are described below:

- Loss of independent living-difficulty with activities of daily life including mobility within and outside their home, ability to recognise faces and objects, reading, writing, personal grooming, self-management/ of medicines and/or devices if the patient has existing co-morbidities.
- Loss of personal safety
- Difficulties with night vision
- Increased risk of falls and fractures. Difficulties with appreciating the width and depth of stairs
- Inability to take care of their children and/or parents
- Loss of employment or reduced hours of employment leading to loss of income and dependence on benefits
- Increased anxiety and stress associated with sudden vision loss and fear of going blind
- Social isolation particularly at night time
- Loss of psychological and emotional well being.
- Dependence on spouses, family and friends who often give up or take significant time off work to provide practical and emotional support for a loved one

The emotional and psychological impact of sight loss through MO secondary to BRVO varies amongst individuals. However, many patients we have spoken to feared losing their sight the most out of

all five senses and ‘preferred to lose a limb’ as opposed to their sight.

Some patients have co-morbidities such as diabetes or hypertension in addition to their MO secondary to BRVO and their sight loss can obstruct their ability to self-manage their co-morbidities-this in turn may lead to other conditions and complications. For example a patient with diabetes and MO secondary to BRVO will have difficulties such as: taking a blood sample from their finger, inserting the test strip into the glucose meter, correctly reading the glucose meter readings, self-administering insulin, checking their feet for foot ulcers and discoloration.

Some patients may have an existing eye condition such as glaucoma which in the majority of cases is self-managed through eye drops. An inability to administer glaucoma eye drops correctly into one or both eyes could lead to irreversible sight loss.

In addition, patients tell us they have difficulties reading patient information leaflets which poses a potential risk to their personal safety. They also report being unable to travel to and from hospital appointments, particularly if there is limited public transport and do not have a caregiver to accompany them.

b) Caregiver experience

Some patients with MO secondary to BRVO are cared for by their family and friends. While families and friends do not perceive this as a burden, the practical and emotional support required can be a huge undertaking.

Treating a patient with Aflibercept, could improve a caregiver’s quality of life as it may reduce:

- Responsibility for tasks that the patient is no longer able to accomplish i.e. mobility within and outside the home, shopping, self grooming, cooking, cleaning, ironing
- Responsibility to remain in close proximity to the patient
- Responsibility to help the patient self-manage other conditions and/or co-morbidities
- Need to inform patient about hospital appointments and medical information pertaining to current/other treatments
- Responsibility to attend multiple hospital appointments

- Responsibility to provide practical and emotional support to the patient, which in turn can have an impact on the physical and psychological wellbeing of the carer
- Negative impact on employment, particularly if the caregiver is not self employed
- Financial constraints

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients tell us the most important outcome is to stop vision loss and irreversible visual damage. Patients want to lead independent lives- this includes being able to remain in employment, carry out every day activities and retain personal safety.

Most patients would also like an improvement in their vision.

All would prefer treatments with a little or no risk of complications and limited/no side effects.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition?

Collectively RNIB and Macular Society have a significant amount of experience of currently available treatments for MO secondary to BRVO.

This has been sourced from:
• Discussions with clinicians, patients and caregivers to examine the treatment of MO secondary to BRVO in England and Scotland and its impact on quality of life
• One to one discussions with clinicians and patients who have used Laser, Ranibizumab, Dexamethasone or Aflibercept to treat MO secondary to BRVO
• Reading peer-reviewed publications
• Summary of Product Characteristics for Aflibercept

• VIBRANT Study- examines the treatment of Aflibercept versus Laser Photocoagulation in MO secondary to BRVO. This study was conducted in 58 study sites in North America and Japan.

How acceptable are these treatments and which are preferred and why?

Treatments currently available for MO secondary to BRVO within NHS are Laser Photocoagulation, Ranibizumab, Avastin (Anti VEGFs) and Dexamethasone (steroid). Laser Photocoagulation, Ranibizumab and Dexamethasone are licensed treatments options for BRVO, while Avastin is not licensed in the UK for this indication.

Treatment with Ranibizumab and Dexamethasone are well tolerated and preferable to Laser Photocoagulation, which can cause retinal scarring, irreversible visual damage and little or no visual improvement. As such Laser Photocoagulation is seldom used within NHS.

Further details on acceptability and preferences of current treatments are discussed in section 4 below.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

We believe the advantages of Aflibercept are:

(I) Safe and effective treatment for MO secondary to BRVO as demonstrated by the VIBRANT study.

(II) Address an unmet clinical need - There is still an unmet clinical need for patients who are either unsuitable or unresponsive (or have a suboptimal response) to Ranibizumab, Dexamethasone and/or Laser Photocoagulation. For example patients with MO secondary to BRVO who are not responsive to Ranibizumab or Laser Photocoagulation and have raised intracocular pressure (IOP) will not be able to receive the steroid Dexamethasone (as prolonged steroid can amplify IOP) and will therefore need another treatment option i.e. Aflibercept.

Patients we have spoken to with MO secondary to BRVO said there was a noticeable improvement in their vision when they switched between treatments i.e. from Laser to Aflibercept. This in turn better helped them undertake day to day tasks safely-, they were no longer solely dependent on family, friends or their 'better seeing eye' to accomplish activities, all of which improved the quality of life for both the patient and caregiver.

(III) VIBRANT study- First study to compare Aflibercept solution for injection, with Laser Photocoagulation in the treatment of visual impairment due to MO secondary to BRVO. The study is a phase III randomised, double masked clinical trial conducted across 52 sites in North America and Japan. Monthly injections of 2 mg intravitreal Aflibercept provided significantly greater visual benefit and reduction in retinal thickness at 24 weeks in comparison to Laser photocoagulation treated eyes with macular oedema due to BRVO. These benefits were maintained in the 2mg Aflibercept group, with treatment regime reduced to every 8 weeks after week 24, through to week 52. 2mg Aflibercept rescue treatment for the Laser Photocoagulation group after week 24 gave rise to rapid improvements in Best Corrected Visual Acuity (BCVA) and retinal thickness (Campochiaro 2015; Clark et al 2015).

(IV) Posology for Aflibercept in MO secondary to BRVO states 'The recommended dose for Aflibercept is 2 mg aflibercept equivalent to 50 microlitres. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat and extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes.'

The dosing regimen for Aflibercept used in the VIBRANT study does not represent its current recommended posology. However, patients do find the posology of this treatment extremely useful as they can work with their ophthalmologist to identify approximate appointment timeframes that meet their individual needs, particularly if they are in employment or a caregiver.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Although NICE recommend Laser Photocoagulation as a first line treatment for MO secondary to BRVO, patients do experience retinal scarring, loss of visual acuity and colour perception along with macular haemorrhage as a result of this therapy. Moreover, as previously discussed patients report visual improvements following Aflibercept treatment in comparison to Laser Photocoagulation.

As previously discussed, Eylea would provide another treatment option for patients, particularly those who are intolerant to Laser Photocoagulation and are unsuitable/unresponsive to Lucentis and Ozurdex. Aflibercept could address an unmet clinical need and improve the quality of life for both the patient and caregiver.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

We are not aware of any differences in opinion.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Reported disadvantages include:

(I) Unsuitability- Anti-VEGF treatments (including Aflibercept) are unsuitable for patients with prior medical history of strokes or heart attacks. Studies show long term suppression of VEGF may induce adverse cardiovascular events or stroke.

(II) Anxiety caused by intravitreal injection- Although patients are apprehensive about intravitreal injections, the thought of losing their vision makes the procedure bearable-they felt this was not a significant problem and the benefits of the treatment outweighed this disadvantage.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being

appraised, please tell us about them.

We are not aware of any differences in opinions.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

As discussed previously (question 4 part II) -Provision of another choice of treatment for patients i.e. Aflibercept for patients who are either unsuitable or unresponsive (or have a suboptimal response) to Ranibizumab, Dexamethasone and/or Laser Photocoagulation.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

As discussed previously (question 5 part I) - Aflibercept as with all anti-VEGFs may be unsuitable for patients with prior medical history of strokes or heart attacks.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

This treatment is not yet in routine use.

However, we would like to note that despite huge efforts many eye clinics in England are unable to sustain delivery services due to capacity issues. In some cases treatment intervals are being extended beyond clinically appropriate timeframes due to the sheer number of patients. This has been identified by recent

research carried out by both RNIB and Macular Society. Therefore, it is unlikely that NHS treatment interval will mirror the clinical trial treatment intervals.

Ophthalmologists are of course doing all they can to treat their patients, even putting on extra clinics in their free time (at evenings and weekends) which patients are extremely grateful for.

Also, in routine practice each patient's needs will determine the best choice of treatment for them and there will be many factors affecting that choice.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

VIBRANT study has captured many significant relevant outcomes. For economic evaluations of a new product, NICE uses the EQ-5D questionnaire, a quality-of-life assessment in which patients rate functioning on a 5-point scale in five areas- mobility, self-care, usual activities, pain/discomfort and anxiety/depression. However, EQ-5D it is not a suitable assessment for all eye conditions and is unable to differentiate patient severity within a particular eye condition.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

We are not aware of any.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ **X** No

If yes, please provide references to the relevant studies.

8. Equality

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

We do not believe there are any equality issues that should be considered.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐**X** No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

If this treatment is approved, we would hope the resulting guidelines state that:

- Clinicians should not have wait for the condition to progress before treating patients. This will ensure patients do not suffer avoidable irreversible damage to their vision.
- Aflibercept should be made available as a treatment option in any eye if deemed beneficial by the clinician and patient.
- Clear guidelines around switching between treatments. Again it is for the clinician and patient to decide which of the treatments is most appropriate.

We hope Aflibercept will be approved for first line treatment as laser is seldom used and causes retinal scarring. We would like NICE to re-assess its recommendations for Dexamethasone and Ranibizumab as we feel these should also be considered as first line treatments.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- VIBRANT clinical trials demonstrate Aflibercept to be a safe and effective treatment for MO secondary to BRVO and should therefore be made available without restrictions to NHS patients in England
- The provision of another choice of treatment i.e. Aflibercept for patients who are unsuitable or unresponsive to Ranibizumab, Dexamethasone or Laser photocoagulation could mean the difference between needlessly losing sight and saving existing sight.
- The provision of another choice of treatment i.e. Aflibercept could enable patients to better manage their condition and lead independent lives i.e. carry out daily living activities, self-manage existing co-morbidities, read, write, remain in employment
- The provision of another choice of treatment i.e. Aflibercept could have a positive impact on carers as it may reduce the responsibility for tasks that the patient is no longer able to accomplish and reduce the negative impact on their quality of life, physical and psychological wellbeing and employment (if employed).
- Aflibercept could address an unmet clinical need and improve the quality of life for both the patient and carer.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Aflibercept for treating visual impairment caused by macular oedema in branch retinal vein occlusion

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Winfried Amoaku

Name of your organisation: University of Nottingham/Nottingham University Hospital

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?✓
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Macular oedema secondary to BRVO has previously been treated with modified grid laser photocoagulation at 3 months or later following the event. That allowed haemorrhage to clear from the macula, as such haemorrhage confounded the interpretation of fundus fluorescein angiography that was required to guide treatment, and interfered with laser energy absorption. In addition the visual acuity should be 6/12 or worse. Only a minority of patients in clinical practice are eligible for this treatment, however, based on these recommendations. As such a significant number of eyes with macular oedema (MO) secondary to BRVO were not treated.
With the advent of pharmacological therapies, the condition is now treated with intravitreal injection of Dexamethasone implant (Ozurdex, Allergan) or ranibizumab (Lucentis, Novartis). Some specialists used off-license bevacizumab before the NICE recommended treatments became available, but such use has declined.
All eyes with the condition benefit from treatment with Dexamethasone implant (NICE TA229) or ranibizumab injections (NICE TA 283). Dexamethasone implants are administered at 4 months or longer intervals, whilst ranibizumab treatment is initiated with 3 injections at monthly intervals followed by a pro re nata regime.
Dexamethasone implant is avoided in eyes with uncontrolled glaucoma, or eyes that are likely to develop uncontrolled IOPs.
Aflibercept (Eylea, Bayer) is a pan-VEGF-A, VEGF-B and placental growth factor (PlGF) blocker that reduces vascular leakage secondary to RVO. Aflibercept (Eylea, Bayer) has recently licensed by the EMA for MO secondary to BRVO based on the VIBRANT Study, and have been shown to be beneficial in eyes with macular oedema secondary to BRVO. In the VIBRANT Study intravitreal aflibercept at monthly

intervals to week 20, were compared to laser photocoagulation at baseline (with 1 other possible laser as rescue). (From week 24 onwards, 8-weekly aflibercept is given to the aflibercept group.The laser group was allowed rescue with 3 monthly injections of aflibercept followed by 8 weekly.) Outcomes were assessed at weeks 24 and 52. A 15 letter gain was achieved in 52.7 % of aflibercept treated eyes compared to 26.7% in laser photocoagulation group ($p<0.0003$), and a 280.5µm reduction in CRT compared to 128.0µm in the aflibercept and laser groups respectively ($p<0.0001$) at 24 weeks. There were no non-ocular adverse events; there was traumatic cataract in the aflibercept injected group. Significantly, 3 eyes in the laser treated group developed retinal neovascularisation (which responded to scatter laser photocoagulation), but no cases of anterior segment neovascularisation. No cases of retinal or iris neovascularisation occurred in the aflibercept treated group. Although data is provided on duration of RVO at baseline, no data is provided on comparative outcomes for the macular oedema in those with short (<3 months) or longer ($\geq$3 months) duration of their RVO. At week 52, 15 letter improvement occurred in 57.1 vrs 41.1% of the aflibercept and laser/aflibercept groups respectively ($p=0.0296$).There was no comparison with ranibizumab, Ozurdex, or bevacizumab.

All patients with macular oedema secondary to BRVO would benefit from treatment, as there are no differences in the benefits derived from treatment in different groups of patients irrespective of VA or degree of global retinal ischaemia.

It is expected that the technology will be used in retinal clinics under the supervision of specialists. Currently, such services are provided in secondary care, and are supported by appropriate equipment. It is expected that irrespective of the site of carte provision with this technology, similar equipment and expertise will be available. The technology is already available and is currently used in the treatment of neovascular AMD, diabetic macular oedema, and macular oedema secondary to central retinal vein occlusions in the NHS under license and appropriate NICE TAs.

The RCOphth RVO Guidelines published in July 2015 provides robust review of the treatments for RVO, and makes recommendations for treatment of eyes with MO secondary to RVO (CRVO and BRVO).

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The technology will be comparable to ranibizumab in the treatment of macular oedema secondary to BRVO. A prn regime is expected after initiation of treatment with 3 injections at monthly intervals. A fixed 8 weekly treatment (after initiation) may allow service planning. However, such a plan is not optimal for patient outcomes as it may result in over-treatment of some patients, and an under-treatment of others. Monitoring (clinical examination and OCT) is also necessary in order to determine continuing efficacy/benefit.

The rules for commencing treatment and stopping rules are well summarised in the RCOphth RVO Guidelines. These guidelines also advise on additional testing, and rules for discontinuing treatment that will apply to Ozurdex, ranibizumab and aflibercept.

The most important outcomes in the management of patients with macular oedema secondary to BRVO are VA, OCT (retinal thickness measurement), and clinical examination. These are the same parameters as were measured in the VIBRANT Study. Current UK practice is reflected in the clinical trials up to a point. Currently,

aflibercept is not used in the treatment of MO secondary to BRVO in England. Re-treatment with ranibizumab is based on clinical findings: treatment until stability achieved ff by prn or treat and extend (rather than fixed dosing as used in the VIBRANT Study), and dependent on the particular treatment option. It is expected that aflibercept regime would be similar.
The adverse events are not different from those associated with treatment with this technology for other conditions eg CRVO, and AMD. There are no new concerns regarding adverse events compared to that reported from clinical trials.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

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Single Technology Appraisal (STA)

There are no concerns regarding equality and diversity.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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Single Technology Appraisal (STA)

There are no issues with implementation.
All the required resources are in place.

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Please do not exceed the 8-page limit.

About you

Your name: Mr Ian Pearce Consultant Ophthalmologist

Name of your organisation: St Paul's Eye Unit, The Royal Liverpool University Hospital

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
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Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Retinal Vein Occlusion (RVO) is presently managed differently dependent on whether the vascular occlusion involves the central retinal vein (CRVO), or a branch of the retinal venous system (BRVO). In addition, there are differences in management strategies dependent on whether the goal is to control neovascularisation and prevent vitreous haemorrhage and/ or rubeotic glaucoma, or in preventing / reversing visual loss due to macular oedema.

For the purposes of this appraisal I will restrict my comments to the management of macular oedema due to BRVO.

Macular oedema due to BRVO can be managed with a period of active observation, to see if there is any spontaneous improvement in a limited number of eyes, macular laser photocoagulation, intravitreal steroid injections or more recently with intravitreal off license bevacizumab, licensed ranibizumab and licensed aflibercept.

MO secondary to BRVO has previously been managed with a period of observation. This provided time for blood to clear from the macular region allowing correct interpretation of FFA necessary to plan and deliver laser photocoagulation treatment effectively. (The presence of blood in the retina interferes with laser placement and absorption, and treatment outcomes). The period of observation also allowed the clinician to identify any cases that spontaneously improved. If at 3 months macular oedema was still reducing

acuity to a level between 6/12 and 6/60, in the absence of significant foveal ischaemia, then macular grid laser photocoagulation has been proven in a large randomised controlled trial (RCT) to be an effective treatment in up to 30% of cases. This approach is still supported by the recent RCOphth Guideline on management of RVO but it is acknowledged that these criteria are only met in a minority of cases and delay in treatment in the presence of more effective treatments can limit potential visual potential.
Since the licensing and NICE approval of intravitreal dexamethasone implant (TA 229) and intravitreal ranibizumab (TA 283) the management landscape for treating BRVO has changed significantly with many patients benefitting from rapid and sustained visual improvements. Prior to the availability of licensed and NICE approved treatments, off license use of intravitreal bevacizumab was used in some NHS units for MO secondary to BRVO management but its use for this indication is almost non-existent in the UK for this indication nowadays.
Alternative therapies such arteriovenous sheathotomy and laser induced chorio-retinal anastomosis have all been tried with varying reports of success but are rarely used in the UK. These are only experimental at the present, and not recommended by the RCOphth Guidelines.
The technology under appraisal aflibercept 2mg intravitreal injection has received regulatory approval for use in BRVO alongside its previous indications for AMD, diabetic macular oedema (DMO) and CRVO. There is wide experience throughout UK NHS with aflibercept for management of wet AMD and growing experience with DMO and CRVO. The results of the VIBRANT trial demonstrated superiority of aflibercept over macular laser in treatment naïve MO secondary to BRVO in terms of visual gain and reduction in MO. The recent RCOphth Guidelines recommend aflibercept as a potential first line treatment in MO secondary to BRVO.
Aflibercept and ranibizumab anti VEGF intravitreal injections have particular advantages over intravitreal dexamethasone implant in patients with history of ocular hypertension or glaucoma due to the potential raising of intraocular pressure with intraocular steroids. In addition the lack of cataract adverse events with anti-VEGF treatments compared to intravitreal steroids in younger phakic patients is a particular advantage.
The technology is unsuitable for use in primary care settings and should be delivered by an ophthalmologist experienced in medical retinal disorders. It is likely to be delivered in an outpatients' clean room setting similar to its use for AMD and DMO.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

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Single Technology Appraisal (STA)

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Aflibercept will likely be used as an alternative first-line treatment to intravitreal ranibizumab and intravitreal dexamethasone implant. In addition, it will be considered as an alternative in patients who have responded sub-optimally to either intravitreal ranibizumab or intravitreal dexamethasone implant. It will have particular advantages over intravitreal dexamethasone implant in patients with history of ocular hypertension or glaucoma due to the potential raising of intraocular pressure with intraocular steroids and in younger phakic patients due to its lack of cataract formation.
It will face no significant barriers to its use as it is widely accepted as a successful treatment for AMD and DMO.
If aflibercept is chosen as the first line treatment, the recent RCOphth Guidelines recommend it is given monthly until maximum visual acuity is achieved, which is defined as stable visual acuity for three consecutive monthly assessments while on aflibercept therapy. If no improvement in visual acuity over the course of the first three injections is observed, cessation of treatment may be considered and is recommended after six injections. Monthly treatment should continue until visual and anatomical outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered. The summary of product characteristics states that monitoring is recommended at the injection visits and that the monitoring schedule should be determined by the doctor responsible for the patient's care based on the response of the condition to treatment.
The significant visual acuity gains in the VIBRANT study are encouraging and the recent real world UK AMD experience with aflibercept have mirrored the gains in acuity and 12 month stability of the pivotal trails with this treatment.
Wide experience with aflibercept in AMD and DMO have not revealed any unsuspected adverse effects and the treatment is well tolerated by patients.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

NONE IDENTIFIED

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Ongoing NIHR supported RCT of ranibizumab vs aflibercept vs bevacizumab (LEAVO study) NIHR CEAT Programme: Ref No: 11/92/03 is presently recruiting to assess clinical and cost effectiveness of these alterantive treatments in MO secondary to CRVO.

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Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There should be no significant barriers to implementation of the technology due to its widespread use in MD and DMO.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

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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

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Contributions of authors

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. Neil Scott 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. 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.

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List of abbreviations

AE	Adverse event
AIC	Academic in confidence
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BRVO	Branch retinal vein occlusion
BSC	Best supportive care
BSE	Best seeing eye
BVOS	Branch Vein Occlusion Study
CFT	Central foveal thickness
CI	Confidence interval
CIC	Commercial in confidence
CMT	Central macular thickness
CrI	Credible interval
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CS	Company submission
CVA	Cerebral vascular accident
DMO	Diabetic macular oedema
EMA	European Medicines Agency
ERD	Exudative retinal detachment
ERG	Evidence review group
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAS	Full analysis set
FEI	Fellow eye involvement
FFA	Fundus fluorescein angiography
HRQoL	Health-related quality of life
HRVO	Hemi-retinal vein occlusion
HS	Health state
ICER	Incremental cost-effectiveness ratio
IOP	Intraocular pressure

LOCF	Last observation carried forward
MI	Myocardial infarction
MO	Macular oedema
NEI VFQ-25	National eye institute visual functioning questionnaire-25
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for health and Care Excellence
NMA	Network meta-analysis
OCT	Optical coherence tomography
OLS	Ordinary least squares
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient access scheme
PlGF	Placental growth factor
PRN	Pro re nata
PSS	Personal social services
PSSRU	Personal social service research unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Risk ratio
RVO	Retinal vein occlusion
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TPM	Transition probability matrix
TTO	Time trade off
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WSE	Worse seeing eye
WTP	Willingness to pay

1 Summary

Branch retinal vein occlusion (BRVO) occurs when a branch of the retinal venous system is blocked by blood clots. There are two distinct subtypes of BRVO: major BRVO (when one major branch retinal vein is occluded) and macular BRVO (when one macular venule is occluded) and these can be further categorised as ischaemic or non-ischaemic types, based on the area of capillary non-perfusion. The most prominent symptom of BRVO is painless loss of vision.

Current treatment options focus on the complications of the occluded venous branch, such as macular oedema, rather than the underlying aetiology. Macular oedema occurs following a cascade of events including thrombosis of the retinal vein, increased retinal capillary intraluminal pressure and increased capillary permeability, leading to leakage of fluid and blood into the retina. The cornerstone of treatment for macular oedema secondary to BRVO has been laser treatment since the publication of the Branch Vein Occlusion Study (BVOS) in 1984. However, clinical management is now moving towards newer treatments, in particular, intravitreal anti-VEGF injections and dexamethasone implants.

There are no prevalence and incidence data for BRVO in England and Wales. In general, the prevalence of BRVO is largely consistent across countries with the age and sex standardised prevalence being 4.42 in the population aged at least 30 years.

1.1 Critique of the decision problem in the company submission

The NICE scope considered the clinical and cost-effectiveness of aflibercept (Eylea®, Bayer Pharma AG, Berlin, Germany) within its licensed indication for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO). Aflibercept is an engineered protein that blocks the action of VEGF-A and, thus, reduces the growth of blood vessels and controls any leakage (of blood or fluid) and swelling. Aflibercept was granted UK marketing approval in February 2015 for treating visual impairment due to macular oedema secondary to BRVO. It is also licensed in the UK for the treatment of neovascular (wet) age-related macular degeneration, visual impairment due to macular oedema

secondary to RVO (BRVO or CRVO), visual impairment due to diabetic macular oedema and visual impairment secondary to myopic choroidal neovascularization.

The decision problem addressed in the company submission deviated from the NICE final scope in that the company did not consider bevacizumab, an alternative anti-VEGF treatment, as a comparator. The company's rationale for this omission was that bevacizumab is an unlicensed treatment in ophthalmology, there has been no regulatory assessment of bevacizumab in the treatment of BRVO and it cannot be considered best or routine practice. Searches by the ERG showed that a number of studies involving bevacizumab have been conducted in the relevant clinical population, although none compared bevacizumab with aflibercept.

The subgroup analyses conducted by the company were consistent with the NICE final scope.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company consisted of one RCT involving aflibercept, VIBRANT, and eight studies involving relevant comparator treatments (laser, ranibizumab or dexamethasone): BRAVO, BRIGHTER, COMRADE-B, Azad 2012, Parodi 2008, Pichi 2014, RABAMES, and Tan 2014. Six trials involved ranibizumab as the main intervention (Azad 2012, BRAVO, BRIGHTER, COMRADE-B, RABAMES, Tan 2014), one trial involved laser photocoagulation (Parodi 2008) and one trial involved dexamethasone (Pichi 2014).

Four studies, VIBRANT, BRAVO, BRIGHTER, and COMRADE-B, were included by the company in the base case network meta-analysis (NMA). The remaining five studies, which were excluded by the company from the base case NMA because they were judged to be heterogeneous, were subsequently included in sensitivity analyses (Azad 2012, Parodi 2008, Pichi 2014, RABAMES, Tan 2014).

The primary outcome of the VIBRANT study was the proportion of participants gaining at least 15 BCVA letters at 24 weeks after randomisation. There was evidence of a statistically significant effect in favour of aflibercept (52.7% vs 26.7%, p=0.0003). There were also benefits in a number of secondary outcomes (i.e. change

from baseline in BCVA, change from baseline in central retinal thickness, mean NEI VFQ-25 total score) and additional efficacy outcomes (i.e. perfusion status, retinal ischemia, retinal fluid status). Later in the trial, participants in both groups could receive rescue treatment and differences between groups at 52 weeks were less pronounced. Aflibercept demonstrated an acceptable safety profile. With the exception of injection-related TEAEs, which were higher in participants treated with aflibercept, there were no clear differences in the incidence of ocular or non-ocular TEAEs compared with laser photocoagulation.

For the primary outcome (gaining ≥15 letters at 6 months), the company's NMA results suggested that aflibercept performed favourably when compared with dexamethasone (OR: 0.34; 95% CrI: 0.12 to 0.96), but that there was no evidence of a difference between aflibercept and ranibizumab 0.5mg (OR: 0.93; CrI: 0.38 to 2.31). Comparable results were observed for a related outcome (change in BCVA), but it was not possible to evaluate other outcomes as the relevant studies did not form a connected network.

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

The VIBRANT trial did not include subgroup analyses according to macular/foveal perfusion (i.e. macular ischaemia present/absent and extension; perifoveal capillaries present/absent), which is an important factor in determining whether treatment should be considered. Similarly, they did not conduct subgroup analyses according to duration of the macular oedema or to CRT measurements (≤400 micrometres, >400 micrometres). Even though these analyses were not specified in the NICE final scope, they would have been clinically relevant and pertinent to the purpose of this appraisal.

For the indirect comparison of aflibercept with other relevant treatments, the company identified nine eligible studies in the current literature but, after assessment of heterogeneity, only four were included in the base case NMA. The remaining five trials were judged to be heterogeneous and were included only in sensitivity analyses.

The ERG is of the opinion that the methods used in the systematic review and network meta-analysis (NMA) were generally appropriate and correctly applied. The principal concerns relate to the transparency of the assumptions used. The company

excluded five studies from the review of clinical evidence. As these studies meet the inclusion criteria specified in the NICE's final scope, although, to some extent, there is clinical heterogeneity between these studies and VIBRANT, the ERG is of the opinion that and a more transparent approach would have been to include them in the primary analyses. The ERG notes that if slightly different assumptions and decisions about the inclusion of studies had been made (e.g. as in a published meta-analysis sponsored by Novartis), a point estimate favouring ranibizumab could have been obtained, although credible intervals were very wide with considerable overlap with the company's results.

1.4 Summary of cost effectiveness submitted evidence by the company

Due to both ranibizumab and dexamethasone being approved for 2nd line use after unsuccessful laser therapy or where laser is not appropriate the company submission seeks to address two questions:

- Is 2nd line rescue aflibercept cost effective compared with 2nd line rescue ranibizumab and 2nd line rescue dexamethasone?
- Is 1st line aflibercept followed by 2nd line rescue laser cost effective compared with 1st line laser followed by 2nd line rescue aflibercept?

A Markov model with a four week cycle is used to simulate the evolution of patients' BCVA in their study eye and in their non-study eye, with the baseline age of 65 years and the female proportion of 45% being taken from the VIBRANT trial. A 6.05% rate of bilateral BRVO at baseline and 2.50% annual incidence of BRVO for the fellow eye during the first 5 years of the model is taken from expert opinion.

Patients' eyes are characterised as falling into five 15 letter BCVA bands:

- VA1: 80 letters to 100 letters, with a mean of 90 letters being assumed
- VA2: 65 letters to 79 letters, with a mean of 72 letters being assumed
- VA3: 50 letters to 64 letters, with a mean of 57 letters being assumed
- VA4: 35 letters to 49 letters, with a mean of 42 letters being assumed
- VA5: 0 letters to 35 letters, with a mean of 17 letters being assumed

Transition probability matrices (TPMs) are estimated for aflibercept-laser and laser-aflibercept from VIBRANT data using the MSM package in R. One four-weekly TPM for each arm is estimated for between week 0 and week 24 and applied seven times. From this point, patients may discontinue from their original treatment and receive rescue treatment. Two four-weekly TPMs for each arm are estimated for between week 28 and 52, one TPM for those remaining on their original treatment and one TPM for those receiving rescue treatment. These TPMs are applied six times.

For the laser-ranibizumab and the laser-dexamethasone arms, the week 0 to week 24 modelling of 1st line laser is exactly the same as in the laser-aflibercept arm. Rates of rescue treatment between week 28 and 52 are also the same. However, the TPM for those receiving rescue ranibizumab or rescue dexamethasone is derived by applying the NMA odds ratios of gaining at least 15 letters of 0.93 for ranibizumab and 0.34 for dexamethasone to the probabilities of gaining letters in the corresponding rescue aflibercept TPM.

For the comparison of aflibercept-laser with laser-aflibercept, for the first year of the model a simpler alternative to the TPMs of applying the VIBRANT four weekly patient distributions is also available, labelled as the “shift-tables” approach by the company.

During the first year of treatment, a constant proportion of patients are assumed to discontinue 1st line treatment each cycle and move into an off treatment health state, receiving neither 1st line treatment or 2nd line rescue treatment. These proportions are based upon the VIBRANT trial, with 11/92 patients discontinuing in the aflibercept-laser arm and 9/92 patients discontinuing in the laser-aflibercept arm. Ranibizumab and dexamethasone are assumed to have the same discontinuation rate as the aflibercept-laser arm.

For the next four years, it is assumed that treatment will continue, though with fewer injections. Visual stability is assumed for this period. For the remainder of the model, it is assumed that all patients will have resolved and there is no need for further treatment. A steady slow annual visual decline of 2% of eyes losing 15 letters is

applied for the remainder of the model, as drawn from the Van der Pols (2000) study of a sample of elderly British people.

Fellow eye BRVO is assumed to be treated in 50% of patients. Treated eyes have the same TPMs applied as outlined above. Untreated eyes are assumed to decline at the common 2% annual rate.

Quality of life for the better seeing eye (BSE) is taken from the Czoski-Murray experimental time-trade off study. Quality of life for the worse seeing eye (WSE) assumes that a given change in its BCVA will have 30% of the quality of life impact of the same change in the BSE. An OLS analysis of the VIBRANT EQ-5D data is used as a sensitivity analysis.

Dosing and administrations are based upon the mean number of treatments in the VIBRANT study during the first year of the model and expert opinion thereafter. Dosing for rescue ranibizumab is assumed to be the same as for rescue aflibercept, while dosing for rescue dexamethasone is based upon the SmPC and expert opinion. Monitoring is based on SmPCs and expert opinion.

The company base case results are:

- For aflibercept-laser compared to laser-aflibercept, a net cost of [redacted], a net gain of [redacted] QALYs and a cost effectiveness estimate of £15,365 per QALY.
- For laser-aflibercept compared to laser-ranibizumab, a net saving of [redacted], a net gain of [redacted] QALYs and so dominance for laser-aflibercept.
- For laser-aflibercept compared to laser-dexamethasone, a net cost of [redacted], a net gain of [redacted] QALYs and a cost effectiveness estimate of £11,792 per QALY.

Among the sensitivity analyses undertaken by the company, results were sensitive to:

- The odds ratios of gaining letters
- The time horizon
- The cohort starting age
- The number of injections

- The cost per monitoring visit
- The proportion of treatment visits that double as monitoring visits
- The application of VIBRANT EQ-5D data
- To some extent the proportion of fellow eyes that are treated

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

The main ERG's critique in terms of model structure and inputs is:

- No consideration of bevacizumab.
- The results from the R MSM derived TPMs not being aligned with that of the shift tables approach for the comparison of aflibercept-laser with laser-aflibercept, which argues for using either the shift tables approach or TPMs based upon patient count data.
- The six month odds ratios of the NMA applying to 1st line treatments, but the model necessarily applying them to 2nd line rescue treatments.
- The six month odds ratios being applied to four-weekly TPMs. These are then compounded seven times. This appears to exaggerate the differences between the treatments and may largely invalidate the comparisons with laser-ranibizumab and laser-dexamethasone. This argues for six month TPMs being used for the second 6 months of the first year of the model.
- The company model not adjusting dosing for cross-over to rescue therapy within the model or for discontinuations.
- The company not reporting the results of its expert survey for dosing and monitoring for years 6+ of the model. The RETAIN trial suggests that there is a requirement for ongoing anti-VEGF dosing, among perhaps as many as half the patient population.
- The probabilistic modelling not implementing the main clinical inputs to the model, the TPMs and shift tables, probabilistically. The company is unaware of any methods to do so. This argues for TPMs derived from patient count data, for which there are well established sampling methods.

The main uncertainties within the economics and the modelling are:

- Whether there would be any difference in dosing between aflibercept and ranibizumab.

- What proportion of patients requires ongoing dosing with anti-VEGFs, at what dose and for how long.
- What proportion of patients requires ongoing dosing with dexamethasone, at what dose and for how long.
- What the most appropriate source for quality of life values is and whether there is a general over-reliance upon the experimental lenses study of Czoski-Murray.
- What the quality of life impact of a loss in BCVA in the worse seeing eye is compared with the quality of life impact of the same loss in BCVA in the better seeing eye.

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

1.6.1 Strengths

The submission was generally coherent and clear and appropriate methods were used for the review of clinical evidence.

The company model was a bilateral model. The presentation of the VIBRANT EQ-5D data alongside estimates from the literature and structural sensitivity analyses permitted the use of individual patient count data for the comparison of aflibercept-laser with laser-aflibercept.

1.6.2 Weaknesses and areas of uncertainty

It is questionable whether the multiple exclusion criteria for VIBRANT (Appendix 3 of the company submission) may threaten the generalisability of results to current clinical practice. If aflibercept should be used in clinical practice in participants with the same characteristics of those excluded from VIBRANT, outcomes and side effects would not be known.

Considering that the main primary and secondary outcomes in VIBRANT were assessed at 24 weeks, one could argue whether a clinical trial of six-month duration would be long enough for any reliable comparison with laser photocoagulation (the BVOS trial demonstrated that after laser treatment visual acuity continued to improve throughout the entire follow-up period - mean 3.1 years).

Only one odds ratio from the clinical effectiveness section, with a point estimate favouring aflibercept over ranibizumab, was used in the cost-effectiveness results. The ERG is of the opinion that the company could have attempted to fully explore the impact of other results in sensitivity analyses, including those of the full network of eligible studies, which were often less favourable to aflibercept but with overlapping credible intervals.

With regard to the cost-effectiveness evidence, weaknesses and areas of uncertainty have been summarised in section 1.5 above.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has revised the model in a number of ways, a full account of which is given in Chapter 5, section 5.4, below. The main changes made by the ERG are:

- Revise dosing to take into account cross-over and discontinuations. Note that the dosing for dexamethasone has not been revised by the ERG due to time constraints.
- Apply the shift tables for the comparison of aflibercept-laser with laser-aflibercept.
- Assume additional ongoing anti-VEGF dosing of 3.2 per year for five years for 30% of the patient population for the base case for the comparison of aflibercept-laser and laser aflibercept. Due to a lack of data for dexamethasone, this is only included as a sensitivity analysis for the comparison of laser-aflibercept with laser-ranibizumab.
- Include SAEs for fellow eyes involvement, with it being assumed that all fellow eye involvement is treated.
- Assume quarterly monitoring for laser during the first year.

For the comparison of aflibercept-laser with laser-aflibercept this results in net costs of [redacted] and a net gain of [redacted] QALYs, so a cost effectiveness estimate of £27,259 per QALY.

Applying the R MSM TPMs rather than the shift tables improves the cost effectiveness estimate to £23,847 per QALY.
Assuming that the WSE QoL impact is 15% that of the BSE worsens the cost effectiveness estimate to £31,581 per QALY, while an assumption of 43% improves it to £24,891 per QALY. The other possible sources for quality of life values worsen the cost effectiveness estimates to be above £30k per QALY.

Assuming that all BRVO has resolved by year 6 with no further treatments being required improves the cost effectiveness estimate to £16,801 per QALY, while assuming that the ongoing treatment is required for 10 years worsens the cost effectiveness estimate to £31,624 per QALY.
For the comparison of laser-aflibercept with laser-ranibizumab net savings of [redacted] are estimated. In all that follows it should be borne in mind that these analyses include the price discount available through the aflibercept patient access scheme but not the price discount available through the ranibizumab patient access scheme. The odds ratio of [redacted] for gaining letters also causes laser-aflibercept to be estimated to be superior, yielding a net [redacted] QALYs. As a consequence, laser-aflibercept is estimated to dominate laser-ranibizumab.

Applying the eight studies NMA odds ratio for gaining letters of 1.08 causes laser-ranibizumab to be clinically superior to laser-aflibercept, with a gain of [redacted] QALYs. However, laser-ranibizumab still costs substantially more and the cost effectiveness of laser-ranibizumab compared to laser-aflibercept is estimated to be £204k per QALY.

The alternative sources of quality of life estimates tend to reduce the gain from laser-aflibercept over laser-ranibizumab but as it is still cost saving it remains dominant.

Assuming that 30% of patients remain unresolved at six years with a need for ongoing dosing with anti-VEGFs increases the cost savings associated with laser-aflibercept and so it remains dominant over laser-ranibizumab. This is not altered by assuming that ranibizumab requires one fewer injection than aflibercept during the first year of treatment.

For the comparison of laser-aflibercept with laser-dexamethasone, net costs of [redacted] are balanced by net gains of [redacted] QALYs resulting in a cost effectiveness estimate of £18,542 per QALY.

Applying the eight studies NMA odds ratio for gaining letters of 0.40 reduces the net gain to [redacted] QALYs and so worsens the cost effectiveness estimate to £20,969 per QALY. The VIBRANT EQ-5D data also somewhat reduces the net gain, pushing the cost effectiveness estimate to over £30k per QALY.

Elements that are uncertain and that the ERG cannot quantify are:

- The VIBRANT trial assumed LOCF for drop-outs. The drop-out rate was quite high. Any tendency for drop-outs to rebound to baseline might worsen the clinical and cost effectiveness estimates for aflibercept-laser compared to laser-aflibercept. Whether it is reasonable to conduct a scenario analysis of rebound to baseline is questionable.
- The VIBRANT trial dosing for 1st line aflibercept in the aflibercept-laser arm was both more frequent and of longer duration than for 2nd line rescue aflibercept in the laser-aflibercept arm. The full clinical benefits of rescue aflibercept may not have been realised in the laser-aflibercept arm. This may have depressed the clinical effectiveness estimates in the laser-aflibercept arm to below what would be realised in clinical practice.

2 Background

Retinal vein occlusion (RVO) is a blockage of the retinal venous system that can involve the central, hemi-central or branch retinal vein.[1]

Central retinal vein occlusion (CRVO) results from an obstruction of the venous outflow, probably at the position of, or posterior to, the lamina cribosa. The main trunk of the central retinal vein is involved and, therefore, the whole venous system of the retina is affected.[2] CRVO is beyond the scope of the present assessment. Hemi-retinal vein occlusion (HRVO) involves one of the two retinal hemispheres (superior or inferior), with the retinal haemorrhages being almost equal in two altitudinal quadrants (the nasal and temporal aspects) of the affected hemisphere. Management of HRVO is similar to that of BRVO[1] and people with HRVO are included in the scope of this appraisal as they may be enrolled in trials that assess people with BRVO.

Branch retinal vein occlusion (BRVO) occurs when a branch of the retinal venous system is affected. Commonly, obstructions are located at arteriovenous crossings or at the optic disc.[2] Therefore, unlike CRVO, BRVO affects only the part of the fundus that is drained by the pertinent vein.[1]

Branch retinal vein occlusion, CRVO & HRVO are different clinical entities with BRVO being more common than CRVO.[3-5] The focus of this appraisal is on BRVO but HRVO is also an eligible condition due to similarities in the treatment of the two conditions.

Branch retinal vein occlusion is divided into two distinct subtypes: major BRVO (when one major branch retinal vein is occluded) and macular BRVO (when one macular venule is occluded).[4] Branch retinal vein occlusion is a frequent cause of vision loss[5] and is second only to diabetic retinopathy as a cause of vascular visual loss and retinal vascular abnormality.[6-8]

Branch retinal vein occlusion can be broadly categorised as ischaemic or non-ischaemic, based on the presence/absence and extension of retinal capillary non-perfusion, and the distinction between the two types is clinically important.[1, 9]

Ischaemic retinal vein occlusion has been defined as at least 10 disc areas of retinal ischaemia.[10, 11] This definition has been further refined to specify a threshold for ischaemic BRVO of at least 5 disc areas.[12] However, the definition of ischaemic RVO based on disc areas of extension of non-perfusion area does not include a specification of whether the ischaemia affects the macular area or the perifoveal capillary network, even though these characteristics are important to establish patients' visual prognosis.

The pathogenesis of BRVO may involve a combination of three primary mechanisms, including compression of the vein at the arteriovenous crossing, degenerative changes of the retinal vessel wall, and abnormal haematological factors.[4, 8] Systemic risk factors include hypertension, hyperlipidaemia, diabetes, and higher BMI.[13, 14] Local anatomic factors such as arteriovenous crossings and glaucoma have also been reported.[8, 15, 16] A positive association between prevalence rate of BRVO and age has also been described,[17] and an association between RVO and smoking has recently been identified.[18] Risk factors for HRVO include hypertension and a history of diabetes or glaucoma.[14]

One of the main complications of RVO is macular oedema, which occurs as a result of a cascade of events including thrombosis of the retinal vein, increased retinal capillary intraluminal pressure and increased retinal capillary permeability leading to leakage of fluid and blood into the retina. Retinal ischaemia may aggravate this process by increasing levels of vascular endothelial growth factor (VEGF), a vascular permeability factor, and, thus, promoting leakage of fluid into the extracellular space, and macular oedema. Macular oedema is the most prominent cause of visual impairment in people with RVO.[1, 19]

According to the Royal College of Ophthalmologists 2015 Guidelines, there are no prevalence or incidence data from England and Wales.[1, 20] In general, the prevalence of BRVO is largely consistent across countries with the age and sex standardised prevalence being 4.42 in the population aged at least 30 years.[17],[20] In the USA, data

published in 2008 showed a 15-year incidence rate for BRVO of 1.8%.[17] The NICE final scope for this assessment indicates that RVO affects 1% to 2% of people over 40 years of age and that macular oedema is the most frequent cause of vision loss in people with RVO. Prevalence rates of RVO in people over 40 years of age of between 0.3%[21] and 2.1%[22] have been reported in the literature. The company submission states that "*…in England and Wales there are around 14,488 people with BRVO and macular oedema [who] have visual impairment*" (page 37, company submission). This figure appears to have been derived from a combination of ONS data and data from the ranibizumab NICE appraisal for treatment of visual impairment caused by macular oedema secondary to RVO (TA283).[23]

The diagnosis of BRVO is generally straightforward. People with major BRVO can be asymptomatic or experience painless loss of vision.[2, 24] If the central retina (macula) is affected, people will complain of central visual loss, or, if not, they may have only blurring of the visual field corresponding with the area of retina drained by the occluded vein. Typical fundus features of BRVO include flame-shaped and dot and blot haemorrhage, cotton wool spots, hard exudates, retinal oedema (including macular oedema) and dilated, tortuous veins. The diagnosis of BRVO is often made by clinical examination on the slit lamp (slit-lamp biomicroscopy) following pupillary dilation (mydriasis).[4] Fundus imaging with fluorescein angiography is required to differentiate the ischaemic from the non-ischaemic types and to determine the presence/absence of macular ischaemia, perifoveal capillary involvement and macular oedema.[2, 4, 25] Although very safe, fluorescein angiography is an invasive procedure that requires the injection of a dye (fluorescein) into a peripheral vein; images of the retina are then obtained as the dye circulates in the eye. Optical coherence tomography (OCT) is a rapid, non-invasive imaging technology that allows sections across the central retina to be obtained. It is now widely used in people with BRVO to determine the presence/absence of macular oedema and its course following treatment.[24, 26, 27]

Ischaemic BRVO exhibits different degrees of capillary non-perfusion (with a minimum requirement to fulfill the definition of "ischaemic"), cotton wool spots, reduced vision and visual field deficits. The development of retinal ischaemia is often followed by the growth of new blood vessels in the retina or optic nerve head which

can then give rise to intraocular haemorrhage (vitreous haemorrhage) and further visual loss. Retinal detachment can also occur as a result of contraction of fibrovascular membranes. The prevalence and incidence of ischaemic BRVO has not been fully described.[1] Non-ischaemic RVOs are characterised by a lower degree of retinal ischaemia and lack of development of intraocular neovascularisation.[2] Patients with HRVO are likely to develop neovascular complications.[28]

Current treatment options for BRVO target the complications of this retinal disorder, including macular oedema, neovascularisation, vitreous haemorrhage and tractional retinal detachment, rather than the underlying aetiology.[4, 8] For many years, grid laser photocoagulation was the cornerstone of treatment for macular oedema secondary to BRVO. The Branch Vein Occlusion Study (BVOS) published in 1984 demonstrated the benefit of laser treatment in eyes with macular oedema secondary to BRVO.[7] The BVOS demonstrated a gain of at least two lines of best corrected visual acuity (BCVA) at three years follow-up from baseline, maintained for two consecutive visits, in 28/43 (65%) laser-treated eyes versus 13/35 (37%) in eyes that did not receive treatment. The cumulative proportion of laser-treated eyes that gained two or more lines of visual acuity increased throughout the entire follow up period (5 years or more) and around one-third of eyes improved spontaneously without treatment.[7]

The clinical management of RVO is now moving towards newer treatments, in particular, anti-vascular endothelial growth factor (VEGF) therapies and intraocular steroids.[1] Thus, for treatment of non-ischaemic BRVO, the Royal College of Ophthalmologists recommends monthly treatments with ranibizumab for three months, or a baseline dexamethasone implant. Based on their guidelines, laser treatment should be considered if these treatments are unsuccessful or unavailable and if macular oedema persists and there is no, or minimal, macular ischaemia.

Vascular endothelial growth factor (VEGF) is a potent, endothelial cell mitogen that stimulates proliferation, migration and tube formation, thus promoting angiogenic growth of new blood vessels.[29-31] If the retina becomes ischaemic, production of VEGF increases with a likely impact upon the development of macular oedema.[32-34]

VEGF-A is a key cytokine that mediates vascular leakage, leading to macular oedema secondary to RVO.[1] There is a growing body of evidence showing that inhibition of VEGF results in considerable long-term benefits for people with macular oedema secondary to BRVO and anti-VEGF therapy is now the preferred treatment for the condition by many ophthalmologists.[1, 35]

Ranibizumab (Lucentis, Novartis, UK) prevents the binding of VEGF-A to its receptors, and, as a result, inhibits endothelial cell proliferation, neovascularisation and vascular leakage. Ranibizumab has UK marketing authorisation for the treatment of visual impairment due to diabetic macular oedema, neovascular (wet) age-related macular degeneration, visual impairment due to macular oedema secondary to retinal vein occlusion (BRVO or CRVO) and visual impairment due to choroidal neovascularisation secondary to pathological myopia.[36]

Aflibercept (Eylea, Bayer Pharma AG, Berlin, Germany) is an engineered protein, which acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) with higher affinity than their natural receptors, thus inhibiting the binding and activation of these cognate VEGF receptors. Aflibercept has UK marketing authorisation for the treatment of neovascular (wet) age-related macular degeneration, visual impairment due to macular oedema secondary to RVO (BRVO or CRVO), visual impairment due to diabetic macular oedema and visual impairment secondary to myopic choroidal neovascularization.[37] Aflibercept was granted marketing approval by the EMA in February 2015 for treating visual impairment due to macular oedema secondary to BRVO.

These anti-VEGF treatments are administered as injections into the vitreous cavity (the space in the centre of the eye), so called “intravitreal injections” (EPAR).[38]

According to the TA 229 on dexamethasone for macular oedema secondary to BRVO, intravitreal corticosteroids are a further available treatment option if laser treatment has not been beneficial or laser treatment is not considered suitable because of the extent of macular haemorrhage (see NICE treatment pathway shown in Figure 1, which reproduces Figure 2 of the company submission).

Dexamethasone (Ozurdex, Allergan Pharmaceuticals, Ireland) is a corticosteroid that blocks the production of VEGF and prostaglandins. Dexamethasone has UK marketing authorisation for visual impairment due to diabetic macular oedema in people who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy, macular oedema following either BRVO or CRVO, or inflammation of the posterior segment of the eye presenting as non-infectious uveitis (SmPC). Ozurdex is the only corticosteroid licensed for macular oedema secondary to BRVO.[1] Dexamethasone is administered as an implant which is injected directly into the vitreous cavity of the eye (EPAR).[38]

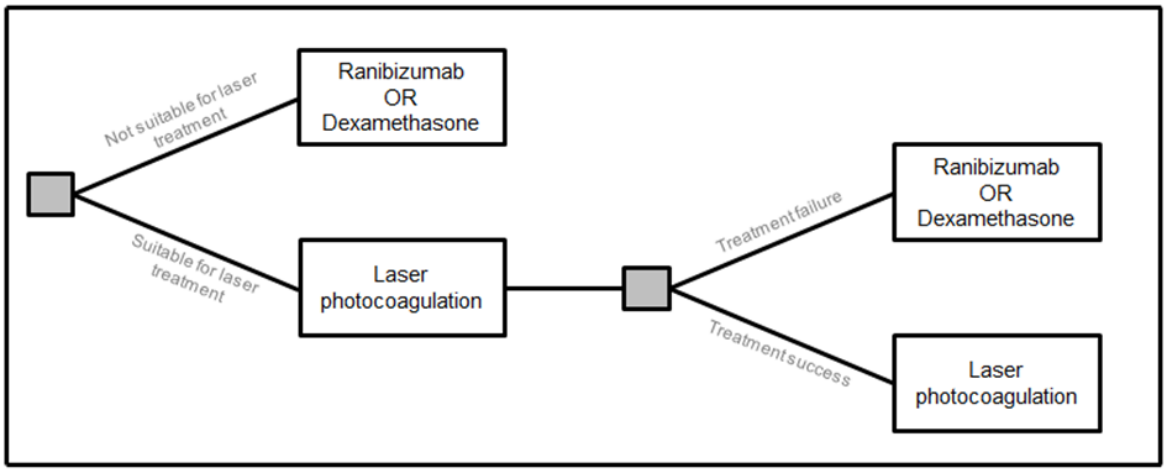

Figure 1 NICE treatment pathway for BRVO

2.1 Critique of company's description of underlying health problems

The company's description of macular oedema secondary to BRVO appears to be, on the whole, accurate but the ERG has identified some potential inconsistencies therein. For example, the company maintains that "*...in cases where, at presentation, visual acuity is better than 6/12 or where macular oedema and haemorrhages are not masking fovea or macular ischaemia is not identified or is mild, regular observation for three months may be warranted*" (page 33, company submission). However, the company does not include the option of an observation period in their proposed care pathway including aflibercept (Figure 2 below that reproduces Figure 3 of the company submission).

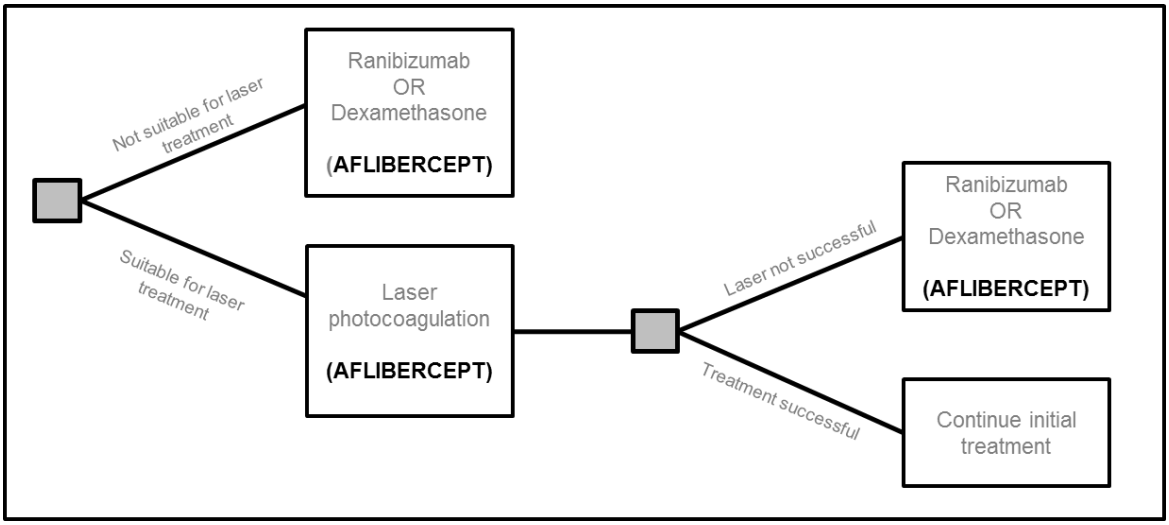

Figure 2 Company's treatment pathway including aflibercept's place

Similarly, the company states "*if severe macular ischaemia is present - no treatment is recommended…"* (page 42, Section 3.6.2.2, company submission) but does not include this option in their proposed care pathway for aflibercept (see Figure 2 above).

The company appears to place emphasis on early treatment. The Royal College of Ophthalmologists, however, recommends a period of observation under certain circumstances ("…*regularly observe for three months if MO [secondary to BRVO] is mild and in the opinion of the clinician likely to spontaneously improve (30% chance)"* and *"if VA better than 6/12 it is reasonable to regularly observe for three months*"). The natural history of macular oedema due to BRVO indicates that macular oedema may resolve or reduce over time and that about one-third of eyes may improve spontaneously, without treatment (for example, BVOS and BRAVO sham arm). Thus, a period of observation may be reasonable in some groups of patients and could potentially save unnecessary long-term treatments. Table 1 below shows the treatment algorithm for BRVO proposed by the Royal College of Ophthalmologists.[1]

Table 1 Royal College of Ophthalmologists treatment algorithm for BRVO

RCO recommendations for non-ischaemic BRVO
Baseline
If VA better than 6/12, regularly observe progress for three months.
If VA 6/12 or worse with macular oedema and haemorrhages are not masking fovea: o FFA is recommended to assess foveal integrity o Regularly observe for three months if macular oedema is mild and in opinion of clinician likely to spontaneously improve (30% chance); o If mild to moderate macular ischaemia is present consider treatment with ranibizumab or Ozurdex [dexamethasone intravitreal implant] if spontaneous improvement is unlikely; o If severe macular ischaemia is present - no treatment is recommended, and regularly observe for neovascular formation.
If VA 6/12 or worse and macular oedema and haemorrhages are masking macula: o Monthly ranibizumab or baseline Ozurdex [dexamethasone intravitreal implant] for three months. o Perform FFA at 3 months to assess foveal integrity; o If severe macular ischaemia is found to be present at three months, no treatment will likely be beneficial and further therapy should be carefully considered.
At three-month follow-up
o Consider laser photocoagulation if persistent macular oedema, no or minimal macular ischaemia and other treatments unsuccessful or unavailable o If VA ≥6/9 or no macular oedema detected, continue to observe (if initially observed). If on anti-VEGF or Ozurdex [dexamethasone intravitreal implant] therapy, continue as suggested in macular oedema due to CRVO.
Further follow up
o If under observation only, follow-up three monthly intervals for 18 months; o In case of recurrence or new macular oedema, consider re-initiating intravitreal ranibizumab or Ozurdex [dexamethasone intravitreal implant] therapy.
RCO recommendations for ischaemic BRVO
o Watch carefully for neovascularisation; o If neovascularisation occurs, consider sector laser photocoagulation applied to all ischaemic quadrants. Intravitreal bevacizumab (off-license) may also be given in combination with laser; o Follow-up at three monthly intervals for up to 24 months.

2.2 Critique of company's overview of current service provision

There are currently two NICE Technology Appraisals relating to treatment for macular oedema secondary to BRVO and one Interventional Procedure Guidance for treating BRVO. The main recommendations of these guidelines are summarised below.

TA283 Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion, May 2013:
Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- Following central retinal vein occlusion **or**
- Following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage **and**
- Only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 274.

TA229 Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion, July 2011:
Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion.

Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following branch retinal vein occlusion when:

- Treatment with laser photocoagulation has not been beneficial, **or**
- Treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage.

IPG 334 Arteriovenous crossing sheathotomy for branch retinal vein occlusion, March 2010:
Current evidence on the efficacy and safety of arteriovenous crossing sheathotomy for branch retinal vein occlusion (BRVO) is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of clinical

research. The company appropriately refers to the above NICE publications in their submission.

There are two further NICE Technology Appraisals relating to aflibercept for other indications: TA305 and TA346.

TA305 Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion, February 2014:
Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept for injection with the discount agreed in the patient access scheme.

TA346 Aflibercept for treating diabetic macular oedema, July 2015:
Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular only if:

- The eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- The company provides aflibercept with the discount agreed in the patient access scheme.

The company also appropriately refers to relevant guidelines of the Scottish Medicines Consortium. Within NHS Scotland:

- Aflibercept[39] has been accepted for the treatment of adults with visual impairment due to macular oedema secondary to BRVO or CRVO;
- Ranibizumab[40] has been accepted for the treatment of adults with visual impairment due to macular oedema secondary to retinal vein occlusion (BRVO or CRVO);
- Dexamethasone[41] has been accepted for restricted use for treatment of adult patients with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion who are not clinically suitable for laser treatment including patients with dense macular haemorrhage or patients who have received and failed on previous laser treatment.

The company appropriately refers to the Royal College of Ophthalmologists Retinal Vein Occlusion Guidelines[1]. The company points out the notable disparity between the NICE guidelines (laser as first line treatment and VEGF if laser treatment is not suitable or effective, Figure Y above) and the Royal College treatment algorithm presented in Table 1 above (observation, ranibizumab or dexamethasone as first line treatment, then consideration of modified grid laser treatment if persistent macular oedema, no or minimal macular ischaemia and other treatments unsuccessful or unavailable).

The company states that no change in service provision is required and no impact on the NHS anticipated for use of aflibercept within their proposed pathway. However, it could be argued that, if aflibercept were to be used as first line treatment, without allowing any observation period, more patients would be treated and increased resources would be required to treat and follow them up. Furthermore, if aflibercept were to be offered as first line therapy instead of laser treatment, there would be an increased workload as the number of visits required for people treated with aflibercept would be higher than those for people treated with laser.

The UK Hospital Episode Statistics data for ‘other specified retinal disorders’ (code H35.8) show that there were 16,025 admissions equating to 16,052 finished consultant episodes and 897 bed days in England for the year April 2014-March 2015.

3 Critique of company's definition of decision problem

3.1 Population

In line with the NICE final scope for this assessment and the licensed indication for aflibercept, the company submission specified the population for this appraisal as "*adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO).*"

The company submission focuses on the evidence of one trial, VIBRANT, which compares the efficacy and safety of aflibercept with macular grid laser photocoagulation for the treatment of macular oedema after BRVO or hemi-retinal vein occlusion (HRVO).

The inclusion and exclusion criteria specified by the company for the VIBRANT trial (Table 10 and Appendix 3, company submission) include 'uncontrolled glaucoma' (intraocular pressure > 25 mmHg or previous filtration surgery) among the exclusion criteria, but it is unclear if this refers to people on maximal therapy. It is questionable whether the multiple exclusion criteria for VIBRANT (Appendix 3 of the company submission) may affect the applicability of results to current clinical practice. If aflibercept should be used in clinical practice in participants with the same characteristics of those excluded from VIBRANT, outcomes and side effects would not be known.

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.[42-45] As a result, aflibercept can inhibit the binding and activation of these related VEGF receptors.[44]

Aflibercept is formulated as a solution for intravitreal injection. Each vial contains 100 microlitres, equivalent to 4mg aflibercept, providing a usable amount for a single

dose of 50 microlitres containing 2mg aflibercept.[37] For visual impairment due to macular oedema secondary to retinal vein occlusion (BRVO or CRVO), the recommended dose is 2mg aflibercept equivalent to 50 microlitres. Following an initial injection, treatment is given monthly, with the interval between treatments not shorter than one month. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive monthly injections may be required. If the visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, aflibercept should be discontinued. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response .[37]

Aflibercept has regulatory approval in the UK and Europe (since February 2015) for the treatment of visual impairment due to macular oedema secondary to BRVO.[38]

3.3 Comparators

The comparators specified in the NICE final scope for this assessment were laser photocoagulation and bevacizumab or, for people for whom laser photocoagulation has not been beneficial or is not suitable, ranibizumab, dexamethasone intravitreal implant or bevacizumab. The company submission differs from the scope in that bevacizumab was not included as a comparator. The company's justification for this strategy was that bevacizumab is an unlicensed treatment in ophthalmology and that several licensed treatments are available. In addition, there has been no regulatory assessment of bevacizumab in the treatment of BRVO and it cannot be considered best or routine practice. The company also argues that in the previous technology assessment of ranibizumab for vision impairment caused by macular oedema secondary to retinal vein occlusion[23] bevacizumab was considered in the final scope but not used as a comparator in the cost-effectiveness analyses.

Focused scoping searches of MEDLINE and EMBASE performed by the ERG have shown that a number of studies involving bevacizumab have been conducted in the relevant clinical population (see Table 2), although none of these studies compared bevacizumab with aflibercept.

3.4 Outcomes

The outcomes specified by the company in Table 1 of the submission were visual acuity (the affected eye), visual acuity (the whole person), adverse effects of treatment, health-related quality of life and mortality. These outcomes are in line with the final NICE scope.

The company maintains (page 15 of the submission) that '*the degree of vision loss [due to BRVO] depends on the extent of retinal involvement and on macular perfusion status.*' Nonetheless, they did not seem to assess macular perfusion status, and subgroup analysis based on macular perfusion is not available. The Royal College of Ophthalmology guidelines suggest that an assessment of macular perfusion status is required to determine whether treatment should be considered (see Table 1 in Chapter 2). Thus, subgroup analyses on macular perfusion (presence/absence of macular ischaemia) would seem pertinent.

3.5 Other relevant factors

The decision problem addressed by the company for the economic analysis was consistent with the NICE final scope.

The NICE final scope specified subgroup analysis according to baseline visual acuity, if evidence allowed. The company submission conducted analysis for the 24-34 and 35-73 letter BCVA subgroups, based on data derived from the VIBRANT study.

These subgroups were determined by the stratification of BCVA at baseline in VIBRANT. At clarification, the company explained that the subgroups resulted from a combination of the stratification and inclusion criteria. The ERG is satisfied with this explanation. The ERG considers that the 24-34 letters group would have very poor vision while the 35-73 letters group would have a better level of vision. The limit for driving in the UK is 69 letters (20/40 vision = 6/12 vision) in one eye no matter what the vision of the other eye is like, provided there is an adequate visual field. Therefore, it is the ERG's opinion that the choice of these subgroups is appropriate.

Table 2 Published studies involving bevacizumab in people with BRVO

Study	Population	Intervention(s)	Study design
Azad 2014[46]	Macular oedema due to BRVO	ranibizumab + laser vs bevacizumab vs laser vs laser	RCT
Cekic 2010[47]	Patients with BRVO and macular oedema	4 mg triamcinolone acetonide monotherapy vs 1.25 mg bevacizumab monotherapy vs 2 mg triamcinolone acetonide + 1.25 mg bevacizumab	RCT
Donati 2012[48]	Patients showing macular oedema secondary to BRVO and visual acuity loss	bevacizumab vs bevacizumab + laser	RCT
Leitritz 2013[49]	Patients with macular oedema secondary to BRVO	bevacizumab vs laser	Prospective interventional consecutive case series
Moradian 2011[50]	Patients with acute BRVO and BCVA $\leq$ 20/50	bevacizumab vs sham	RCT
Narayanan 2015[51]	Centre-involving macular oedema due to BRVO of less than 9 months duration; minimum CRT of 250 μm in the central subfield; BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye	bevacizumab vs ranibizumab	RCT
Parodi 2015[52]	Macular oedema secondary to BRVO, previous conventional grid laser photocoagulation with documented resolution of macular oedema and subsequent recurrence of macular oedema, BCVA between 20/400 and 20/40, and central foveal thickness (CFT) ≥250 μm	bevacizumab vs laser	RCT

Study	Population	Intervention(s)	Study design
Rezar 2015[35]	Patients with macular oedema due to BRVO	bevacizumab vs ranibizumab	Cross-sectional comparative study
Russo 2009[53]	Patients with cystoid macular oedema secondary to non-ischemic BRVO	bevacizumab vs laser	Cross-sectional comparative study
Tomomatsu 2015[54]	Patients with unilateral acute major BRVO who were at least 35 years old and had a reduction in BCVA of between 20/30 and 20/320 due to macular oedema	bevacizumab vs bevacizumab + laser	RCT

The company also conducted analyses of the following subgroups for the primary and secondary efficacy endpoints: gender; age; race; ethnicity; smoking history; anti-drug antibody response; geographic region; baseline retinal perfusion status. The latter was used to determine whether eyes were "perfused" (presence of < 10 disc areas of retinal capillary non-perfusion) or "non-perfused" (presence of ≥ 10 disc areas of retinal capillary non-perfusion). It is important to note that these definitions provide no information on the status of perfusion at the macula/fovea (i.e. presence or absence of macular ischaemia).

Subgroup analyses were not conducted according to macular/foveal perfusion (i.e. macular ischaemia present/absent; perifoveal capillaries present/absent), CRT or duration of the macular oedema. The ERG is of the opinion that these analyses are clinically relevant as they may provide further information on efficacy, and, albeit not specified in the NICE final scope, should have been considered..

The company stated that no subgroup comparisons of aflibercept versus ranibizumab or dexamethasone were possible as a connected evidence network could not be formed. The ERG agrees with the company's position.

Table 3 details the discrepancies between the NICE final scope and the decision problem addressed by the company and includes both the company's and the ERG's comments for clarity.

Table 3 Comparison of NICE final scope and decision problem addressed by company

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	• Adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)	• Adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)	N/A	The ERG considers the specified population to be appropriate
Intervention	• Aflibercept 40mg/ml solution for injection	• Aflibercept 40mg/ml solution for injection	N/A	The ERG considers the intervention to be appropriate and clinically relevant
Comparators	• Grid laser photocoagulation • Bevacizumab (not licensed in the UK for this indication) For people for whom laser photocoagulation has not been beneficial or is not suitable: • Ranibizumab • Dexamethasone intravitreal implant • Bevacizumab (not licensed in the UK for this indication)	• **Grid laser photocoagulation** • **Ranibizumab** • **Dexamethasone**	• Bevacizumab is an unlicensed treatment in ophthalmology and several licensed treatments are available • There has been no regulatory assessment of bevacizumab in BRVO and it cannot be considered best or routine practice • Bevacizumab was listed in the scope but was not used as a comparator in the cost-effectiveness analysis referred to in the decision making for ranibizumab (TA283)	The ERG agrees with the company's comments. The ERG notes that there are a number of published studies involving bevacizumab in the relevant clinical population, even though none of them involves a direct comparison with aflibercept

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Outcomes	• Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life • Mortality	• Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life • Mortality	N/A	The ERG agrees that the outcomes addressed in the company submission are in line with the NICE final scope
Economic analysis	• Incremental cost per quality adjusted life year • Time horizon should be sufficiently long to reflect any differences in costs or outcomes between the 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 • NHS and Personal Social Services • The submission uses the PAS price for aflibercept but not for the comparators • Cost effectiveness analysis included consideration of the benefit in the best and worst seeing eye	• A lifetime horizon was chosen because BRVO is a chronic disease and time horizons that exceed typical treatment durations are a common feature of previous cost-effectiveness models in BRVO and other back-of-the eye conditions	The ERG notes that the PAS price for aflibercept and the list prices for the comparators were used in the company submission.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Subgroups	• If the evidence allows, consideration will be given to a subgroup according to baseline visual acuity	• Subgroup analysis has been conducted for the 24-34 and 35-73 letter BCVA subgroups. This analysis has been conducted based on data from the VIBRANT study • Further subgroup analyses were also conducted, based on: gender; age; race; ethnicity; smoking history; anti-drug antibody response; geographic region; baseline retinal perfusion status	No subgroup comparisons versus ranibizumab or dexamethasone were possible as a connected evidence network could not be formed	The ERG agrees with the company's comments.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases MEDLINE EMBASE and CENTRAL were searched on 21st September 2015 using the OVID platform for publications written in English. No date restrictions were imposed. In addition, conference proceedings from 2012-2015 of seven European and American ophthalmic organisations were searched for further data.

The search strategies are documented in full in Appendix 8.2 of the company submission and are reproducible. The MEDLINE and EMBASE searches combine three search facets using the Boolean operator AND: aflibercept or the comparator interventions (ranibizumab, dexamethasone and laser coagulation); branch retinal vein occlusion; and study design (RCTs, systematic reviews or meta-analyses). The search in the Cochrane Library excluded the study design facet, which was appropriate.

A comprehensive range of terms were included in the search strategies using the Ovid mapping function as well as the most relevant controlled vocabulary terms (MeSH and Emtree). The searches for conference abstracts mostly searched for variations of the term, BRVO. The ERG considered the search strategies fit for purpose.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria used in the company's systematic review of clinical evidence are presented in Table 4.

Table 4 Inclusion and exclusion criteria used in the company's systematic review of clinical effectiveness (reproduced from Table 6 of the company submission)

Clinical evidence	Inclusion criteria	Exclusion criteria
Population	Adults with BRVO (studies reporting results for BRVO patients as "general population" or as subgroup of RVO)	Patients with RVO only, CRVO, DMO and AMD
Interventions	Aflibercept OR Dexamethasone OR Ranibizumab OR Laser	-
Comparators	Dexamethasone OR Ranibizumab OR Laser OR Placebo/BSC/sham/observation	-
Outcomes	Efficacy outcomes related to visual acuity e.g. percentage of patients gaining/losing 15 letters of BCVA, BCVA mean change from baseline (ETDRS, LogMAR, CRT change from baseline Safety outcomes (adverse events) e.g. percentage of patients experiencing intra-ocular pressure HRQoL	-
Study design	RCTs Recent systematic reviews and meta-analyses	Editorials OR Notes OR Comments OR Letters OR Observational studies OR Abstracts not reporting sufficient data for extraction
Restrictions	English language	Non-English language

Note: BRVO Branch retinal vein occlusion; RVO Retinal vein occlusion; CRVO Central retinal vein occlusion; DMO Diabetic macular oedema; AMD Age-related macular degeneration; BSC Best supportive care; BCVA Best corrected visual acuity: ETDRS Early treatment diabetic retinopathy study; LogMAR Logarithm of the minimum angle of resolution; CRT Central retinal thickness; HRQoL Health-related quality of life; RCT Randomised controlled study

Among the outcome measures considered relevant for inclusion in the systematic review of clinical evidence (Table 6, page 46, company submission), the company did not include mortality, despite it being specified as an outcome in Table 1 of the submission, i.e. in both the NICE final scope and the decision problem addressed by the company. At clarification, the company explained that mortality was omitted from Table 6 in error and that the search strategy did not specify any outcomes. In addition, the company stated that they conducted specific searches for studies reporting an association between BRVO and mortality risk. The ERG consider the clarification provided by the company satisfactory.

The study design specifies "recent systematic reviews and meta-analyses" but no definition of "recent" was provided in the company submission. At clarification, the company stated that the word "recent" should be ignored and that all systematic reviews and meta-analyses were captured in their review.

The company's systematic review was restricted to studies published in English.

4.1.3 Identified studies

The systematic review of clinical effectiveness conducted by the company identified one RCT assessing the efficacy and safety of aflibercept versus laser photocoagulation, VIBRANT,[55] and eight studies involving comparator treatments: BRAVO,[56] BRIGHTER, [57] COMRADE-B,[58] Azad 2012,[59] Parodi 2008,[60] Pichi 2014,[61] RABAMES,[62] Tan 2014.[63] Six of these eight trials involved ranibizumab as the main intervention.[56-59, 62, 63] One trial involved laser as the main intervention[60] and the remaining trial involved dexamethasone.[61]

Four of the nine identified studies were included by the company in the base case network meta-analysis: VIBRANT, BRAVO, BRIGHTER, COMRADE-B.[55-58] The remaining five studies were excluded from the base case NMA after assessment of heterogeneity, but included in sensitivity analyses.[59-63]

The VIBRANT trial was sponsored by Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA. The BRAVO trial was supported by Genentech, Inc., South San Francisco, California, USA. The BRIGHTER, COMRADE-B and RABAMES trials were

sponsored by Novartis Pharmaceuticals. The studies by Azad 2012[59] and Pichi 2014[61] declared no source of funding support. Parodi 2008 did not report funding support.[60]

4.1.4 Characteristics of included studies

Studies included in the base case NMA

VIBRANT was a phase 3, multicentre, double-masked, active controlled, 52-week RCT conducted at 58 sites in North America and Japan. Participants with BRVO or HRVO causing oedema involving the centre of the macula were randomised in a 1:1 ratio to receive either aflibercept (n=91) or grid laser photocoagulation (n=92). Only one eye per participant was designated as the 'study eye' and received treatment. Participants in the aflibercept group received 2mg aflibercept every 4 weeks from baseline to week 20 and then every 8 weeks from week 24 to week 48 with sham injections in between. A sham laser treatment was also administered at baseline. Participants in the laser group received macular laser photocoagulation at baseline and sham injections every 4 weeks from baseline to week 48.

Both treatment groups were eligible for rescue treatment from week 12 onwards; the criteria for rescue treatment were (a) >50 µm increase in CRT compared with the lowest previous measurement; (b) presence of new or persistent cystic retinal changes, subretinal fluid, or persistent diffuse oedema in the central OCT subfield; or (c) loss of >5 letters compared with the best previous measurement because of BRVO in conjunction with any increase in CRT. Participants in the aflibercept group who met at least one rescue treatment criterion received sham laser at week 12, 16 or 20; no treatment at weeks 24, 28, 32, 40, 44 and 48; or active laser at week 36. Participants in the laser group meeting at least one rescue treatment criterion before week 24 received one additional laser from week 12 to week 20. From week 24 to week 48, eligible participants received 2mg aflibercept every 8 weeks after 3 initial monthly doses. Any study eyes that developed clinically significant ocular neovascularisation during the study period could receive scatter laser photocoagulation. The company noted that "*scatter laser photocoagulation differs from grid-laser photocoagulation and does not impact visual acuity*".

BRAVO was a 6-month, phase 3, multicentre RCT conducted in the USA with an additional follow-up of 6 months. A total of 397 participants with macular oedema

following BRVO were randomised in a 1:1:1 ratio to receive monthly injections of 0.3mg ranibizumab, 0.5mg ranibizumab or sham injections.

BRIGHTER was a 24-month, phase 3b, multicentre, active-controlled RCT. A total of 455 participants with visual impairment due to macular oedema secondary to BRVO were randomised 2:2:1 to receive ranibizumab 0.5mg or ranibizumab 0.5mg + laser (3 injections at monthly intervals then PRN) or laser alone.

COMRADE-B was a 6-month, phase 3b, multicentre RCT. A total of 244 participants with visual impairment due to macular oedema following BRVO were randomised 1:1 to either ranibizumab 0.5mg (3 x monthly injections then PRN) or dexamethasone 0.7mg implant.

Table 5 presents the study characteristics of the four above studies.

Studies included in sensitivity analyses

Table 6 presents the characteristics of the five studies excluded by the company from the base case NMA but included in sensitivity analyses.

Table 5 Characteristics of the four studies included in the base case NMA

Study ID	Country	Intervention & comparator(s)	Number randomised/ analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
VIBRANT[55, 64]	USA, Canada, Japan (58 sites)	Aflibercept 2q4 vs laser	183/181	• ≥18 years old • BRVO or HRVO causing oedema involving the centre of the macula • Occlusion occurred within last 12 months • BCVA between ≤73 and ≥24 ETDRS letters (20/40-20/320 Snellen equivalent) in study eye	• History of vitreoretinal surgery or anticipated within 12 months of study day 1 • Current bilateral BRVO • Any intraocular surgery in last 3 months • Reduction in VA from causes other than BRVO • DMO or DR, ocular inflammation, or uncontrolled glaucoma • Uncontrolled diabetes mellitus • Uncontrolled blood pressure	Proportion of eyes that gained ≥15 ETDRS letters in BCVA from baseline at week 24
BRAVO[56]	USA (93 sites)	Ranibizumab 0.3mg vs ranibizumab 0.5mg vs sham	397/397	• ≥18 years old • Foveal centre-involved macular oedema secondary to BRVO	• Prior episode of RVO • Brisk afferent pupillary defect • History of radial optic neurotomy or	Mean change from baseline BCVA at month 6

Study ID	Country	Intervention & comparator(s)	Number randomised/ analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
				• BCVA using ETDRS charts of 20/40 to 20/400 (Snellen equivalent) • Mean central subfield thickness ≥250µm on 2 OCT measurements	sheathotomy • Any anti-VEGF treatment in study eye in last 3 months • Laser photocoagulation for MO in last 4 months • Panretinal scatter photocoagulation or sector laser photocoagulation in last 3 months or anticipated in next 4 months • Intraocular steroid use in last 3 months • Improvement of >10 letters on BCVA between screening and day 0 • CVA or MI in last 3 months • History or presence of wet or dry AMD	

Study ID	Country	Intervention & comparator(s)	Number randomised/ analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
BRIGHTER [65, 66]	Europe, Australia and Canada (81 sites)	Ranibizumab 0.5mg vs ranibizumab 0.5mg + laser vs laser	455/424[a]	• ≥18 years old • Visual impairment exclusively due to macular oedema secondary to BRVO • BCVA score at screening and baseline between 73 and 19 ETDRS letters	• Any systemic anti-VEGF drugs in previous 6 months • Panretinal laser photocoagulation in last 3 months or anticipated/scheduled in next 3 months • Focal or grid laser photocoagulation in last 4 months • Intra- or periocular corticosteroids in last 3 months • Any use of intraocular corticosteroid implants in study eye • Stroke or MI in 3 months before screening • Uncontrolled blood pressure • Any active periocular infection/inflammation • Uncontrolled glaucoma • Neovascularisation of	Mean change in visual acuity at 6 months

Study ID	Country	Intervention & comparator(s)	Number randomised/ analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
					iris or neovascular glaucoma	
COMRADE-B[67]	Germany, UK, Hungary, Poland, Czech Republic (73 centres)	Ranibizumab 0.5mg vs dexamethasone 0.7mg implant	244/244[b]	• Visual impairment due to macular oedema following BRVO • Diagnosis of BRVO at maximum 6 months before screening • BCVA using ETDRS chart of 20/40 to 20/400 in study eye	• Prior episode of RVO in study eye • CRT<250μm in study eye • Active formation of new vessels in study eye • Anti-VEGF treatment in study or fellow eye in last 3 months • IOP≥30mmHg or uncontrolled glaucoma • Improvement of >10 letters on BCVA between screening and baseline • Adequate fundus photographs not possible	Mean change in BCVA at 6 months

Note. [a]For BRIGHTER, reported sample size varies across sources: n=424 (number completing 6 months of study; Mones 2014), n=354 (Regnier 2014), n=357 (Regnier 2015). The published abstracts of BRIGHTER report number randomised as reported above, [b]For COMRADE-B, Reported number analysed varies across sources: n=244 (NCT 01396057), n=241 (Regnier 2014 & Regnier 2015). Sample sizes reported here from Eter 2015 abstract and Novartis CSR

Table 6 Characteristics of the five studies excluded from the base case NMA but included in sensitivity analyses

Study ID	Country	Intervention & comparator(s)	Number randomised/ Analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
Azad 2012[59]	NR (no. of centres NR)	Ranibizumab 0.5mg (1 injection) vs ranibizumab 0.5mg (3 injections) vs laser	30/30	• BRVO of at least 6 weeks duration • Perfused as confirmed on fluorescein angiography, with CMT ≥250μm and BCVA of 20/40 or worse	• Previous treatment for BRVO • Glaucoma • Macular oedema secondary to other causes, such as AMD and DR	Change in BCVA at 6 months
Parodi 2008[60]	Italy (1 centre)	Laser vs observation	31/31	• ERD secondary to ischaemic BRVO • ERD involvement of the macular area • BCVA approx. 20/40 or worse on standard ETDRS charts (Snellen equivalent) • Duration of BRVO not longer than 3 months	• Detection of features and conditions able to alter BCVA, other than those associated with BRVO • Identification of features typical of other diseases presenting ERD • Any other eye condition that could compromise vision in the study eye • Previous laser photocoagulation	Number of eyes that had gained at least 15 letters at 24 months
Pichi 2014[61]	Italy (“multicentre”; no. of centres NR)	Dexamethasone vs dexamethasone + laser	50/50	• Macular-involved BRVO with decreased visual acuity and perfused macular	• Foveal haemmorhages not disappeared after 3 months of observation • Ischaemic maculopathy	Final BCVA at 6 months

Study ID	Country	Intervention & comparator(s)	Number randomised/ Analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
				oedema for at least 3 months • Naïve to treatment • Baseline CRT >300µm	detected by FA • History of ocular surgery or rubeotic or advanced glaucoma • Underlying cause of oedema suspected not to be BRVO	
Tan 2014[63]	Australia (5 centres)	Ranibizumab 0.5mg vs sham	36/36	• Vision loss attributable to macular oedema following BRVO • Duration of vision loss between 6 weeks and 9 months before baseline • Macular oedema involving centre of fovea • Non-ischaemic macula • Baseline BCVA between 20 and 60 ETDRS letters • Mean central subfield thickness ≥250µm by OCT at baseline • Clear ocular media and adequate pupillary dilation	• Significant ischaemia following BRVO • Dry or wet AMD • Diabetic retinopathy • Any other ocular condition that would prevent improvement in VA • Treatment with intravitreal corticosteroids, intravitreal anti-VEGF agents or macular grid laser in 3 months before baseline • Retinal detachment or pars plana vitrectomy • Recent cataract extraction or post-op complications in last 12 months • Active ocular infection or immune uveitis	Mean change in BCVA at 12 months

Study ID	Country	Intervention & comparator(s)	Number randomised/ Analysed	Main inclusion criteria	Main exclusion criteria	Primary outcome
					• Recent CVA, MI or major ischaemic event • Known sensitivity to any anti-VEGF agent and sodium fluorescein	
RABAMES[62]	Germany (4 centres)	Ranibizumab 0.5mg vs ranibizumab 0.5mg + laser vs laser	31/30	• ≥18 years old • Chronic (>3 months, < 18 months) macular oedema secondary to BRVO • Baseline BCVA between 20/320 and equivalent to 20/40 (ETDRS) • CRT>225µm	• Relevant ocular disease potentially associated with increased intraocular VEGF levels • Relevant malignant systemic disease possibly associated with increased systemic VEGF levels • Previous treatment for macular oedema	Mean change in BCVA (logMAR) at 6 months

Duration of active drug treatment varied between trials. Duration was 52 weeks in total for VIBRANT, 6 months for BRAVO and 3 times monthly doses followed by PRN treatment for BRIGHTER and COMRADE-B.

The active drug treatment periods for the five studies included in sensitivity analyses but excluded from the base case NMA were as follows: 2 months for Azad 2012; 6 times monthly doses then PRN for Tan 2014 and 3 months for RABAMES. The dexamethasone implant in the study by Pichi 2014 was conducted at the first study visit. The study by Parodi 2008 did not involve drug treatment.

The majority of the identified trials involved assessment of primary outcomes at 6 months (VIBRANT, BRAVO, BRIGHTER, COMRADE-B, Azad 2012, Pichi 2014, RABAMES). Parodi 2008 assessed primary outcomes at 24 months and Tan 2014 at 12 months.

Duration of follow-up reported by the trials was either 12 months (VIBRANT [reported as 52 weeks], BRAVO, Tan 2014), 24 months (BRIGHTER, Parodi 2008) or 6 months (COMRADE-B, Azad 2012, Pichi 2014, RABAMES).

Baseline demographics and disease characteristics of participants enrolled in the four trials included in the company's base case NMA are presented in Table 7.

Table 7 Baseline demographics and disease characteristics of trials included in baseline NMA

	VIBRANT		BRAVO			BRIGHTER[a]			COMRADE-B[b]	
	AFL 2mg (n=91)	**Laser (n=90)**	**IVR 0.3mg (n=134)**	**IVR 0.5mg (n=131)**	**Sham (n=132)**	**IVR 0.5mg (n=183)**	**IVR 0.5mg + Laser (n=180)**	**Laser (n=92)**	**IVR 0.5mg (n=126)[c]**	**Dex (n=118)[c]**
Mean age (SD), years	67.0 (10.4)	63.9 (11.4)	66.6 (11.2)	67.5 (11.8)	65.2 (12.7)	64.7 (SD NR)	67.3 (SD NR)	67.8 (SD NR)	65.7 (10.9)	65.6 (10.0)
Sex, n (%)										
Male	44 (48.4)	54 (60)	67 (50)	71 (54.2)	74 (56.1)	50.8%	53.3%	40.2%	50 (39.7)	61 (51.7)
Female	47 (51.6)	36 (40)	67 (50)	60 (45.8)	58 (43.9)	49.2%	46.7%	59.8%	76 (60.3)	57 (48.3)
Race, n (%)										
White	70 (76.9)	62 (68.9)	112 (83.6)	107 (81.7)	108 (81.8)	NR	NR	NR	125 (99.2)	115 (97.5)
Black/African American	8 (8.8)	11 (12.2)	11 (8.2)	13 (9.9)	13 (9.8)	NR	NR	NR	0	NR
Asian	12 (13.2)	11 (12.2)	NR	NR	NR	NR	NR	NR	1 (0.8)	2 (1.7)
Other	1 (1.1)	6 (6.7)	12 (9)	11 (8.4)	12 (9.1)	NR	NR	NR	0	1 (0.8)
Mean (SD) BCVA, ETDRS letters	58.6 (11.4)	57.7 (11.3)	56 (12.1)	53 (12.5)	54.7 (12.2)	59.5 (SD NR)	56.6 (SD NR)	56.5 (SD NR)	57.9 (SD NR)[c]	58.4 (SD NR)[c]
Retinal perfusion status, n (%)			NR	NR	NR	Retinal ischaemia present in 87 patients	Retinal ischaemia present in 71 patients	Retinal ischaemia present in 41 patients	NR	NR
Perfused	55 (60.4)	62 (68.9)								
Nonperfused	20 (22.0)	16 (17.8)								
Unable to grade/missing	16 (17.6)	12 (13.3)								
Mean (SD) CRT/CFT, µm	CRT: 558.9 (185.9)	CRT: 553.5 (188.1)	CFT: 522.1 (201.9)	CFT: 551.7 (223.5)	CFT: 488.0 (192.2)	NR	NR	NR	NR	NR

	VIBRANT		BRAVO			BRIGHTER[a]			COMRADE-B[b]	
	AFL 2mg (n=91)	**Laser (n=90)**	**IVR 0.3mg (n=134)**	**IVR 0.5mg (n=131)**	**Sham (n=132)**	**IVR 0.5mg (n=183)**	**IVR 0.5mg + Laser (n=180)**	**Laser (n=92)**	**IVR 0.5mg (n=126)[c]**	**Dex (n=118)[c]**
Mean (SD) IOP, mmHg	14.6 (3.1)	14.9 (3.0)	15.0 (3.3)	14.9 (3.3)	14.8 (3.0)	NR	NR	NR	NR	NR
Mean (SD) time since BRVO diagnosis	42.4 (43.4) days	43.1 (38.8) days	3.6 (4.1) months	3.3 (3.1) months	3.7 (3.7) months	NR	NR	NR	NR	NR
Mean (SD) NEI-VFQ-25 score	77.8 (15.4)	75.6 (16.4)	NR	NR	NR	NR	NR	NR	NR	NR
HRVO classification, n (%)	1 (1)	3 (3)	16 (12)	17 (13.2)	17 (3.1)	NR	NR	NR	NR	NR

Note. [a]Data for BRIGHTER taken from Table 152 of company submission. Table 31 of company submission reports sample sizes of BRIGHTER as 142/143/69 and Regnier 2015 reports 142/143/72 (and the associated demographics differ from those in the table above). Table 152 and the published abstracts of BRIGHTER report sample sizes as shown above; [b]Data for mean age, sex and race taken from Novartis CSR; mean BCVA taken from Table 152 of company submission; [c]Regnier 2015 reports sample sizes as n=124 (ranibizumab arm) and n=117 (dexamethasone arm). Sample sizes reported here from Eter 2015 abstract and Novartis CSR

In general, demographics were balanced among intervention groups within trials, with few exceptions. In the VIBRANT trial, mean age was higher in the aflibercept group (67 years) than the laser group (63.9 years), whereas in the BRIGHTER trial, mean age was lower in the ranibizumab group (64.7 years) than the combined treatment group (67.3 years) or the laser group (67.8 years). In the laser group of VIBRANT, there was a larger proportion of males (60%) than females (40%), whereas in the ranibizumab group of the COMRADE-B trial there were more females (60.3%) than males (39.7%). In the BRAVO trial, mean baseline central foveal thickness varied across intervention groups: 522.1μm in the ranibizumab 0.3mg group, 551.7μm in the ranibizumab 0.5mg group, and 488.0μm in the sham group.

There were also some differences in disease characteristics between trials. For example, the BRAVO trial included more participants with HRVO (total 12.6%) than the VIBRANT trial (total 2.2%). Mean time since BRVO diagnosis was shorter in the VIBRANT trial (42.4/43.1 days) than the BRAVO trial (3.1/3.3/3.7 months). In clinical practice, people may present later than the mean 42.4 or 43.1 days in the VIBRANT trial. As a result, the findings of VIBRANT may not be reproducible in clinical practice.

Baseline demographics and disease characteristics of the five studies included in the sensitivity analyses are presented in Table 8.

Table 8 Baseline demographics and disease characteristics of studies included in sensitivity analyses

	Azad 2012			Parodi 2008		Pichi 2014		Tan 2014		RABAMES		
	IVR 0.5 mg x 1 (n=10)	**IVR 0.5 mg x 3 (n=10)**	**Laser (n=10)**	**Laser (n=16)**	**Obs (n=15)**	**Dex (n=25)**	**Dex + Laser (n=25)**	**IVR 0.5 mg (n=15)**	**Sham (n=21)**	**IVR 0.5 mg (n=10)**	**IVR 0.5 mg + Laser (n=10)**	**Laser (n=10)**
Mean age (SD), years	NR	NR	NR	68.2 (6.8)	66.8 (5.9)	Median (range) 68 (53-81)	Median range 69 (52-78)	69.6 (11.6)	66.7 (10.7)	64.2 (8.6)	65.9 (11.2)	68.8 (9.5)
Sex, n (%)						Total 22 males (44%), 28 females (56%)						
Male	5 (50)	6 (60)	6 (60)	9 (56.3)	9 (60)			8 (53.3)	9 (42.9)	4 (40)	6 (60)	5 (50)
Female	5 (50)	4 (40)	4 (40)	7 (43.7)	6 (40)			7 (46.7)	12 (57.1)	6 (60)	4 (40)	5 (50)
Race, n (%)	NR	NR	NR	NR	NR	NR	NR			NR	NR	NR
White								14 (93.3)	19 (90.5)			
Black/African American								0	0			
Asian								0	2 (9.5)			
Other								1 (6.7)	0			
Mean (SD) BCVA, ETDRS letters	0.18 (0.04) Decimal system	0.144 (0.02) Decimal system	0.158 (0.01) Decimal system	0.96 LogMAR	0.94 LogMAR	0.62 (0.32) LogMAR	0.53 (0.21) LogMAR	39.5 (21.2)	46.2 (15.1)	0.53 (0.24) LogMAR	0.41 (0.11) LogMAR	0.52 (0.13) LogMAR
Retinal perfusion status, n (%)	NR	NR	NR	100% ischaemic	100% ischaemic	NR	NR	NR	NR	NR	NR	NR
Perfused												
Nonperfused												
Unable to grade/missing												
Mean (SD) CRT/CFT, µm	493.2 (140) Mean	515.7 (126) Mean	500.2 (141) Mean	CFT: 695.7 (87.3)	CFT: 706.5 (97.8)	CRT: 466 (91)	CRT: 426 (109)	CFT: 615.6 (270.1)	CFT: 519.2 (183.7)	CRT: 584.2 (250.9)	CRT: 505.6 (81.8)	CRT: 570.6 (158.1)

	Azad 2012			Parodi 2008		Pichi 2014		Tan 2014		RABAMES		
	IVR 0.5 mg x 1 (n=10)	**IVR 0.5 mg x 3 (n=10)**	**Laser (n=10)**	**Laser (n=16)**	**Obs (n=15)**	**Dex (n=25)**	**Dex + Laser (n=25)**	**IVR 0.5 mg (n=15)**	**Sham (n=21)**	**IVR 0.5 mg (n=10)**	**IVR 0.5 mg + Laser (n=10)**	**Laser (n=10)**
	OCT thickness	OCT thickness	OCT thickness									
Mean (SD) IOP, mmHg	NR	NR	NR	NR	NR	NR	NR	15.7 (2.9)	14.1 (2.7)	NR	NR	NR
Mean (SD) time since BRVO diagnosis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mean (SD) NEI-VFQ-25 score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
HRVO classification, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Overall, demographics were generally balanced between groups within trials, with some imbalances evident. For example, within the Tan 2014 trial, the two arms showed a marked difference in baseline central foveal thickness (CFT) (615.6µm in the ranibizumab group versus 519.2µm in the sham group). It was generally not possible to make a comparison of demographics between trials due to variations in metrics used. However, some differences between trials were noted. For example, central retinal thickness (CRT) was lower in both arms of the trial by Pichi 2014 (466/426µm) than all arms of the RABAMES trial (584.2/505.6/570.6µm). Central foveal thickness was greater in the Parodi 2008 trial (695.7/706.5µm) than the trial by Tan 2014 (615.6/519.2µm).

4.1.5 Critique of data extraction

The company did not specify whether they based the methods of their systematic review of clinical evidence on published guidance. Title/abstract screening and full text screening were carried out by two independent reviewers, with any disagreements resolved by discussion or arbitration by an independent third party. The data extraction process used by the company and the number of reviewers involved are not detailed in the submission.

4.1.6 Quality assessment

The number of reviewers involved in the quality assessment process and their level of independence were not reported in the submission. The company stated that the NICE quality appraisal checklist was used to assess within-trial risk of bias. It appears to the ERG that the summary reported in Table 34 is in terms of the criteria recommended by the CRD for assessing the risk of bias in RCTs. These criteria, which involve assessment of selection (or allocation) bias, performance bias, detection bias, attrition bias and reporting bias, are considered appropriate by the ERG.

The ERG noted some potential issues with the company's quality assessment. For example, the ERG was unable to locate the quality assessment for the RABAMES study in the company submission. However, RABAMES is included in the company's summary of within-trial risk of bias table (Table 34). In addition, BRIGHTER and COMRADE-B are also included in the summary table (Table 34), even though they

were not part of the quality assessment performed by the company since they were available only as abstracts. The ERG disagreed with some of the classifications reported for the RABAMES and BRIGHTER studies in Table 34. For example, in RABAMES, the company's decision to consider 'blinding' as being at 'low' risk of bias is queried by the ERG. The primary publication for the RABAMES study[62] states that the OCT scans were evaluated by an independent expert who was masked to treatment allocation. The relevant ClinicalTrials.gov record[68] states that the trial was 'open label'. Therefore, it appears that the RABAMES trial was, at best, single blinded.

BRIGHTER is described as 'open label' in both the ClinicalTrials.gov record[66] (and relevant published abstracts[69-72] but judged to be at 'low' risk of bias for 'blinding' by the company (Table 34). The source of the data for the other domains of the quality assessment of BRIGHTER and for the quality assessment of COMRADE-B (Table 34) is unclear to the ERG.

Further potential inconsistencies in the company's quality assessment were noted by the ERG. The ERG does not agree with the company's judgement of 'low' risk of bias with regard to the 'baseline characteristics' for the BRAVO study. Marked differences in mean central foveal thickness between the intervention groups (522.1μm, ranibizumab 0.3mg group; 551.7μm, ranibizumab 0.5mg group; 488.0μm, sham group) were reported in the BRAVO study.

In Table 157 of Appendix 6, which reports the company's quality assessment of the Azad 2012, BRAVO and Tan 2014 trials, columns 5 and 6 appear to be duplicates, with column 6 considered by the ERG to be the correct one.

Azad 2012 was judged by the company to be at 'high' risk of bias for allocation concealment and blinding (Table 34). The company further stated that the "Azad 2012 study was associated with a high risk of bias in terms of allocation concealment and blinding, strengthening the decision to remove this study from the base case analysis" (page 110). On the other hand, in Table 157, Appendix 6, the company indicate that allocation concealment was "not clear" and blinding was "not reported". In the ERG's

opinion, quality-related criteria that are not reported equate to an 'unclear' risk of bias, as it is not possible to assess the risk of bias in the absence of the relevant information. Therefore, the company's assertion of high risk of bias for allocation concealment and blinding in the Azad 2012 study is disputed by the ERG.

In assessing selection bias, concealment of the treatment allocation is the key factor. According to the Cochrane Handbook for Systematic Reviews of Intervention (section 8.10.1),[73] "adequate concealment of treatment allocation shields those who admit participants to a study from knowing the upcoming assignments". In Table 142 of Appendix 4 and Table 157 of Appendix 6, the company appears to have assessed 'concealment of treatment allocation' in terms of masking of patients and study personnel to the identity of the actual treatment received, post allocation rather than at the time of allocation. Masking following allocation of treatment is assessed within the performance bias and detection bias categories. A check by the ERG showed that there appear to be no issues in any of the studies that reported sufficient information on which to make an assessment of 'concealment of treatment allocation', as defined by current methods guidelines.[73]

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 9.

Table 9 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?	No
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.

4.1.7 Evidence synthesis

Only one randomised controlled trial assessing the efficacy and safety of aflibercept for the treatment of macular oedema secondary to BRVO versus grid laser photocoagulation (VIBRANT)[58] was identify by the company. Therefore no standard meta-analyses were possible. As no head-to-head trials were identified comparing aflibercept with treatments other than laser photocoagulation, the company undertook a network meta-analysis (NMA) including aflibercept and all relevant comparators (laser photocoagulation, ranibizumab and dexamethasone).

Bevacizumab, which was listed among the relevant comparators in the NICE's final scope, was not included in the company's analyses. The company maintains that bevacizumab is not licensed for use in the UK and was not included as a comparator in a previous NICE appraisal (TA283 on ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion).[23]

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

VIBRANT was the only head-to-head trial assessing aflibercept versus laser photocoagulation. It is described in detail in the company submission and generally appears to be a well-designed and well-reported trial.[55]

The primary outcome in VIBRANT was the proportion of participants gaining ≥15 letters from baseline to week 24. Secondary outcomes included the change in BCVA score from baseline to week 24 and the change from baseline in central retinal thickness (CRT). Vision-related quality of life was also assessed using the mean NEI VFQ-25 (National Eye Institute Visual Functioning Questionnaire-25) total score at week 24. Additional efficacy outcomes reported in VIBRANT included perfusion status, retinal ischaemia and retinal fluid status at week 24. At week 24 the frequency of aflibercept injections in the aflibercept group was reduced to every 8 weeks. Rescue treatment according to pre-specified criteria could be given to all patients as required, for the remainder of the study (up to week 52).

Considering that the main outcomes in VIBRANT were assessed at 24 weeks, one could argue whether a clinical trial of six-month duration would be long enough for any reliable comparison with laser photocoagulation (the BVOS trial demonstrated that after laser treatment visual acuity continued to improve throughout the entire follow-up period - mean 3.1 years).

Furthermore, in VIBRANT the mean number of days since BRVO diagnosis was 43.1 days in the laser group and 42.4 days in the aflibercept group.[55] If, as the company maintains, early anti-VEGF treatment is required in people with BRVO, it is questionable whether this early treatment will be feasible in clinical practice due to current capacity constraints within the NHS. On the other hand, if people are treated later it is unclear whether the results observed in VIBRANT can be reproduced in clinical practice.

The company defined three study populations for statistical analysis. The full analysis set (FAS) included all randomised participants who received study treatment and had a baseline and at least one post-baseline BCVA assessment. The per protocol set included all patients in the FAS except those excluded due to major protocol violations (24 week evaluation only). The safety analysis set (SAF) included all randomised patients who received any study medication. Efficacy outcomes were analysed according to the full analysis set. In addition, a per-protocol analysis was performed by the company as a supportive analysis at week 24. The last observation carried forward (LOCF) approach was used to impute missing data except for baseline values.

Table 10 provides the summary results for the primary, secondary and additional efficacy outcomes assessed at week 24 and week 52. At week 24, compared with participants in the laser group, those in the aflibercept group were twice as likely to gain at least 15 letters (52.7% versus 26.7%; between group difference: 26.1% p=0.0003). There was also evidence that they had a greater decrease in CRT and greater improvement in the NEI-VFQ-25 quality of life scores at week 24. Improvements were also observed with regard to retinal ischaemia and retinal perfusion. Moreover, analysis of participants' retinal fluid status at week 24 showed that statistically significantly more participants treated with aflibercept, compared

with those treated with laser photocoagulation, were classified as ‘dry’ across the entire centre subfield as well as for the foveal centre only.

Table 10 Summary of the results of the VIBRANT study

	Laser (n=90) n (%)	**Aflibercept (n=91) n (%)**
WEEK 24: PRIMARY OUTCOME		
Patients who gained at least 15 letters in BCVA Difference (aflibercept vs laser)(%) p-value	24 (26.7)	48 (52.7) 26.1% (adjusted difference 26.6% (95% CI 13.0, 40.1%) 0.0003
WEEK 24: SECONDARY EFFICACY VARIABLES		
Change in BCVA (ETDRS letter score) Mean (SD) score LS mean change in BCVA Difference in LS mean vs aflibercept [+ aflibercept](95%CI) p-value	 6.9 (12.91) 3.2	 17.0 (11.88) 13.7 10.5 (7.1, 14.0) <0.0001
Change in CRT (by OCT, µm) Mean (SD) change LS mean change in CRT Difference in LS mean vs laser [+ aflibercept](95% CI) p-value	 -128.0 (195.02) -98.9	 -280.5 (189.7) -247.5 -148.6 (-179.8, -117.4) <0.0001
Change in NEI-VFQ-25 total score Mean (SD) score LS mean change in NEI-VFQ-25 total score Difference in LS mean vs aflibercept [+ aflibercept](95%CI) p-value	 6.3 (12.341) 2.7	 7.7 (11.081) 5.3 2.6 (-0.3, 5.5) 0.08
Perfusion status (%) p-value	67.1%	80.2% 0.05
Retinal ischaemia decrease (%)	17.6%*	29%* Not stated
“Dry” retinal fluid status in entire centre subfield (%) p-value	7.8%	34.1% 0.0001 (nominal)

	Laser (n=90) **n (%)**	**Aflibercept (n=91)** **n (%)**
"Dry" retinal fluid status in the foveal centre (%) p-value	38.9%	90.1% 0.0001 (nominal)
WEEK 52	**Laser + aflibercept**	**Aflibercept**
Patients who gained at least 15 letters in BCVA Difference (aflibercept vs laser)(%) p-value	37 (41.1)	52 (57.1) 16% (adjusted difference 16.2% [95% CI 2.0, 30.5] 0.03 (nominal)
Perfusion status (%) p-value	78%	78% Not stated
Retinal ischaemia decrease (%) % difference	29.6%	34.7% 5.1% (adjusted difference 5.7%)
"Dry" retinal fluid status in entire centre subfield (%) p-value	31.1%	38.5% 0.28 (nominal)
"Dry" retinal fluid status in the foveal centre (%) p-value	84.4%	94.5% 0.03 (nominal)

*Source: CHMP Assessment Report[77]

From week 24 rescue aflibercept treatment could be offered to participants in the laser group if required. In the aflibercept group laser rescue was permitted from week 36. Seventy four per cent (67/90) of participants in the laser photocoagulation group received rescue aflibercept treatment and 10% (9/91) in the aflibercept group received laser treatment.

At week 52 there was still a statistically significant difference in the proportion of participants gaining at least 15 letters in BCVA (57.1% in the aflibercept group versus 41.1% in the laser group.

The company performed **subgroup analyses** on the FAS population based on the following variables: gender, age, race, ethnicity, smoking history, geographical

region, retinal perfusion, baseline BVCA (>20/200 or ≤ 20/200) and anti VEGF response. In general, results of the subgroup analyses were consistent with those observed in the overall population. However, some subgroups had too few participants to draw any reliable conclusion.

It is worth pointing out that although the company recognised that "the degree of vision loss depends on the extent of retinal involvement and on macular perfusion status" (page 32 of the submission), they did not present subgroup analyses according to macular/foveal perfusion (i.e. macular ischaemia present/absent and extension; perifoveal capillaries present/absent), which is an important factor to determine whether treatment should be considered (as per current Royal College of Ophthalmologist guidelines). Similarly, they did not conduct subgroup analyses according to duration of the macular oedema or to CRT measurements (≤400 micrometres, >400 micrometres). It worth mentioning that the TA346 on aflibercept for treating diabetic macular oedema published in July 2015 recommends aflibercept as an option for treating visual impairment caused by diabetic macular only if the eye has a CRT of 400 micrometres or more at the start of treatment given that in those with CRT of less than 400 micrometres laser was a more cost-effective strategy.

Although macular oedema due to retinal vein occlusion is a different clinical entity, a subgroup analysis based on CRT would have been pertinent. In general, the ERG is of the opinion that the results of these subgroup analyses would have been clinically relevant, as they could have provided further information on efficacy outcomes.

The safety profile of aflibercept for the treatment of participants with BRVO was evaluated in the 52-week VIBRANT study. With regard to the incidence of ocular or non-ocular treatment-emergent adverse events (TEAEs), aflibercept was well tolerated by participants with BRVO with the exception of injection-related TEAEs. At week 24, the incidence of injection-related ocular TEAEs in the study eye was 25.3% in the aflibercept group compared to 8.7% in the laser group. By week 52, the difference between groups decreased (aflibercept 29.7%, laser 19.6%) due to the use of aflibercept rescue injections in the laser group. In general, TEAEs in the study eye consistent with the injection procedure were more common in the aflibercept groups (e.g. conjunctival haemorrhage; eye irritation, foreign body sensation), whereas

TEAEs consistent with disease worsening were more common in the laser groups (see Table 43, company submission). At week 24, the most common non-ocular TEAE was hypertension, which was balanced across treatment groups. Nasopharyngitis was observed more often in the aflibercept group (6.6% versus 1.1%). With regard to arterial thromboembolic disorders, two events (non-fatal stroke, non-fatal MI) were observed in the laser group in VIBRANT (2%) and none in the aflibercept group.

Table 11 shows the overall adverse event profile of participants in the VIBRANT study.

Table 11 Overall adverse event profile through week 24 and week 52 (reproduced from Table 42 of the company submission)

	Through week 24		Through week 52	
	Laser (N=92) n (%)	**Aflibercept (N=91) n (%)**	**Laser (N=92) n (%)**	**Aflibercept (n=91) n (%)**
Any TEAE	**54 (58.7)**	**58 (63.7)**	**75 (81.5)**	**76 (83.5)**
Non-ocular (systemic)	46 (50.0)	43 (47.3)	63 (68.5)	61 (67.0)
Ocular (study eye)	25 (27.2)	34 (37.4)	44 (47.8)	45 (49.5)
Any study drug-related AE				
Ocular drug-related (study eye)	1 (1.1)	1 (1.1)	2 (2.2)	2 (2.2)
Non-ocular drug-related	2 (2.2)	1 (1.1)	2 (2.2)	3 (3.3)
Any injection-related TEAE	**8 (8.7)**	**23 (25.3)**	**19 (20.7)**	**27 (29.7)**
Injection-related ocular TEAE	8 (8.7)	23 (25.3)	19 (20.7)	27 (29.7)
Study eye	8 (8.7)	23 (25.3)	18 (19.6)	27 (29.7)
Any laser-related TEAE	**3 (3.3)**	**2 (2.2)**	**5 (5.4)**	**2 (2.2)**
Laser-related ocular TEAE	3 (3.3)	2 (2.2)	5 (5.4)	2 (2.2)
Study eye	3 (3.3)	2 (2.2)	5 (5.4)	2 (2.2)
Any serious TEAE	**9 (9.8)**	**9 (9.9)**	**10 (10.9)**	**14 (15.4)**
Non-ocular (systemic)	9 (9.8)	8 (8.8)	10 (10.9)	13 (14.3)
Ocular (study eye)	0	1 (1.1)	0	1 (1.1)
Drug-related serious TEAE	**0**	**0**	**0**	**0**
Any injection-related serious TEAE (study eye)	**0**	**1 (1.1)**	**0**	**1 (1.1)**
Any laser-related serious TEAE	**0**	**0**	**0**	**0**
Any AEs leading to discontinuation of study drug	**0**	**3 (3.3)**	**0**	**4 (4.4) [a]**
Any death	**1 (1.1)**	**0**	**1 (1.1)**	**0**
Any APTC adjudicated events	**1 (1.1)**	**0**	**2 (2.2)**	**0**

Notes: aflibercept administered as 2mg every 4 weeks through week 24, then every 8 weeks through week 48. Laser treatment administered on day 1; rescue laser treatment possible after week 12 and aflibercept rescue treatment (67 of 90 patients) possible after week 24.
APTC: Anti-Platelet Trialists' Collaboration

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

Bevacizumab was not considered a relevant comparator for this appraisal and therefore was not included in the company's NMA. The ERG has not evaluated the effect of including bevacizumab as a comparator treatment.

The company's search identified nine eligible studies, but five of these were excluded from the primary (base-case) analyses due to heterogeneity and were only included in sensitivity analyses. When evaluating heterogeneity the company compared the similarity of trials to VIBRANT, as the only available aflibercept study. Trials could be excluded for up to six reasons: study population, duration of disease, baseline BCVA, baseline CRT, time points and treatment regimen:

- Azad 2012 was excluded because it had higher mean baseline BCVA than VIBRANT and for the number of doses of ranibizumab.[59]
- Parodi 2008 was excluded because it enrolled patients exclusively with exudative retinal detachment secondary to BRVO, because it had slightly lower mean BCVA at baseline and because outcomes were reported at two years.[60]
- Pichi 2014 was excluded because the mean duration of disease was longer and because it had lower mean baseline central retinal thickness (CRT) at baseline.[61]
- Tan 2014 was excluded because it had lower BCVA at baseline compared with VIBRANT.[63]
- RABAMES was excluded because of the number of doses of ranibizumab[62].

Unlike for the previous four studies, the company explored the inclusion of RABAMES in separate sensitivity analyses.[62]

The network diagram for the four-study base case NMA is reproduced in Figure 3.

Seven treatment arm labels have been included: aflibercept, laser, ranibizumab 0.5 mg, ranibizumab 0.5 mg plus laser, ranibizumab 0.3 mg plus laser, dexamethasone and sham plus laser. The company chose to label some trial arms differently to the published reports (Table 35 of the company submission). The differences usually

relate to the inclusion of "laser" in the label if participants could be treated with laser as required. Therefore, some arms originally named as "sham" or "ranibizumab" have been relabelled as "sham plus laser" or "ranibizumab plus laser" by the company. This has resulted in a different network diagram than might otherwise have occurred.

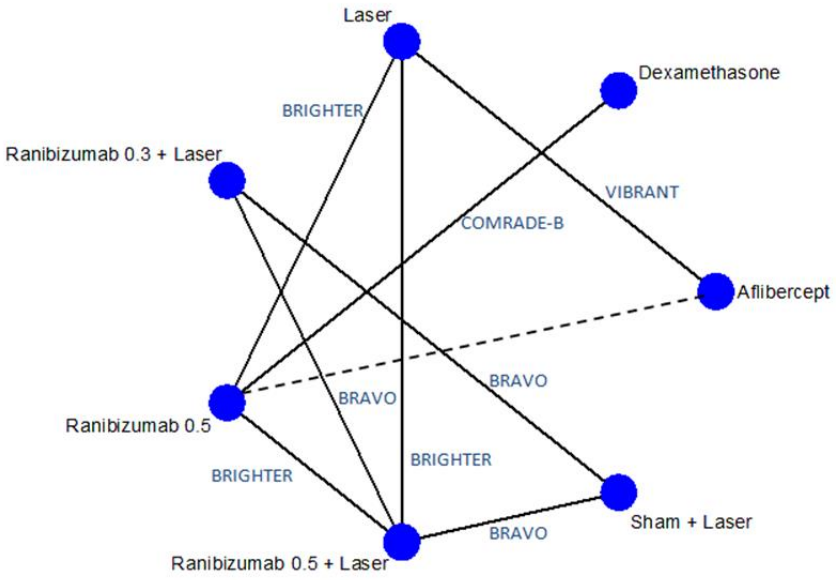

Figure 3 The network diagram used in the company's base-case analyses (reproduced from Figure 18 of the company submission)

NMAs were undertaken for two related outcomes: the proportion of patients gaining ≥ 15 letters from baseline and change in BCVA from baseline. Change in BCVA was available for all nine identified studies. The gaining ≥ 15 letters outcome was available for eight studies (all except Pichi 2014).[61]

For the gaining ≥ 15 letters outcome, the company's base-case NMA results using the four-study network and a fixed effect model (median odds ratio (95% CrI)) were 0.93 (0.38, 2.31) for ranibizumab versus aflibercept and 0.34 (0.12, 0.96) for dexamethasone versus aflibercept. Odds ratios were less than one, favouring aflibercept, but credible intervals were wide and only the latter result was statistically significant. The corresponding results including all eight studies with available data were 1.08 (0.45, 2.61) and 0.40 (0.14, 1.10) respectively.

For the change in BCVA outcome, the base-case results (median difference (95% CrI)) were -2.68 (-7.43, 2.05) for ranibizumab versus aflibercept and -10.59 (-16.08, -5.10) fpr dexamethasone versus aflibercept, where differences less than zero favour aflibercept. The corresponding results including all nine studies in the network were -2.43 (-7.13, 2.17) and -10.32 (-15.80, -4.93) respectively.

Although other outcomes were considered (mortality, losing ≥ 15 letters, etc.), it was not possible to include these in an NMA because they were infrequently reported and because the network diagrams for these outcomes did not lead to a connected network.

The full network diagram containing all the nine identified studies was not provided by the company and the ERG had to reconstruct this from the treatment numbers provided in the WinBUGS programs (Appendix 7 of the data company submission). The full network contained two additional treatment nodes (labelled 8 and 9 in Appendix 7) but the ERG noted an apparent error with node 8 as this was used for both the Parodi 2008[60] and the Pichi 2014[61] studies, which do not share any common treatment arms. This concerns only the change in BCVA outcome as there are no ≥ 15 letter data for Pichi 2014.[61]

The ERG noted some inconsistencies between the trial data presented in Table 37 of the company's main submission, the data reported in Appendix 7 and the data in trial publications. At clarification the company provided a revised version of Table 37 and confirmed that the data in the Appendix were correct. The ERG then noted further discrepancies with data in the revised Table 37, although these mainly concerned the studies included in the full network.

Data in the revised Table 37 still did not agree with Appendix 7 for the Azad 2012 study,[59] but the ERG were able to confirm that the data in the Appendix 7 were correct. The ERG also noted slight inconsistencies with the data used for the COMRADE-B study. The company used data reported in an NMA conducted by Novartis[58, 74] although the ERG noted that the CSR[75] and an abstract by Eter[76] for this study included slightly different results. The ERG also requested clarification on the

source of data for the BRIGHTER study. The company confirmed that this was sourced from either the Novartis NMA or from an abstract by Mones.[57]

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

Nine eligible studies were identified but five were excluded from the base-case analyses because of their lack of similarity to VIBRANT. Of the four studies included in the base-case NMA, only one was available as a full text peer-reviewed publication while all five excluded studies were available as full text peer-reviewed publications. Although the ERG agrees that these five excluded trials have important clinical differences compared to VIBRANT, they could have been considered eligible for inclusion according to the inclusion criteria specified in NICE's final scope. The ERG does, however, note that using the DIC statistic the NMA models including only four studies did seem to provide considerably better model fit than the full models. It is worth noting that the company presented the results of sensitivity analyses including all studies in the clinical effectiveness section of the submission but did not use these results in their cost-effectiveness analyses.

The company's NMA used the recommended WinBUGS programs included in the NICE Decision Support Unit Technical Support Document 2 (DSU TSD 2). Results were only presented for two of the possible pairwise comparisons in the network: ranibizumab 0.5 mg versus aflibercept and dexamethasone versus aflibercept. Two other ranibizumab arms were included in the network (ranibizumab 0.5 mg plus laser and ranibizumab 0.3 mg plus laser) but no comparison with aflibercept was reported. The company presented results for both fixed and random effects models and using both mean and median as the summary statistic. Ninety-five percent credible intervals were provided.

The NMA was restricted to two outcomes and only analyses at six months were considered. This is reasonable given that after six months VIBRANT allowed aflibercept rescue treatment in the laser arm, but it means that data at 12 months, which suggested a more modest difference between aflibercept and laser, were not considered. Other studies within the network also allowed rescue treatment, but at variable time points.

The company presented four sets of results based on fixed or random effect models and whether the mean or median is used as the summary statistic. The base-case results use the median from the fixed effect model. The fixed effect model was selected based on a lower model DIC statistic and because the random effects model produced models with very wide credible intervals. The ERG noted that the DIC for the fixed and random effects models were actually very similar with the random effects DIC slightly lower for the change in BCVA outcome. The ERG was unable to replicate the company's random effects results (see below) and to investigate this further in the available time.

Due to clinical heterogeneity between studies in the network it would be important to investigate the impact of this on the results. The ERG agrees that it would be difficult to assess this using meta-regression techniques, because of the limited number of studies. The company reported that they had attempted meta-regression but that the model failed to converge.

The company did not test for inconsistency within the NMA and stated that this was unnecessary because there were no closed loops in the evidence network. The ERG believes that inconsistency could have been assessed as there were closed loops in the network diagram (Figure 3), although none involved aflibercept as a comparator.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG attempted to repeat the company's NMA results using the programs supplied in Appendix 7 of the company submission.

For the gaining ≥ 15 letters outcome, the ERG was able to replicate the two base-case results - these used only the four-study network and reported median OR (95% CrI) using a fixed effect model. The results were 0.93 (0.38 to 2.31) for aflibercept versus ranubizumab and 0.34 (0.12 to 0.96) for aflibercept versus dexamethasone. As mentioned above the ERG noted that the corresponding random effects model results produced by the company had extremely wide CrIs but were unable to run the company's supplied code. The ERG was also able to confirm the company's results using the full network of eight studies, although with a small difference in the 95% CrIs.

The ERG was also able to confirm some of the results for the change in BCVA outcome. Although the ERG were unable to run the company's WinBUGS code for generating initial values, the results obtained after automatically generating initial values were similar to the company's results. As there appeared to be an error in the coding of the Pichi 2014[61] study in the Appendix 7 data, the ERG also conducted an additional NMA in which the codes for this study were changed from 8 versus 9 to 7 versus 9, since code 7 appeared to relate to dexamethasone and code 8 to observation. The results were similar to those obtained by the company.

The ERG is also aware of the results of the published NMA sponsored by Novartis which was used as the source of data for two studies included in the company submission.[58, 74] For the gaining ≥ 15 letters outcome, the point estimate results of Novartis' random effects NMA favour ranibizumab over aflibercept (Table 12 below), although with a wide CrI (median OR: 1.06; 95% CrI 0.16 to 8.94). The corresponding results for dexamethasone versus aflibercept were similar to those in the company submission, although with a much wider CrI, but results for the change in BCVA outcome appeared to be rather different to those in the company submission (Table 13 below). The Novartis NMA includes a different network of studies and there are differences in the labelling of treatment arms. The ERG believes that both companies' analyses appear to have made reasonable assumptions but that different assumptions regarding inclusion of trials and choice of model can affect the observed results.

Table 12 Summary of NMA results for gaining ≥ 15 letters (OR<1 favours aflibercept)

		No. of studies in network	Ranibizumab vs aflibercept (median (95% CrI))	Dexamethasone vs aflibercept (median (95% CrI))
Company submission	**Fixed effect**	**4**	**0.93 (0.38, 2.31) ***	**0.34 (0.12, 0.96) ***
Company submission	Random effects	4	0.91 (0.02, 37.84) **	0.33 (0.00, 31.52) **
Company submission	Fixed effect	8	1.08 (0.45, 2.61) *	0.40 (0.14, 1.10) *
Regnier NMA[58, 74]	Random effects	7	1.06 (0.16, 8.94)	0.36 (0.04, 4.54)

* ERG ran company's program and could confirm results

** ERG was unable to confirm results

Table 13 Summary of NMA results for change in BCVA (difference<0 favours aflibercept)

		No. of studies in network	Ranibizumab vs aflibercept (median (95% CrI))	Dexamethasone vs aflibercept (median (95% CrI))
Company submission	**Fixed effect**	**4**	**-2.68 (-7.43, 2.05) ***	**-10.59 (-16.08, -5.10) ***
Company submission	Random effects	4	-2.56 (-12.25, 7.41) *	-10.51 (-22.25, 1.54) *
Company submission	Fixed effect	9	-2.43 (-7.13, 2.17) *	-10.32 (-15.80, -4.93) *
ERG reanalysis	Fixed effect	9	-2.45 (-7.14, 2.17) **	-10.33 (-15.84, -4.95) **
Regnier NMA[74]	Random effects	7	1.4 (-5.2, 8.5)	-6.7 (-14.0, 1.3)

* ERG ran company's program and obtained similar results

** ERG ran company's program after changing code 8 to code 7 for the Pichi 2014 study

4.6 Conclusions of the clinical effectiveness section

The ERG believes that the methods used in the systematic review and network meta-analysis (NMA) were generally appropriate and correctly applied. When conducting the NMA the company used the recommended WinBUGS programs from the NICE DSU TSD 2.

The principal concerns relate to the transparency of the assumptions used. The company excluded five studies from the review of clinical evidence. Although the ERG agrees that there is clinical heterogeneity between these studies and VIBRANT, the ERG is of the opinion that these studies meet the inclusion criteria specified in the NICE's final scope and a more transparent approach would have been to include these studies in the primary analyses, or at least to use these results in the economic model (cost-effectiveness sensitivity analyses). The reasons for exclusion did not appear to be pre-specified. Data for two of the four remaining studies were taken from a conference poster presented by a rival company. The ERG also noted that the four excluded studies were all of small sample size (<100 participants per treatment arm).

Apart from excluding some of the eligible studies, the company has also taken a number of other decisions: to use median instead of mean in the NMA, to use fixed effect rather than random effects models in the NMA, to use gaining ≥ 15 letters as the principal outcome measure and to use only data at 6 months. Although individually these decisions are reasonable and justifiable, the results used in the economic model had a point estimate favouring aflibercept over ranibizumab.
It is worth noting that if other assumptions had been made (as those made by Novartis),[58, 74] a point estimate favouring ranibizumab could have been obtained, although credible intervals were very wide with considerable overlap with the company's results.

5 Cost effectiveness

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

5.1.1 State objective of cost effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

A systematic literature search was performed which aimed to identify economic evaluations in the area of BRVO and RVO.

Reports of cost effectiveness were sought by searching MEDLINE (Ovid), EMBASE (Ovid), NHS Economics Evaluation Database (NHS EED) and EconLit on 7th October 2015 for economic evaluations published from 2000 in English. In addition, ISPOR conference proceedings were searched on 23rd November 2015. The search strategies are documented in full in Appendix 8 of the company submission. The MEDLINE and EMBASE searches combine three search facets using the Boolean operator AND: aflibercept or the comparator interventions (ranibizumab, dexamethasone and laser coagulation); branch retinal vein occlusion; and study design (economic evaluations). The searches in NHS EED and Econlit excluded the study design facet, which was appropriate.

A comprehensive range of terms were included in the search strategies using the Ovid mapping function as well as the most relevant controlled vocabulary terms (MeSH and Emtree). The searches for conference abstracts mostly searched for variations of the term, BRVO. The ERG considered the company's search strategies fit for purpose.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Economic evaluations of patients with BRVO or RVO were eligible for inclusion. Relevant interventions were aflibercept, ranibizumab, dexamethasone, laser and placebo/BSC/sham/observation. Apart from the exclusion of bevacizumab, the inclusion and exclusion criteria used for study selection appear to be clear and appropriate (Table 45 of the company submission).

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies.

Three cost-utility analyses[78-80] and two costing studies[81, 82] were identified. Appendix 8, section 8.8.5, provides a list of the 12 studies that were excluded at full text assessment. The ERG considered that two of these studies met the inclusion criteria.[80, 83] An exploratory focused search undertaken by the ERG identified an additional conference abstract[84] and a recent paper[85] that was published after the company undertook their searches.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

A recent study by Adedokun & Burke[a] [85] estimated the cost effectiveness of ranibizumab compared with aflibercept for patients with macular oedema secondary to BRVO. A lifetime bilateral Markov model with health states defined by 10 letter bands was developed. An initial six month cycle was followed by monthly cycles.

Treatment was limited to two years. Treatment effectiveness was based upon the NMA of Regnier et al[74] with an odds ratio of gaining 10+ letters of 1.06 (0.16-8.94) for the first six months. Thereafter, treatment effectiveness was assumed to be the same.

Quality of life values were drawn from Czoski-Murray[86] though the assumptions about the WSE effects upon quality of life are not explicit. The number of ranibizumab injections during the first six months was estimated to be 5.1, a weighted average of 4.8 during BRIGHTER, 4.9 during COMRADE-B and 5.7 during BRAVO, while that for aflibercept was estimated as 5.7 from VIBRANT. Injection frequency for the second 6 months was 2.7 for ranibizumab from BRAVO compared to 3.3 for aflibercept from VIBRANT. List prices used were £742 for ranibizumab and £816 for aflibercept. The lifetime cost per patient for ranibizumab was £15,273 compared to £17,347 for aflibercept, with ranibizumab also providing a gain of [redacted]

[a] Funded by Novartis

QALYs and so dominating aflibercept. The model used was apparently based upon that previously submitted to NICE.

The main elements of interest are the clinical effectiveness estimates and dosing assumptions of Adedokun & Burke[85]:

- Is ranibizumab better than aflibercept?
- Does ranibizumab require fewer administrations than aflibercept?

An abstract by Lovato et al[84] reports cost effectiveness estimates for aflibercept compared with ranibizumab for patients with macular oedema secondary to BRVO. It appears to be largely consistent with the company submission for this STA, with a median odds ratio for gaining 15 letters of 1.06 favouring aflibercept. Due to confidential PASs, the abstract reports that, at price parity, aflibercept yielded a gain of 0.045 QALYs, while reducing drug costs by £4 per patient.

Taylor et al[b] [80] reported estimates of the cost effectiveness of ranibizumab compared with laser photocoagulation for patients with macular oedema secondary to RVO, with estimates specific to BRVO and CRVO. Clinical effectiveness estimates were drawn from the BRAVO trial for the first six months, with equivalent clinical efficacy being assumed thereafter. Efficacy for the second six months was drawn from BRAVO with efficacy for the second year being drawn from HORIZON. A bilateral Markov model appears to have been constructed, with the WSE quality of life impact being 30% that of the BSE. The frequencies of treatment were drawn from BRAVO and CRUISE for the first year of ranibizumab treatment, and from the HORIZON trial for the second. Due to treatment switching during BRAVO, the number of laser administrations was taken from the SCORE trial for the first two years. It was assumed that there would be no further ranibizumab or laser treatments. For BRVO, ranibizumab was estimated to result in a net gain of 0.518 QALYs for an incremental cost of £8,141 resulting in a cost effectiveness estimate of £15,710 per QALY.

[b] Funded by Novartis

A Bres Med poster presentation, Almond et al[c] [83] estimated the cost effectiveness of dexamethasone compared with bevacizumab for patients with macular oedema secondary to BRVO. It was estimated that patients would receive 9.96 bevacizumab injections compared to 2.24 dexamethasone implants. The MTC suggested that, at day 60, dexamethasone resulted in a net gain of 2.55 (-5.28, 10.48) letters compared to bevacizumab but that by day 180 this had reversed to a loss of -1.74 (-9.57, 6.19) letters. The 180 day results suggested a net loss of -0.03 QALYs. Nonetheless, dexamethasone was estimated to have lower total costs of £3,693 compared with £6,253 for bevacizumab. This was largely due to the high number of bevacizumab administrations, seemingly coupled with administrations for both drugs being costed assuming 25% day case and 75% outpatient administration.

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

5.2.1 NICE reference case checklist

Table 14 below illustrates the NICE reference case checklist.

Table 14 NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	The scope specifies: – Laser – Bevacizumab And for those not suitable for or not benefitting from 1st line laser: – Ranibizumab – Dexamethasone – Bevacizumab	The submission compares a number of treatment sequences of 1st line treatment followed by a change to 2nd line rescue treatment from month 6 if required or ongoing 1st line treatment if 2nd line rescue is not required: – Aflibercept-laser – Laser-aflibercept – Laser-ranibizumab – Laser-dexamethasone

[c] Funded by Allergan

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Patient group	As per NICE scope. "*Adults with visual impairment caused by macular oedema secondary to branch retinal vein occlusion*"	Yes. The submission is based upon the patient population of the VIBRANT trial.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility.
Time horizon	Sufficient to capture differences in costs and outcomes	35 years which given the baseline age of 65 is sufficient.
Synthesis of evidence on outcomes	Systematic review	The main clinical effectiveness estimates are drawn directly from the VIBRANT trial. The odds ratio estimates for ranibizumab and dexamethasone are drawn from the company NMA.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Not for the base case. This relies upon an experimental time trade-off study in the literature: Czoski-Murray (2009) which has been used in previous NICE assessments for eye conditions. A scenario analysis using the OLS analysis of the VIBRANT EQ-5D data is presented.
Benefit valuation	Time-trade off or standard gamble	Time trade off.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Not for the base case. The experimental study recruited UK healthy volunteers. 42 were respondents to a random sample of 2000 invitations. The other 66 respondents were recruited by word of mouth. The mean age

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		was 32 years, with 66 being in employment and 28% having a university degree. The mean TTO QoL was 0.960. The VIBRANT EQ-5D analysis uses the UK social tariff which was measured with 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	Partial. The main clinical inputs on which it rests are not implemented probabilistically.
Sensitivity analysis		A range of sensitivity analyses are presented.

5.2.2 Model structure

Due to both ranibizumab and dexamethasone being approved for 2nd line use after unsuccessful laser therapy or where laser is not appropriate, the company submission seeks to address two questions:

- Is 2nd line rescue aflibercept cost effective compared to 2nd line rescue ranibizumab and 2nd line rescue dexamethasone?
- Is 1st line aflibercept followed by 2nd line rescue laser cost effective compared to 1st line laser followed by 2nd line rescue aflibercept?

The model structure adopted to try to answer the first question is largely driven by the data available from the NMA. The base case model structure adopted to answer the

second question is the same as that adopted to answer the first question, but does not rely upon the data available from the NMA.

A Markov model with a four week cycle is used to simulate the evolution of patients' BCVA in their study eye and in their non-study eye, with the baseline age of 65 years and the female proportion of 45% being taken from VIBRANT. The 6.05% rate of bilateral BRVO at baseline and 2.50% annual incidence of BRVO for the fellow eye during the first 5 years of the model is from expert opinion.

Patients' eyes are characterised as falling into five 15 letter BCVA bands:

- VA1: 80 letters to 100 letters, with a mean of 90 letters being assumed
- VA2: 65 letters to 79 letters, with a mean of 72 letters being assumed
- VA3: 50 letters to 64 letters, with a mean of 57 letters being assumed
- VA4: 35 letters to 49 letters, with a mean of 42 letters being assumed
- VA5: 0 letters to 35 letters, with a mean of 17 letters being assumed

Transition probability matrices (TPMs) are estimated for aflibercept-laser and laser-aflibercept from VIBRANT data using the MSM package in R. One 4-weekly TPM for each arm is estimated for between week 0 and week 24 and applied 7 times. From this point, patients may discontinue their original treatment and receive rescue treatment. Two 4-weekly TPMs for each arm are estimated for between week 28 and 52; one TPM for those remaining on their original treatment and one TPM for those receiving rescue treatment. These TPMs are applied 6 times.

For the laser-ranibizumab and the laser-dexamethasone arms, the week 0 to week 24 modelling is exactly the same as in the laser-aflibercept arm. Rates of rescue treatment between week 28 and 52 are also the same. However, the TPM for those receiving rescue ranibizumab or rescue dexamethasone is derived by applying the NMA odds ratios of gaining at least 15 letters of 0.93 for ranibizumab and 0.34 for dexamethasone to the probabilities of gaining letters in the laser-aflibercept week 28 to 52 rescue aflibercept TPM of the laser-aflibercept arm.

For the comparison of aflibercept-laser with laser-aflibercept, for the first year of the model, a simpler alternative to the TPMs of applying the VIBRANT 4 weekly patient distributions is also available, labelled as the "shift-tables" approach.

During the first year of treatment, a constant proportion of patients is assumed to discontinue 1st line treatment each cycle and move into an off treatment health state, receiving neither 1st line treatment nor 2nd line rescue treatment. These proportions are based upon the VIBRANT trial, with 11/92 patients discontinuing in the aflibercept-laser arm and 9/92 patients discontinuing in the laser-aflibercept arm. Ranibizumab and dexamethasone are assumed to have the same discontinuation rate as the aflibercept-laser arm.

For the next four years, it is assumed that treatment will continue, though with fewer injections. Visual stability is assumed for this period.

For the remainder of the model, it is assumed that all patients will have resolved and there is no need for further treatment. A steady slow annual visual decline of 2% of eyes losing 15 letters is applied for the remainder of the model, as drawn from the van der Pols[87] study of a sample of elderly British people.

Deaths are based upon UK life tables. Those with one or both eyes in VA5 have a mortality multiplier of 1.23 applied, drawn from Christ et al.[88]

Fellow eye BRVO is assumed to be treated in 50% of patients. Treated eyes have the same TPMs applied as outlined above. Untreated eyes are assumed to decline at the common 2% annual rate.

SAEs were relatively uncommon during VIBRANT. Raised intraocular pressure (IOP) and cataract are included in the model for the first five years, with the annual rates being taken from the VIBRANT study.

Quality of life for the better seeing eye (BSE) is taken from the Czoski-Murray[86] experimental time-trade off study. Quality of life for the worse seeing eye (WSE) assumes that a given change in its BCVA will have 30% of the quality of life impact

of the same change in the BSE. An OLS analysis of the VIBRANT EQ-5D data is used as a sensitivity analysis.

Dosing and administrations are based upon the mean number of treatments in the VIBRANT study during the first year of the model and expert opinion thereafter. Dosing for rescue ranibizumab is assumed to be the same as for rescue aflibercept, while dosing for rescue dexamethasone is based upon the SmPC and expert opinion.

Monitoring is based on SmPCs and expert opinion. It is assumed that 100% of administration visits can double as monitoring visits.

5.2.3 Population

The population broadly reflects that of the VIBRANT trial:

- Baseline age 65 years
- Proportion female 45%

The baseline bilateral BRVO proportion of 6.05% and additional fellow eye incidence of BRVO of 12.3% during the first five years of the model is drawn from an expert survey. It is unclear why the baseline bilateral BRVO proportion is not drawn from the VIBRANT trial. The ERG did not ask about this at clarification.

5.2.4 Interventions and comparators

Two sets of comparisons are made by the company. One compares:

- 1st line laser followed by 2nd line rescue aflibercept: laser-aflibercept
- 1st line laser followed by 2nd line rescue ranibizumab: laser-ranibizumab
- 1st line laser followed by 2nd line rescue dexamethasone: laser-dexamethasone

to determine if aflibercept is cost effective compared to the other injections/implants that are currently recommended by NICE.

The other compares:

- 1st line laser followed by 2nd line rescue aflibercept: laser-aflibercept
- 1st line aflibercept followed by 2nd line rescue laser: aflibercept-laser

to determine if 1st line aflibercept is cost effective compared to 2nd line rescue aflibercept; i.e. should anti-VEGFs, or at least aflibercept, be moved up the line to

become 1st line treatment rather than the current NICE recommendation of using them as 2nd line rescue therapy.

5.2.5 Perspective, time horizon and discounting

The perspective for benefits is that of the patient and, for cost, is that of the NHS/PSS. A 35 year time horizon is applied which is effectively a lifetime horizon, given the baseline age of 65. Costs and benefits are discounted at an annual 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness: year 1: TPMs

The TPMs for the first year of the model for aflibercept-laser and laser-aflibercept are estimated by pooling 4-weekly data from the VIBRANT trial using the MSM package in R. Three 4-weekly TPMs are estimated for each arm:

- A 4-weekly TPM for all patients on 1st line treatment for week 0 to week 24, so applied 6 times
- A 4-weekly TPM for patients remaining on 1st line treatment for week 28 to week 52, so applied 7 times
- A 4-weekly TPM for patients receiving 2nd line rescue treatment for week 28 to week 52, so applied 7 times

Tables 15-17 below show the 4-weekly probabilities of moving from one health state to each of the other five health states.

Table 15 4-weekly TPMs: 1st line treatment: week 0 to week 24

		1st line aflibercept					**1st line laser**				
		VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
Prob. moving to :	VA1	83.3%	20.4%	7.7%	2.1%	2.2%	88.0%	7.1%	1.1%	0.1%	0.0%
	VA2	16.4%	76.4%	39.0%	15.2%	15.6%	11.0%	79.4%	23.6%	3.9%	0.6%
	VA3	0.4%	3.2%	51.6%	13.1%	18.1%	0.9%	13.0%	70.5%	22.8%	4.6%
	VA4	0.0%	0.0%	1.6%	61.5%	27.2%	0.0%	0.4%	4.5%	63.0%	13.8%
	VA5	0.0%	0.0%	0.1%	8.1%	36.9%	0.0%	0.0%	0.3%	10.3%	81.0%

Table 16 4-weekly TPMs: 1st line treatment: week 28 to week 52

		1st line aflibercept					1st line laser				
		VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
Prob. moving to :	VA1	89.1%	11.2%	2.3%	0.0%	0.0%	91.4%	7.4%	0.1%	0.0%	0.0%
	VA2	10.5%	85.3%	27.3%	0.6%	0.2%	8.5%	91.4%	3.4%	0.0%	0.0%
	VA3	0.4%	3.4%	66.0%	3.3%	1.4%	0.1%	1.2%	96.4%	0.0%	0.0%
	VA4	0.0%	0.1%	3.8%	79.7%	56.4%	0.0%	0.0%	0.0%	87.5%	0.0%
	VA5	0.0%	0.0%	0.5%	16.3%	42.0%	0.0%	0.0%	0.0%	12.4%	100.0%

Table 17 4-weekly TPMs: 2nd line rescue treatment: week 28 to week 52

		2nd line rescue laser					2nd line rescue aflibercept				
		VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
Prob. moving to :	VA1	89.0%	4.3%	4.3%	0.0%	0.0%	79.6%	10.9%	1.4%	0.2%	0.0%
	VA2	9.1%	79.0%	79.0%	0.0%	0.0%	19.8%	84.3%	21.0%	3.8%	0.6%
	VA3	1.9%	16.6%	16.6%	0.0%	0.0%	0.6%	4.8%	75.6%	27.2%	4.3%
	VA4	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.1%	2.0%	68.8%	0.1%
	VA5	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	95.0%

The TPMs for receiving 2nd line rescue ranibizumab or dexamethasone treatment during week 28 to week 52 are derived by applying the odds ratios of the NMA of improving by 15 letters to the probabilities of gaining letters from 2nd line rescue aflibercept: 0.93 for ranibizumab and 0.34 for dexamethasone.

Given the odds ratio:

$$OR = (P_{RANI}/(1 - P_{RANI}))/(P_{AFLI}/(1 - P_{AFLI}))$$

It follows that:

$$P_{RANI}/(1 - P_{RANI}) = OR.P_{AFLI}/(1 - P_{AFLI})$$

Hence:

$$P_{RANI} = (1 - P_{RANI}).OR.P_{AFLI}/(1 - P_{AFLI})$$

Hence:

$$P_{RANI} + P_{RANI}.OR.P_{AFLI}/(1 - P_{AFLI}) = OR.P_{AFLI}/(1 - P_{AFLI})$$

Hence:

$$P_{RANI} = (OR.P_{AFLI}/(1 - P_{AFLI}))/(1 + OR.P_{AFLI}/(1 - P_{AFLI}))$$

Hence:

$$P_{RANI} = (OR.P_{AFLI})/((1 - P_{AFLI}) + OR.P_{AFLI})$$

For instance, given the NMA odds ratio of 0.93 and the 2nd line rescue aflibercept probability of improving from VA2 to VA1 of 10.9%, the parallel probability for 2nd line rescue ranibizumab is:

$$P_{RANI} = (0.93 * 10.9\%)/((1 - 10.9\%) + 0.93 * 10.9\%) = 10.2\%$$

Table 18 Inferred 4 weekly TPMs: 2nd line rescue treatment: week 28 to week 52

		2nd line rescue ranibizumab					2nd line rescue dexamethasone				
		VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
Prob. moving to :	VA1	79.6%	10.2%	1.3%	0.2%	0.0%	79.6%	4.0%	0.5%	0.1%	0.0%
	VA2	19.8%	85.0%	19.8%	3.5%	0.5%	19.8%	91.2%	8.3%	1.3%	0.2%
	VA3	0.6%	4.8%	76.9%	25.8%	4.0%	0.6%	4.8%	89.3%	11.3%	1.5%
	VA4	0.0%	0.1%	2.0%	70.5%	0.1%	0.0%	0.1%	2.0%	87.3%	0.0%
	VA5	0.0%	0.0%	0.0%	0.0%	95.4%	0.0%	0.0%	0.0%	0.0%	98.3%

Coupled to these TPMs, for the 4 weekly cycles during week 24 to week 52, the following proportions of patients are modelled as crossing over to receive 2nd line rescue treatment.

Table 19 Treatment switch probabilities by cycle

Cycle	6	7	8	9	10	11	12
Aflibercept-laser	0.0%	0.0%	0.0%	10.0%	0.0%	0.0%	0.0%
Laser-aflibercept	58.9%	10.0%	2.0%	0.0%	2.0%	1.0%	0.0%

These probabilities of switching to the 2nd line treatment are applied equally to all health states; for example, in cycle 9, an aflibercept patient with their study eye in VA1 has the same 10% chance of switching treatment as an aflibercept patient with their study eye in VA5.

The probabilities of receiving 2nd line rescue ranibizumab in the laser-ranibizumab and 2nd line rescue dexamethasone in the laser-dexamethasone arm are assumed to be the same as those of receiving 2nd line rescue aflibercept in the laser-aflibercept arm.

Treatment effectiveness: year 1: shift tables

The model also contains the facility for a simpler approach to modelling the patient distributions for the comparison of aflibercept-laser with laser-aflibercept. The patient

counts can be taken directly from the VIBRANT trial as outlined below. The pooled patient distribution at baseline is applied to both arms.

Table 20 Shift tables: aflibercept-laser: all patients

	1st line aflibercept					2nd line rescue laser				
Week	VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
0										
4										
8										
12										
16										
20										
24										
28										
32										
36										
40										
44										
48										
52										

Table 21 Shift tables: laser-aflibercept: all patients

	1st line laser					2nd line rescue aflibercept				
Week	VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
0										
4										
8										
12										
16										
20										
24										
28										
32										
36										
40										
44										
48										
52										

Stable phase: years 2-5

During years 2-5, patients are assumed to receive treatment as required. Those remaining on treatment are assumed to have stable visual acuity. However, the discontinuation rates estimated for year 1 are still applied with some patients coming off treatment. These patients are modelled as having the annual 2% probability of worsening by 15 letters.

Decline phase: years 6+

Eyes with BRVO that are not being treated, either due to treatment discontinuation or due to treatment cessation at the end of the first five years of the model, are modelled as having an annual 2% probability of worsening by 15 letters.

This estimate is based upon van der Pols[87] and relates to the general population. As a consequence, it may be something of an underestimate for patients who are modelled as having discontinued treatment, particularly those discontinuing during their 1st year of treatment among whom the BRVO may not have resolved. This might bias the analysis if the rates of discontinuation differ between the arms, tending to favour the treatment with the higher discontinuation rate.

Mortality

The TPMs are also conditioned by having age specific general population mortality rates applied. The columns of the TPMs are made to sum to unity by subtracting the mortality probability from the probability of remaining in the same health state.

The mortality probability for those with one or both eyes in VA5 is increased by a mortality multiplier of 1.23, as drawn from Christ et al.[88]

Fellow eye involvement and treatment

As already noted, a baseline 6.05% of bilateral involvement coupled with an incidence of 12.3% during the first five years of the model was estimated from expert opinion. It is assumed that 50% of fellow eye involvement is treated.

The fellow eyes that are treated are modelled in exactly the same way as outlined above.[d]

The fellow eyes that are not treated are modelled as having the annual 2% likelihood of declining by 15 letters. This may be regarding as an underestimate for untreated BRVO given that the estimate is for the general population rate of visual worsening. However, considering that it is more reasonable to assume that 100% of fellow eye involvement will be treated, it may be considered a non-issue.

Extrapolation

During years 2 to 5 of treatment, is it assumed that vision is stable among those remaining on treatment. Among those eyes that are off treatment, a constant annual 2% are modelled as losing 15 letters, as drawn from van der Pols.[87]

Once all eyes come off treatment after 5 years, the constant annual 2% decline is applied.

In effect, this maintains the differences in the patient distributions between the arms for years 2 to 5 of treatment, and broadly maintains them for the remainder of the model.

SAEs

The rates of SAEs for raised IOP and cataract are taken from the VIBRANT study and converted to monthly rates: 1 patient with raised IOP and 1 patient with cataract in the aflibercept-laser arm and 1 patient with raised IOP and 0 patients with cataract in the laser-aflibercept arm. These are converted to monthly rates based upon 12 months exposure during the first year and applied to those remaining on treatment. Those receiving 2nd line rescue aflibercept have the 1st line aflibercept rate applied while those receiving 2nd line rescue laser have the 1st line laser rate applied.

The SAE rates for ranibizumab and dexamethasone are assumed to be the same as those of aflibercept.

[d] This is a slight simplification since mortality is accounted for in the modelling of the study eye, and as a consequence is not applied in the modelling of the fellow eye.

Within the modelling, because of the cross over to rescue treatment from month 6, the 12 monthly rates for aflibercept, for example, will not be applied to all patients in the aflibercept-laser arm and there will be some underestimation of the cataract rate in the aflibercept-laser arm. Similarly, there will be some overestimation of the cataract rate in the laser-aflibercept arm.

5.2.7 Health related quality of life

Reports of HRQoL were sought by the company by searching MEDLINE (Ovid), EMBASE (Ovid), NHS Economics Evaluation Database (NHS EED) and EconLit on 9th October 2015 for reports of HRQoL published from 2000 in English. In addition, ISPOR conference proceedings were searched on 23rd November 2015. The search strategies are documented in full in Appendix 10 of the company submission. The searches combined two search facets using the Boolean operator AND: BRVO or macular degeneration or diabetic retinopathy; and study design HRQoL values. A comprehensive range of terms was included in the search strategies using the Ovid mapping function as well as the most relevant controlled vocabulary terms (MeSH and Emtree). The searches for conference abstracts mostly searched for variations of the term BRVO. The ERG considered the search strategies appropriate. The company identified 25 studies but did not identify any BRVO specific utilities to be included in the model.

For the base case, the company relies upon the experimental Czoski-Murray et al[86] results, coupled with an assumption that a given change in the BCVA of the WSE has 30% of the quality of life impact had that BCVA change happened in the BSE. This is coupled with an assumed mean number of letters for each health state as below.

Table 22 Mean health state letters, LogMAR and Czoski-Murray QoL values

Health state	VA1	VA2	VA3	VA4	VA5
Letters range	80-100	65-79	50-64	35-49	0-34
Mean letters	90	72	57	42	17
Mean LogMAR	-0.10	0.26	0.56	0.86	1.36
Mean CM QoL	0.832	0.699	0.589	0.479	0.295

For reasons that are unclear, the company rounds the quality of life values to two decimal places. This has little effect upon results and translates into the following bilateral quality of life values (Table 23).

Table 23 Czoski-Murray bilateral QoL values

		BCVA BSE				
		VA1	**VA2**	**VA3**	**VA4**	**VA5**
BCVA WSE	**VA1**	0.830				
	VA2	0.800	0.700			
	VA3	0.780	0.670	0.590		
	VA4	0.750	0.650	0.560	0.480	
	VA5	0.710	0.610	0.520	0.440	0.290

The company also presents some OLS analyses of the VIBRANT EQ-5D data. The first used OLS to explore whether age, sex, BMI, race, duration of BRVO, CRT, IOP, perfusion status, BCVA of the WSE and its logarithm and BCVA of the BSE and its logarithm were individually statistically significant determinants of patients EQ-5D quality of life. Age was significant with a p-value of 0.01, being Asian was significant with a p-value of 0.04 and all of BCVA WSE, BCVA BSE, Ln(BCVA WSE) and Ln(BCVA BSE) were significant with p-values of 0.00.

Those that were statistically significant in the univariate analyses were included in a range of multivariate analyses which included OLS, fixed effects, random effects and Tobit modelling. The random effects models apparently addressed the panel nature of the data.

Appendix 13 of the company submission only present the results of the OLS regression, but the company has since supplied the full set of analyses. There is little explanation of why the other multivariate models were rejected. The company states that "*after testing all possible model types OLS regression … was determined to offer the best interpretability and most clinically plausible results… The random effects model could have potentially been used for prediction; however it offered no advantages over the OLS regression, with less significance and a less plausible predicted range*". Given the repeated measures nature of the data, the random effects model might be preferable on a priori grounds.

Table 24 shows the logarithmic and linear models derived from the multivariate OLS modelling. Note that in the logarithmic model the logarithm of age was not taken.

Table 24 VIBRANT EQ-5D OLS model coefficients

	Linear model		Log. model	
	coef	**p-value**	**coef**	**p-value**
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
BCVA BSE	[redacted]	[redacted]	[redacted]	[redacted]
BCVA WSE	[redacted]	[redacted]	[redacted]	[redacted]

For a 65 year old this results in the following estimates.

Table 25 VIBRANT EQ-5D OLS model estimates

		BCVA BSE									
		Linear model					**Logarithmic model**				
		VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
BCVA WSE	VA1	0.900					0.889				
	VA2	0.877	0.840				0.876	0.843			
	VA3	0.858	0.821	0.789			0.862	0.829	0.794		
	VA4	0.838	0.801	0.769	0.738		0.844	0.811	0.776	0.730	
	VA5	0.805	0.768	0.737	0.705	0.652	0.790	0.758	0.723	0.677	0.542

The R^2 of all the company regression models was typically quite small at less than [redacted], but this is perhaps as would be expected. Patients were elderly, would have had a range of other conditions such as arthritis as the main determinants of their quality of life, with the BCVA of their study eye, which was typically their WSE, having relatively little impact.

The company notes that due to the small number of observations with low visual acuity and the dataset appearing to be consistent with both the linear and logarithmic models, the predicted EQ-5D values for the lower visual acuity health states should be viewed with caution. This is reasonable but, apart from the bilateral (VA4,VA5) and (VA5,VA5) health states, the values of both OLS models are reasonably closely aligned. The model simulates few patients in these health states, and very few in legal

blindness as shown by the minimal estimates for the costs of blindness. As a consequence, for modelling purposes, this may not be a particular concern.

When reviewing the QoL values, as will be outlined later, it should be borne in mind that the model only requires health states for the BSE in VA1 and in VA2. The RESONATE EQ-5D data are also presumably largely limited to this. Hence, it makes little sense to examine the values extrapolated to the bilateral health states of VA5-VA5 as these are both largely outside the RESONATE EQ-5D data and not applied within the model. Any sense check should concentrate upon the health states for the BSE in VA1 and in VA2.

Due to the RESONATE EQ-5D data being panel data, it may make more sense to apply the random effects EQ-5D models. The company outlines that repeated measures were considered within this, with the subject being the random intercept, but that the OLS had a superior R^2. The R^2 appears virtually identical to the ERG, though, as the company also noted, the coefficients on BCVA of the BSE were significant for the OLS modelling but not for the random effects modelling.

Table 26 VIBRANT EQ-5D Random effects model coefficients

	Linear model		Log. model	
	coef	**p-value**	**coef**	**p-value**
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
BCVA BSE	[redacted]	[redacted]	[redacted]	[redacted]
BCVA WSE	[redacted]	[redacted]	[redacted]	[redacted]

For a 65 year old, this results in the following estimates.

Table 27 VIBRANT EQ-5D Random effects model estimates

		BCVA BSE									
		Linear model					Logarithmic model				
		VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
BCVA WSE	VA1	[redacted]					[redacted]				
	VA2	[redacted]	[redacted]				[redacted]	[redacted]			
	VA3	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
	VA4	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
	VA5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The declines with visual worsening are typically somewhat less than those of the OLS model.

SAEs QALYs

Cataracts are estimated to have a -0.14 QALY impact, based upon Brown et al (2007).

Raised IOP is assumed to have no impact upon quality of life.

5.2.8 Resources and costs

Number of treatments

The mean number of aflibercept treatments and the number of laser treatments during the first year of the model is estimated from the VIBRANT trial. The number of 2nd line rescue ranibizumab treatments during the first year is assumed to be equal to that of 2nd line rescue aflibercept. The number of 2nd line rescue dexamethasone treatments during the 1st year is taken from the SmPC.

The company received responses to a survey from 37 ophthalmologists out of 569 who were contacted. This explored a number of issues, the number of treatments being required among them. It was clear to respondents that the survey was being sponsored by the company with a view to modelling of aflibercept. Table 28 below shows that the survey respondents tended to estimate the need for ranibizumab injections as significantly more compared with aflibercept injections. Given the similar posology of ranibizumab and aflibercept and the greater experience with ranibizumab, the company rejected the results of the expert survey and assumed that

the number of aflibercept injections after the first year would be the same as those suggested by the expert survey for ranibizumab.

Table 28 Expert survey treatment frequency responses

	Year 1	Year 2	Year 3	Year 4	Year 5
Laser	2.00	1.12	0.36	0.12	0.03
Aflibercept	5.15	2.97	1.94	1.12	0.38
Ranibizumab	6.73	4.15	2.61	1.12	0.58
Dexamethasone	2.28	1.69	0.93	0.21	0.1

A copy of the survey was supplied at clarification. One of the survey questions was about the numbers of treatments in years 6+. These data do not appear to have been presented in the company submission, which assumes that there will be no treatments for years 6+.

This results in the following number of treatments being applied within the model among those remaining on treatment.

Table 29 Treatment frequencies modelled

	Aflibercept-laser		Laser-aflibercept		Laser-ranibizumab		Laser-dexamethasone	
	Afli.	Laser	Laser	Afli.	Laser	Rani	Laser	Dexa.
Year 1	9.00		1.70		1.70		1.70	
6-12 mths		1.00		4.40		4.40		1.00
Year 2	4.15	1.12	1.12	4.15	1.12	4.15	1.12	1.69
Year 3	2.61	0.36	0.36	2.61	0.36	2.61	0.36	0.93
Year 4	1.12	0.12	0.12	1.12	0.12	1.12	0.12	0.21
Year 5	0.58	0.03	0.03	0.58	0.03	0.58	0.03	0.10
Year 6+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

For reasons of space, the above does not present the 3.00 aflibercept treatments that are modelled among those receiving laser rescue therapy in the aflibercept-laser arm.

Monitoring

The monitoring frequency was based upon the expert survey.

Table 30 Expert survey monitoring frequency responses

	Year 1	Year 2	Year 3	Year 4	Year 5
Laser	5.60	2.74	1.76	1.0	0.65
Aflibercept	5.40	4.49	3.40	2.17	1.09
Ranibizumab	7.47	5.62	4.09	2.44	1.35
Dexamethasone	5.20	3.87	3.00	1.70	0.93

Regarding the number of treatments, the expert survey estimated a higher monitoring frequency for ranibizumab than for aflibercept. The expert survey asked about the monitoring frequency in years 6+, but, as for the number of treatments, these data do not appear to have been presented in the company submission.

The number of monitoring visits during the first year for aflibercept and ranibizumab are assumed to be equal to the number of treatments. However, due to the company's assumption that 100% of treatment visits can double as monitoring visits, there are no costs associated with these.

This assumption results in the following number of monitoring visits being applied within the model among those remaining on treatment.

Table 31 Monitoring frequencies modelled

	Aflibercept-laser		Laser-aflibercept		Laser-ranibizumab		Laser-dexamethasone	
	Afli.	Laser	Laser	Afli.	Laser	Rani	Laser	Dexa.
Year 1	9.00		5.60		5.60		5.60	
6-12 mths		3.00		4.40		4.40		3.00
Year 2	5.62	2.70	2.74	5.60	2.74	5.60	2.74	3.87
Year 3	4.09	1.76	1.76	4.10	1.76	4.10	1.76	3.00
Year 4	2.44	1.00	1.00	2.40	1.00	2.40	1.00	1.70
Year 5	1.35	0.70	0.65	1.40	0.65	1.40	0.65	0.93
Year 6+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Treatment, administration and monitoring unit costs

Aflibercept is associated with a [redacted] PAS to yield a drug cost of [redacted]. The company's model applies the following costs per administration.

Table 32 Unit costs per administration

	Tx	Admin	Total cost
Aflibercept	[redacted]	£204	[redacted]
Laser	£111	£150	£261
Ranibizumab	£742	£204	£946
Dexamethasone	£870	£266	£1,136

The administration cost of £204 for the anti-VEGFs is based upon £54 for RD40Z: ultrasound scan of less than 20 minutes plus the £150 monitoring cost as outlined below. The £266 administration cost of dexamethasone is based upon a 25:75 weighted average of a day case BZ86B: intermediate vitreous retinal procedures and an OP cost BZ87A: minor vitreous retinal procedures. The cost per laser administration of £111 is also based upon the OP cost BZ87A, with an additional administration cost of £150 being based upon the unit cost per monitoring visit as outlined below.

A cost per dedicated monitoring visit of £150 is applied, based upon the £81[e] cost per consultant-led OP appointment code 130 plus an administration cost of around £69 as used in the TA346 aflibercept for treating DMO. It is assumed that 100% of administration visits can double as monitoring visits. As a consequence only the number of monitoring visits in excess of the number of administration visits incur this cost.

Table 33 Monitoring frequencies incurring costs

	Aflibercept-laser		Laser-aflibercept		Laser-ranibizumab		Laser-dexamethasone	
	Afli.	Laser	Laser	Afli.	Laser	Rani	Laser	Dexa.
Year 1	0.00		3.90		3.90		3.90	
6-12 mths		2.00		0.00		0.00		2.00
Year 2	1.47	1.58	1.62	1.45	1.62	1.45	1.62	2.18
Year 3	1.48	1.40	1.40	1.49	1.40	1.49	1.40	2.07
Year 4	1.32	0.88	0.88	1.28	0.88	1.28	0.88	1.49
Year 5	0.77	0.67	0.62	0.82	0.62	0.82	0.62	0.83
Year 6+	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

[e] These costs are not explicit within the company submission, and these reported here are based upon the ERG taking them from 2013-14 reference cost WF10A service cost 130 with the remaining £ cost being the residual from the total of £150. Note also that this differs from the £96 cost per consultant led OP visit of table 87 of the company submission used to calculate the cost per cataract.

All patients are assumed to incur the costs of a single fluorescein angiography at £117, and, as a consequence, this nets out between the arms.

SAEs

Cataracts are estimated to cost £1,161, based upon NHS reference cost £872 for BZ23A: cataract extraction and lens implant plus three consultant led OP visits at £96.

Raised IOP is estimated to cost £3.57, based upon the NICE TA305 aflibercept for treating visual impairment caused by macular oedema secondary to CRVO.

Blindness

An annual cost of blindness of £7,429 is applied to those with both eyes in VA5 based upon Meads & Hyde,[89] adjusted for the costs of depression in the King's Fund report of McCrone et al.[90] This cost has been used quite extensively in previous NICE appraisals for eye conditions. As shown in the results section below, virtually no patients are modelled as falling into blindness and, therefore, the costs of blindness are largely irrelevant.

5.2.9 Cost effectiveness results

The company base case results are presented in Table 34. Note that, due to the ERG presenting results across all comparators, for reasons of space there may be some very minor discrepancies between the ERG results and the company submission. Any discrepancies are minor to the point of irrelevance. All results include the aflibercept PAS of [redacted] but not the comparator PASs. The cost estimates are presented separately for the study eye (SE) and the non-study fellow eye (NSE).

Table 34 Company deterministic base case results

	AFLI-LASE			LASE-AFLI			LASE-RANI			LASE-DEXA		
	SE	NSE	Total	SE	NSE	Total	SE	NSE	Total	SE	NSE	Total
1st line	[redacted]											
2nd line	[redacted]											
Monit.	[redacted]											
FA	[redacted]											
Cat.	[redacted]											
IOP	[redacted]											
Blind	[redacted]											
Total	[redacted]											
VA			[redacted]			[redacted]			[redacted]			[redacted]
Cat.	[redacted]											
IOP	[redacted]											
Total			[redacted]			[redacted]			[redacted]			[redacted]
ICER AFLI-LASE versus						£15,365			£8,939			£14,303
ICER LASE-AFLI versus									DOM			£11,792

For the comparison of aflibercept-laser with laser-aflibercept, the costs of 1st line aflibercept are around [redacted] higher than the costs of 1st line laser. This is balanced to some extent by the laser-aflibercept arm having quite considerable 2nd line aflibercept costs of around [redacted]. Monitoring costs are also somewhat less in the aflibercept-laser arm at only £540 compared to £905 in the laser-aflibercept arm. This results in a net cost estimate of [redacted] which, when coupled with the estimated gain of [redacted] QALYs, results in a cost effectiveness estimate of £15,365 per QALY.

For the comparison of aflibercept-laser with laser-ranibizumab, the higher net costs of 1st line treatments remains. However, the costs of 2nd line ranibizumab in the laser-ranibizumab arm are somewhat larger than if aflibercept had been used instead, at around [redacted]. Consequently, the net costs fall to [redacted]. Given the odds ratio of 0.93 for gaining letters for ranibizumab compared to aflibercept the patient gains also increase to [redacted] QALYs, resulting in a cost effectiveness estimate of £8,939 per QALY.

For the comparison of aflibercept-laser with laser-dexamethasone the higher net costs of 1st line treatments are as before. In contrast, the costs of 2nd line dexamethasone in

the laser-dexamethasone arm are somewhat lower than if aflibercept had been used instead at around [redacted]. Hence, the net costs increases to [redacted]. However, given the odds ratio of 0.34 for gaining letters for dexamethasone compared to aflibercept, the patient gains increase by quite a large amount to [redacted] QALYs. The change in QALYs more than offsets the change in costs and the cost effectiveness for aflibercept-laser compared with laser-dexamethasone is £14,303 per QALY.

If aflibercept-laser is not a comparator and the comparison is between what treatments should be used 2nd line to laser, for the comparison of laser-aflibercept with laser-ranibizumab, the higher 2nd line costs of ranibizumab result in an estimated net saving of [redacted]. Given the relative risk of 0.93, the patient gains are muted at [redacted] QALYs, but the cost savings cause laser-aflibercept to dominate laser-ranibizumab.

For the comparison of laser-aflibercept with laser-dexamethasone, net costs of [redacted] are estimated but reasonable net gains of [redacted] QALYs result in a cost effectiveness estimate of £11,792 per QALY.

The following presents the incremental analyses.

Table 35 Company deterministic base case incremental results

	Cost	QALY	Δ Cost	Δ QALY	ICER
LASE-DEXA	[redacted]	[redacted]			
LASE-AFLI	[redacted]	[redacted]	[redacted]	[redacted]	£11,792
LASE-RANI	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
AFLI-LASE	[redacted]	[redacted]	[redacted]	[redacted]	£15,365

The company submission presents the probabilities of cost effectiveness, the scatterplots, the pairwise CEACs and the CEAF across all comparators. The CEAF presented in Figure 4 does not appear to be within the submitted company model.

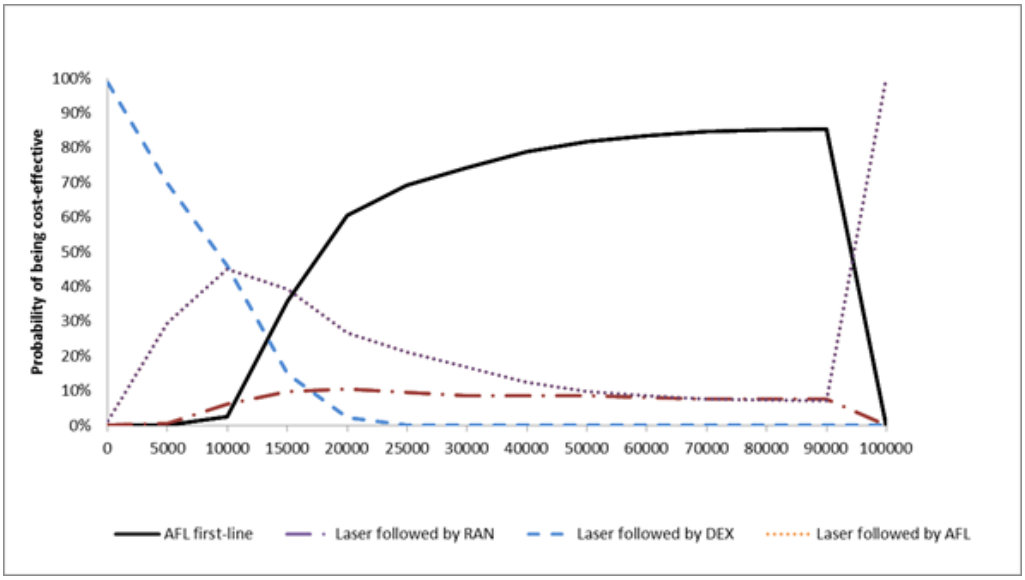

Figure 4 Cost effectiveness frontier (reproduced from Figure 66 of the company submission)

The ERG has not been able to reproduce the company's CEAF, and the values above a willingness to pay of £90k per QALY look peculiar. The ERG derived CEAFs should be presented in section 5.3 of this report but they are reported here for ease of reference. Their calculation is based upon 5,000 iterations and is available to the company within the ERG's amended company model. Since aflibercept does not qualify for end of life, the ERG has only presented these for willingness to pay values up to £50k per QALY, but has checked that there are no oddities within their calculations for willingness to pay values above £90k per QALY.

Committee members may wish to consider all comparators alongside one another, but may also wish to compare the laser followed by 2nd line treatments alongside one another. For this reason, the results of the probabilistic modelling are presented across all comparators and across the laser followed by 2nd line treatment comparators.

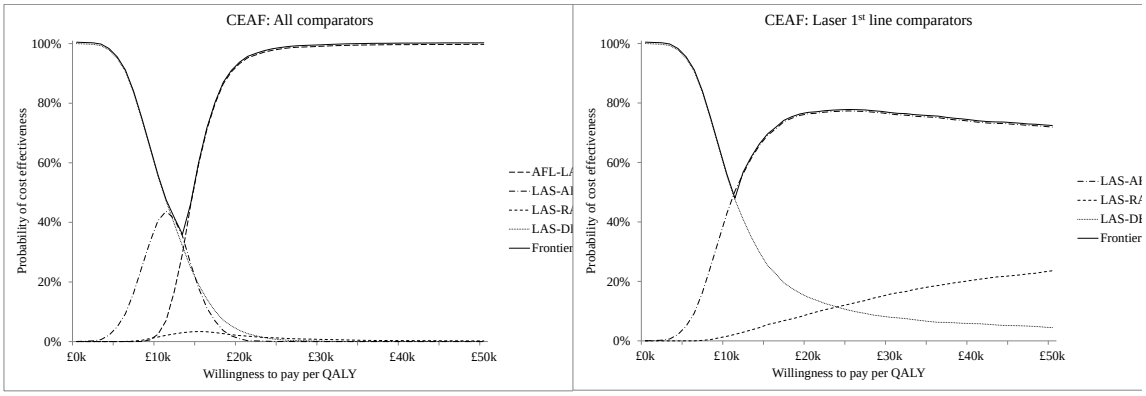

Figure 5 ERG derived CEAFs

Across all comparators, laser-dexamethasone has the highest probability of being cost effective up to a willingness to pay of £13k per QALY. Thereafter, aflibercept-laser has the highest probability of being cost effective. For willingness to pay values of between £5k per QALY and £20k per QALY, there are reasonable probabilities of laser-aflibercept being cost effective. There is little probability of laser-ranibizumab being cost effective at any willingness to pay, but it should be borne in mind that the above is inclusive of the aflibercept PAS but exclusive of the ranibizumab PAS.

Restricting attention to just the 1st line laser comparators, up to a willingness to pay of around £12k per QALY, laser-dexamethasone has the highest probability of being cost effective. Thereafter, laser-aflibercept has the highest probability of being cost effective. Laser-ranibizumab has little probability of being cost effective, though the probability of this does steadily increase beyond a willingness to pay of £10k per QALY. Again, it should be borne in mind that the above includes the aflibercept PAS but not the ranibizumab PAS.

To economise on space, the following table does not report the value for the frontier. For each of the willingness to pay values reported, the frontier corresponds to the treatment sequence with the highest probability of cost effectiveness.

Table 36 ERG derived probabilities of cost effectiveness

	Across all comparators				Across laser 1st line comparators		
	AFL-LAS	LAS-AFL	LAS-RAN	LAS-DEX	LAS-AFL	LAS-RAN	LAS-DEX
£0k	0%	0%	0%	100%	0%	0%	100%
£10k	2%	41%	2%	55%	43%	2%	56%
£20k	93%	1%	2%	4%	76%	9%	15%
£30k	99%	0%	1%	0%	76%	16%	8%
£40k	100%	0%	0%	0%	74%	20%	6%
£50k	100%	0%	0%	0%	72%	24%	4%

The central cost effectiveness estimates for the probabilistic modelling do not appear to be presented within the submission. They differ quite substantially from those of the deterministic modelling.

Table 37 ERG derived deterministic and probabilistic estimates

	AFLI-LASE		LASE-AFLI		LASE-RANI		LASE-DEXA	
	Cost	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The absolute cost reductions are somewhat larger in the aflibercept-laser and the laser-aflibercept arms, but the absolute QALY reductions are more similar across the arms. Similar differences in the cost estimates are apparent in the submitted company's model and seem to be even greater though this may be probably due to the fact that they have only being based upon 1,000 simulations. It is unclear why this has not been addressed in the company's submission.

The probabilistic estimates suggest better cost effectiveness ratios as shown in Table 38, though laser-ranibizumab is no longer dominated by laser-aflibercept but is extendedly dominated by aflibercept-laser.

Table 38 ERG derived central probabilistic cost effectiveness estimates

					ICERs	
	Cost	**QALY**	**Δ Cost**	**Δ QALY**	**All comp.**	**Laser 1st**
LASE-DEXA	[redacted]	[redacted]				
LASE-AFLI	[redacted]	[redacted]	[redacted]	[redacted]	£11,198	£11,198
LASE-RANI	[redacted]	[redacted]	[redacted]	[redacted]	Ext. DOM	£10mn
AFLI-LASE	[redacted]	[redacted]	[redacted]	[redacted]	£13,902	n.a.

5.2.10 Sensitivity analyses

The company presents a range of sensitivity analyses in the submission. As it appears that the electronic model has had elements removed, it was not possible for the ERG to re-run these using the model VBA. As a consequence, the reader is referred to Table 90 on page 222 and Table 91 on page 226, which outline the values applied within the one way sensitivity analyses, and the tornado diagrams of Figure 51 through to Figure 55 on page 248 to page 252 of the company's submission.

In general, the company one way sensitivity analyses suggest that results are sensitive to:

- The odds ratios of gaining letters
- The time horizon
- The cohort starting age
- The number of injections
- The cost per monitoring visit
- The proportion of treatment visits that double as monitoring visits
- And, to some extent, the proportion of fellow eyes that are treated.

Four scenario analyses are also presented:

- Equivalent efficacy between 2nd line aflibercept and 2nd line ranibizumab.
  - For aflibercept-laser compared with laser-ranibizumab, the gain is reduced from [redacted] QALYs to [redacted] QALYs, which worsens the cost effectiveness estimate from £8,939 per QALY to £9,259 per QALY.
  - For laser-aflibercept compared with laser-ranibizumab, clinical equivalence applies, but laser-aflibercept still dominates due to its lower cost.

- Efficacy based upon the NMA not excluding trials from the network, yielding an odds ratio for gaining letters of 1.08 for ranibizumab rather than the 0.93 of the base case.
  - For aflibercept-laser compared with laser-ranibizumab the gain is reduced from [redacted] QALYs to [redacted] QALYs, which worsens the cost effectiveness estimate from £8,939 per QALY to £9,632 per QALY.
  - For laser-aflibercept compared with laser-ranibizumab, the gain of [redacted] QALYs is reversed to a loss of [redacted] QALYs, while the savings of [redacted] are largely unaffected. This results in a point in the S.W. quadrant and a cost effectiveness estimate for laser-ranibizumab compared to laser-aflibercept of £159k per QALY.
- Using the VIBRANT OLS EQ-5D estimates.

		Base case		VIBRANT EQ-5D	
Comparison	**Δ Costs**	**Δ QALYs**	**ICER**	**Δ QALYs**	**ICER**
AFLI-LASE vs LASE-AFLI	[redacted]	[redacted]	£15,365	[redacted]	£25,471
AFLI-LASE vs LASE-RANI	[redacted]	[redacted]	£8,939	[redacted]	£14,848
AFLI-LASE vs LASE-DEXA	[redacted]	[redacted]	£14,303	[redacted]	£23,971
LASE-AFLI vs LASE-RANI	[redacted]	[redacted]	DOM	[redacted]	DOM
LASE-AFLI vs LASE-DEXA	[redacted]	[redacted]	£11,792	[redacted]	£20,289

- Using the VIBRANT patient distributions rather than applying the transition probabilities estimated using the R MSM package.
  - For aflibercept-laser compared with laser-aflibercept, the net costs change slightly from [redacted] to [redacted] and the net gain is reduced from [redacted] QALYs to [redacted] QALYs. This worsens the cost effectiveness estimate from £15,365 per QALY to £17,976 per QALY.

5.2.11 Model validation and face validity check

For the comparison of aflibercept-laser with laser-aflibercept, the end of treatment[f] distribution of patients modelled using the company monthly R MSM TPMs for the comparison of aflibercept-laser with laser-aflibercept can be compared with that which uses the actual patient distributions of VIBRANT, what the company calls the "shift-tables" approach.

Table 39 Patient distributions after 1 year of treatment: TPM modelling

	Aflibercept-laser arm					Laser-aflibercept arm					Net effect				
	VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
VA1															
VA2															
VA3															
VA4															
VA5															

Table 40 Patient distributions after 1 year of treatment: shift-tables modelling

	Aflibercept-laser arm					Laser-aflibercept arm					Net effect				
	VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5	VA1	VA2	VA3	VA4	VA5
VA1															
VA2															
VA3															
VA4															
VA5															

The above shows how the R MSM TPM modelling compared to the shift-tables patient count data from VIBRANT tends to over-estimate the gains in the proportions of patients in:

- the very best health states of VA1-VA1 and VA1-VA2; and,
- the somewhat worse health states of VA1-VA5 and VA2-VA5.

This is reflected in the company sensitivity analysis that uses the shift-tables patient count data from VIBRANT with a cost effectiveness estimate of £17,976 per QALY compared to the £15,365 per QALY of the base case. The discrepancies between the two modelling approaches appears likely to be due to using the R MSM package to

[f] Taken to be the distribution at cycle 14 of the model.

derive the TPMs and the compounding of these TPMs through their repeated application, rather than using cycle specific patient count data as has been more commonly applied within previous NICE appraisals in eye conditions.

For the comparison of aflibercept-laser with laser-aflibercept, the ERG is of the opinion that it is more reasonable to use the shift tables for the base case and the R MSM TPMs as a sensitivity analysis. This is with the proviso that the baseline distributions between the health states in VIBRANT were well balanced between the arms. Patient count data supplied at clarification suggests the following baseline distributions of study eyes.

Table 41 Baseline distribution between the arms: VIBRANT

	VA1	VA2	VA3	VA4	VA5
Aflibercept-laser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laser-aflibercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

To the extent that there was any imbalance between the arms in VIBRANT, it appears to suggest slightly fewer study eyes in VA2 and VA3 in the laser-aflibercept arm and slightly more in VA4 and VA5. Consequently, to the extent that there is any bias in the shift tables approach due to different baseline distributions, it may tend to slightly favour aflibercept. In other words, the move from using the R MSM derived TPMs to using the shift tables, which worsens the cost effectiveness estimate for aflibercept-laser, does not worsen the cost effectiveness estimate due to the VIBRANT baseline distributions being biased against aflibercept-laser.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has rebuilt the deterministic base case with most of the company assumptions. This is with the exceptions of the company indexing for rescue treatments in the study eye and the indexing for the number of treatments in fellow eye incidences of BRVO in years 1, 2, 3 and 4. The ERG has corrected the company model for this and the ERG rebuild also adopts these assumptions. The company model results below reflect these corrections. The ERG rebuild shows a good correspondence with the revised company model.

Table 42 Company base case with minimal revisions

	AFLI-LASE			LASE-AFLI			LASE-RANI			LASE-DEXA		
	SE	NSE	Total	SE	NSE	Total	SE	NSE	Total	SE	NSE	Total
1st line	[redacted]											
2nd line	[redacted]											
Monit.	[redacted]											
FA	[redacted]											
Cat.	[redacted]											
IOP	[redacted]											
Blind	[redacted]											
Total	[redacted]											
VA			[redacted]			[redacted]			[redacted]			[redacted]
Cat.	[redacted]											
IOP	[redacted]											
Total			[redacted]			[redacted]			[redacted]			[redacted]
ICER AFLI-LASE versus						£14,603			£7,807			£14,141
ICER LASE-AFLI versus									DOM			£13,048

Table 43 ERG model rebuild with corresponding assumptions

	AFLI-LASE			LASE-AFLI			LASE-RANI			LASE-DEXA		
	SE	NSE	Total	SE	NSE	Total	SE	NSE	Total	SE	NSE	Total
1st line	[redacted]											
2nd line	[redacted]											
Monit.	[redacted]											
FA	[redacted]											
Cat.	[redacted]											
IOP	[redacted]											
Blind	[redacted]											
Total	[redacted]											
VA			[redacted]			[redacted]			[redacted]			[redacted]
Cat.	[redacted]											
IOP	[redacted]											
Total			[redacted]			[redacted]			[redacted]			[redacted]
ICER AFLI-LASE versus						£14,594			£7,782			£14,151
ICER LASE-AFLI versus									DOM			£13,103

For reasons that are unclear, the ERG estimates of the quality of life exclusive of the SAE quality of life impacts are around 0.02 less than those of the company. However, as this applies across all comparators, the cost effectiveness estimates are very similar.

5.3.2 Data inputs: correspondence between written submission and sources cited

Quality of life

There are a variety of quality of life papers included in the literature summary of the company in Appendix 10 of the submission. These are considered in section 5.3.4 below.

Mortality multiplier

The mortality multiplier for having one eye in VA5 of 1.23 corresponds with the value in Christ et al[88] and has been used in previous NICE assessments of treatments for visual disorders. It could be argued that the Christ et al mortality multiplier of 1.54 for both eyes being in VA5 should be applied. As the model simulates virtually no patients falling into this category, the impact of this would be minor.

Ranibizumab for RVO Novartis submission

The Novartis submission for ranibizumab for RVO states in table B42 that the number of ranibizumab injections during the first year of the BRAVO trial for BRVO was 8.0[g]. This will be explored as a sensitivity analysis by the ERG, but will only vary costs. It is questionable whether the different dosing might have affected relative clinical effectiveness.

Dosing: long term

The company expert survey asked respondents about treatment and monitoring during years 6+. The company, however, has chosen to focus on the responses for years 2-5 and does not report the survey results for years 6+.

The ERG undertook a focused search in MEDLINE (OVID) on 22nd March 2016 to ascertain whether there were any additional studies that reported long term follow up

[g] Due to ranibizumab only being administered as 2nd line rescue therapy during the second 6 months of the first year, this is crudely implemented by subtracting 1 from the corresponding input cell C50 in the *Tx_Input* worksheet .

of anti-VEGF treatment for RVO. The search strategy used is detailed in Appendix 1. Campochiaro[91] and three additional studies were identified.[12, 35, 92]

Campochiaro et al[h] report the results of the RETAIN long terms follow-up study of ranibizumab among 34 BRVO and 32 CRVO patients, with PRN dosing during the post RCT follow-up.[91] This study built upon the 12 month open label HORIZON extension study of CRUISE and BRAVO. With a mean follow-up of 49 months, 17 patients (50%) of BRVO patients had oedema resolution, which was defined as no intra-retinal fluid for at least 6 months after their last injection during RETAIN. Five patients (15%) had no fluid for a prolonged period of a mean of 32 months, but a small amount of fluid reappeared within 6 months of the end of the RETAIN study, which required re-treatment. The mean numbers of injections by year were 7.3, 2.6, 2.1 and 2.0. The mean number of injections in unresolved patients in year 4 was 3.2. Given these treatments, the mean BCVA increased from a mean of 54.0 letters to 72.6 letters at six months and then remained stable. Campochiaro et al concluded that *"Long-term outcomes in BRVO patients treated with ranibizumab were excellent, and although half still required occasional injections after 4 years, they maintained good visual potential".*[91]

Farinha et al[12] report the results of a Portuguese retrospective analysis of 16 BRVO patients and 16 CRVO patients treated with PRN 0.5mg ranibizumab from baseline with a minimum follow up of 3 years. The average number of injections during each of the first three years among BRVO patients was 3.5, 1.3 and 0.6 to give a total over three years of 5.9 administrations. Among the BRVO patients, there was an initial increase in BCVA from 51.8 letters to 65.1 letters at 6 months and 63.3 letters at 12 months, but this subsequently fell back to 57.8 letters at 24 months and 58.1 letters at 36 months, with a final mean of only 53.3 letters. The results may suggest some rebound to baseline if dosing is sub-optimal.

Rezar et al[35] report the results of an Austrian cross-sectional study of 28 BRVO patients with a mean follow-up of five years. Fourteen patients received bevacizumab monthly for 3 months then PRN and 14 patients received ranibizumab PRN. The

[h] Funded by Genetech

dose(s) per administration does not appear to be stated. The mean numbers of injections are not reported separately by arm, the mean number of treatments each year for the first four years being 6.0, 1.6, 0.6 and 0.5. BCVA in the bevacizumab group improved from a baseline of 54 letters to 70 letters at 1 year, falling back to 59 letters after a mean of 5 years. BCVA in the ranibizumab group improved from a baseline of 44 letters to 63 letters at 1 year, and further to 76 letters at a mean of five years. No statistical comparison between the groups was performed.

Sophie et al,[92]co-authored by Campochiaro, report the results of a US post-hoc open label clinical trial of 20 patients with BRVO and 20 patients with CRVO, with patients being randomised between 0.3mg ranibizumab and 0.5mg ranibizumab monthly for 3 months and then it seems to have been PRN. Patients who still had unresolved oedema at month 40 received ultra-wide fluorescein angiography and then scatter laser photocoagulation to all areas of retinal non-perfusion outside the fovea, followed by an injection of ranibizumab. Resolution of oedema was defined as a minimum of 6 months since the last injection without evidence of intraretinal fluid. Of the 9 patients who withdrew before 5 years, 5 had resolved, 1 was unresolved and still requiring injections and 3 were indeterminate. Of the 11 patients who had 5 years follow-up, 4 resolved through injections alone, 4 with the addition of laser and 3 remained unresolved. Consequently, of the 20 BRVO patients 9 resolved through injections alone (45%), 4 resolved through injections and laser (20%), 4 were unresolved (20%) and 3 (15%) were indeterminate.

The results of Campochario et al[91] suggest that perhaps as many as 50% of ranibizumab BRVO patients remain unresolved after 4 years of treatment. Perhaps 15% of these patients have relatively little oedema and are unlikely to require routine ongoing treatment, though they may require ongoing monitoring. Those that require ongoing treatment may require an annual 3.2 injections. These results are supported to some extent by those of Sophie et al,[92] which suggest that around 20%-35% of ranibizumab BRVO patients remain unresolved after 5 years of treatment.

The company's model does not implement the year 6+ dosing input within the model. Therefore, to explore the impact of ongoing treatment, the ERG has had to construct a second, simple cohort flow at the end of the company's model. Essentially, this

models the proportion of patients requiring ongoing treatment during the 6th year and assumes that these patients require ongoing treatment with an annual 3.2 anti-VEGF treatments. The proportion requiring ongoing treatment is modelled as declining due to discontinuations and death. The duration of this ongoing treatment is uncertain so is explored through sensitivity analyses of 0, 5 and 10 years.

Due to the fact that there is nothing obvious to assume for the year 6+ dosing for dexamethasone, the ERG has not implemented any year 6+ treatments for dexamethasone. Any analysis which assumes year 6+ treatments for the anti-VEGFs may consequently be biased when compared with dexamethasone.

There is also nothing obvious to assume about whether those having been treated with laser without having required rescue anti-VEGF would receive further ongoing laser treatments during year 6+, though the company survey for year 5 suggests not.

As the model revision assumes that there are no ongoing monitoring requirements associated with ongoing anti-VEGF treatment, it may underestimate the additional costs of anti-VEGF treatment during years 6+.

Notably, this modelling does not apply the 1st line aflibercept cross-over percentages as the data in the literature appear to relate to the entire baseline population. Similarly, it could be argued that the aflibercept discontinuation rate should not be applied within this. For years 6+, the ERG has conditioned the treatment percentage by the proportion modelled as remaining on treatment. The ERG is aware that this modelling is imperfect. However, considering the submitted model structure, it is all that it could feasibly be done.

Administration and monitoring unit costs

For the previous NICE TA283 on ranibizumab for treating visual impairment caused by macular oedema secondary to RVO, the company costed anti-VEGF administration as £192, based upon the OP procedure BZ23Z Vitreous Category 1 plus an additional £55 for OCT based upon the diagnostic imaging RA23Z. Laser administrations were also costed at £192. Dedicated monitoring visits were costed as

£151 based upon £96 for a consultant led follow-up appointment plus £55 for an OCT.

For the previous NICE TA346 on aflibercept for treating diabetic macular oedema, the company costed anti-VEGF administrations at £192. Laser administrations were costed as £117 for an OP BZ23Z minor intravitreal procedure plus an additional £139 for monitoring. This was criticised by the ERG, which noted that the TA274 ranibizumab for treating diabetic macular oedema only applied the OP BZ23Z minor intravitreal procedure cost.

Costings for dexamethasone administrations have typically followed the original dexamethasone assessment, which finally assumed 25% day case, costed using BZ86B, and 75% OP, costed using BZ87A.

Considering that all anti-VEGF treatment visits were assumed to double as monitoring visits, it seems unreasonable to add an additional monitoring visit cost to each laser administration raising its total cost to £261. It seems more reasonable to equalise the laser administration cost with the anti-VEGF administration cost[i].

5.3.3 Data inputs: correspondence between written submission and electronic model

1st line and 2nd line aflibercept dosing frequencies and model clinical effectiveness estimates

Among patients in the aflibercept-laser arm, the dosing schedule was monthly injections for the first six months followed by injections every other month to the end of trial. Among those remaining on treatment, this resulted in 6 aflibercept doses between baseline and week 20, with another 4 aflibercept doses between week 24 and the end of trial: a total of 10 doses.

The dosing schedule for 2nd line rescue aflibercept in the laser-aflibercept arm did not match that of the first 6 months of the aflibercept-laser arm, being monthly injections for 3 months followed by injections every other month. In the laser-aflibercept arm, [redacted] patients received rescue aflibercept from week 24, [redacted] from week 28, [redacted] from week 32, [redacted] from week 40 and [redacted] from week 48. These patients consequently received a maximum of 5, 4, 4 and 3 aflibercept injections, less than

[i] Implemented in the *Cost_inputs* worksheet by setting C27=0 and G27=G26

those in the aflibercept-laser arm. This may indicate that patients in the laser-aflibercept arm, who received rescue aflibercept, did not receive the maximum benefit of aflibercept treatment compared with the aflibercept-laser arm for the first six months of their aflibercept treatment.

It is worth noting that this only considers the patient benefits side of the equation and ignores the costs of aflibercept dosing. It is possible that the monthly dosing of the first six months of the aflibercept-laser arm is not the most cost effective option and that the aflibercept rescue schedule of the laser-aflibercept arm may be more cost effective.

Within the aflibercept-laser arm, there appears to be evidence of ongoing benefit from treatment with aflibercept between six months and one year. Those in the laser-aflibercept arm who received rescue aflibercept did not receive the benefits of a second six months of aflibercept treatment.

As a consequence, the benefits of 2nd line aflibercept in the laser-aflibercept arm may have been underestimated due to:

- Aflibercept dosing during the first six months of aflibercept treatment being less than that of the aflibercept-laser arm; and,
- No second six months of aflibercept dosing occurring in the laser-aflibercept arm.

Since the 52 week distributions of BCVA are, in essence, assumed to persist for the remainder of the model, this may bias the estimated benefits in favour of aflibercept-laser compared to laser-aflibercept.

LOCF, dropouts and model clinical effectiveness

Aflibercept has a faster initial increase in BCVA than laser, as shown in Figure 9 of the submission. Aflibercept is also an ongoing course of treatment whereas treatment with laser is to a large extent upfront. Figure 9 also shows that there are ongoing benefits during treatment with aflibercept.

Drop-out rates were quite high in both arms: 6 (7%) at 6 months and an additional 12 (13%) at 1 year to give a total of 18[j] (20%) in the aflibercept-laser arm and 9 (10%) at 6 months and an additional 6 (7%) at 1 year to give a total of 14[k] (16%) in the laser-aflibercept arm. It seems likely that many of these patients, and possibly the majority, will not have resolved when they drop out. Drop-outs were handled by using the Last Observation Carried Forward (LOCF) approach.

Since many, if not most, will not have resolved by the time they drop out there may be some unobserved rebound among these patients. Given the different immediate treatment effects and the different administration schedules, the size of this rebound may differ between the arms. There are reasons to believe that this rebound among drop outs may be bigger in the aflibercept-laser arm than in the laser-aflibercept arm, particularly among patients discontinuing before 6 months.

The results of Farinha et al[12] may, if anti-VEGF dosing was sub-optimal, provide support of an assumption of BCVA rebounding towards baseline among drop-outs.

While any rebound among drop-outs is unobservable, the drop-out rates may be a cause for concern when measuring relative treatment effects. The only immediately obvious alternative assumption to LOCF of rebound to baseline might have quite a large impact upon results and might have been worthwhile for the company to have explored.

Dosing: RESONATE versus model

At clarification, the company provided the following number of treatment administrations for RESONATE. These can be converted to the mean number of doses per patient. For simplicity, the ERG has simply divided them by the number of patients in the arm at baseline. Hence, the 2nd line treatment numbers appear too low when compared with, for example, the 4.40 doses of 2nd line rescue aflibercept since the denominator, for this 4.40 is the number of patients who received 2nd line rescue aflibercept.

[j] Note that one patient who dropped out had metastatic breast cancer while another had pelvic abscess and small bowel obstruction.
[k] Note that among the 14 one patient died.

Table 44 RESONATE treatment administrations per patient year 1

	RESONATE number of treatments				RESONATE mean number of treatments			
	AFLI-LASE		LASE-AFLI		AFLI-LASE		LASE-AFLI	
	AFLI	LASE	LASE	AFLI	AFLI	LASE	LASE	AFLI
Week 0	91		90		1.00		1.00	
Week 4	[redacted]		[redacted]		[redacted]		[redacted]	
Week 8	[redacted]		[redacted]		[redacted]		[redacted]	
Week 12	[redacted]		[redacted]		[redacted]		[redacted]	
Week 16	[redacted]		[redacted]		[redacted]		[redacted]	
Week 20	[redacted]		[redacted]		[redacted]		[redacted]	
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The values in the electronic model are based upon the number on treatment multiplied by a month treatment rate: e.g. 9 / 12 = 0.75 for aflibercept. This is an area where the model and RESONATE diverge, with RESONATE having a 4 week treatment schedule and the model having a monthly treatment schedule[l] for costing purposes. The values reported below have been corrected for apparent errors in indexing.

[l] In other words in the *Markov-Aflibercept* worksheet the 9.00 injections of cell LE100 are spread out over the 12 cells of LE112:LE123

Table 45 Model treatment administrations per patient year 1

	Model mean number of treatments			
	AFLI-LASE		LASE-AFLI	
	AFLI	LASE	LASE	AFLI
Mth 1	0.75		0.14	
Mth 2	[redacted]		[redacted]	
Mth 3	[redacted]		[redacted]	
Mth 4	[redacted]		[redacted]	
Mth 5	[redacted]		[redacted]	
Mth 6	[redacted]		[redacted]	
Mth 7	[redacted]	[redacted]	[redacted]	[redacted]
Mth 8	[redacted]	[redacted]	[redacted]	[redacted]
Mth 9	[redacted]	[redacted]	[redacted]	[redacted]
Mth 10	[redacted]	[redacted]	[redacted]	[redacted]
Mth 11	[redacted]	[redacted]	[redacted]	[redacted]
Mth 12	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

The model tends to underestimate the mean number of treatments. Discrepancies arise mainly due to the patient numbers receiving treatment being reduced by both cross-over and discontinuations in the model. For example, if the average number of aflibercept injections was six but 100% switched to rescue laser at month 6, then the modelled dose per month would be 6/12=0.5 with this being applied to 100% of patients during the first 6 months but none thereafter due to all crossing over, resulting in a total number of doses of only 3 rather than the actual trial average of 6.

The simplest means of aligning the two is to make the 1st year mean number of treatments in the aflibercept arm to be much as per the treatment schedule. Setting this to be equal to 9.75[m], this being slightly less than 10 due presumably to some patients missing doses, results in a mean number of aflibercept treatments in the 1st year of 8.99.

There is some ambiguity between the clarification response and the electronic model, in that patients receiving rescue laser could also continue to receive aflibercept with

[m] Implemented in the *Tx_Input* worksheet by setting cell G39=9.75.

an average of 3.00 aflibercept treatments in the rescue laser group. Taking these administrations into account would require the number of aflibercept administrations to only be increased to 9.60[n] to arrive at a year 1 total mean of 8.99 aflibercept treatments. This will be the default value for the revised ERG base case.

Similarly, to get the mean number of treatments to tally with the inputted mean values during the first year of the model requires that the number of 1st line laser administrations be set equal to 2.55.[o] This may seem a large increase but it should be borne in mind that the majority of patients in the laser-aflibercept arm received 2nd line rescue aflibercept. Thus, the model suggests that few patients remain in 1st line laser from the 6th month, but the number of 1st line laser administrations per cycle is averaged over the first 12 months of the model.

The numbers of 2nd line rescue laser, aflibercept and ranibizumab administrations also appear to need to be set equal to 0.3, 5.6 and 5.6.[p] The number of 2nd line rescue dexamethasone administrations differ as the value is not based upon trial values but is rather by assumption. The model average within the cohort flow appears to be broadly in line with that assumed.

Similar considerations apply to the subsequent years mean numbers of treatment due to discontinuations. The mean values that are inputted to the model are not the mean per prevalent patient at the start of the year. It can be argued that the year 2, 3, 4 and 5 aflibercept numbers of administrations should be increased in the model inputs from 4.15, 2.61, 1.12 and 0.58 to 4.40, 2.75, 1.20, 0.60. If so, the number of year 2, 3, 4 and 5 laser administrations should be correspondingly increased from 1.12, 0.36, 0.12 and 0.03 to 1.18, 0.38, 0.13 and 0.03.

The above dosing is specific to the company assumed discontinuation rates. Therefore, there should not be any sensitivity analyses around discontinuation rates without a parallel consideration of how dosing inputs should be revised to result in model averages that reflect the RESONATE trial and additional assumptions.

[n] Implemented in the *Tx_Input* worksheet by setting cell G39=9.60.
[o] Implemented in the Tx_Input worksheet by setting cell G60=2.55.
[p] Implemented in the *Tx_Input* worksheet by setting cell G92=0.30, G81=5.60 and G50=5.60.

Discontinuation rates

Annual discontinuation rates within the model are assumed to be 11/91 in the aflibercept-laser arm and 9/92 in the laser arm. This does not correspond with anything obvious in Figure 6 of the company submission and the ERG is unclear why these values have been used.

These are also the first year discontinuation rates and it may be questionable to have applied them for the remainder of the treatment phase of the model[q].

5.3.4 ERG commentary on model structure, assumptions and data inputs

Application of NMA odds-ratios

The odds ratios of the NMA for aflibercept compared to ranibizumab and dexamethasone are derived from data relating to week 0 to week 24 for 1st line treatment with aflibercept, ranibizumab and dexamethasone. They are applied to the week 24 to week 52 VIBRANT data for 2nd line rescue treatment with aflibercept.

Data limitations may mean that these are the most reasonable odds ratios to apply, but they do not obviously apply to the data under consideration. At a minimum, this increases the uncertainty around the estimates of the cost effectiveness of laser-aflibercept compared to laser-ranibizumab and laser-dexamethasone.

Compounding of TPMs and odds-ratios

For the comparisons with laser-ranibizumab and with laser dexamethasone, the odds ratios of gaining 15+ letters of 0.93 and 0.34 respectively are applied to the monthly laser-aflibercept TPM that relates to cycles 7 to 13 of the model (i.e. seven times within the model). These odds ratios are applied to the probabilities of gaining letters as below.

The resulting odds ratios for the probabilities of remaining in the same health state can then be inferred from the requirement that the resulting TPMs' transition probabilities are required to sum to one; i.e. everyone has to go somewhere. For

[q] This can be implemented by setting the discontinuation rates in the TPMs of cells F28:W45 and AA28:AR45 of the Markov worksheets to zero. While imperfect, this also requires that the ERG revisions to dosing be turned off for years 2 to 5.

instance, the probability of remaining in VA3 for 2nd line aflibercept is calculated as 75.6%. After the odds ratio of 0.93 has been applied to the probability of gaining letters and the probability of losing letters has been assumed to be equal to those of aflibercept, there is a 76.9% probability of remaining in VA3 for 2nd line ranibizumab. This implies an odds ratio of remaining in VA3 of (76.9%/(1-76.9%))/(75.6%/(1-75.6%)) = 107%.

Table 46 2nd line odds ratios effectively applied within the model every cycle

	Odds ratios compared to 2nd line aflibercept									
	2nd line ranibizumab					**2nd line dexamethasone**				
	VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
VA1	100%	93%	93%	93%	93%	100%	34%	34%	34%	34%
VA2	100%	105%	93%	93%	93%	100%	193%	34%	34%	34%
VA3	100%	100%	107%	93%	93%	100%	100%	268%	34%	34%
VA4	100%	100%	100%	108%	93%	100%	100%	100%	313%	34%
VA5	100%	100%	100%	100%	108%	100%	100%	100%	100%	296%

The effect of compounding these odds ratios seven times can be explored by multiplying the resulting monthly TPMs by themselves six times (i.e. the corollary of raising them to the power seven). This results in the following TPMs.

Table 47 Compounded 7 month TPM: laser-aflibercept

	From				
To	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
VA1	38.0%	29.3%	20.2%	13.2%	3.1%
VA2	53.2%	57.9%	53.2%	43.8%	12.2%
VA3	8.4%	12.1%	24.2%	33.5%	13.9%
VA4	0.4%	0.7%	2.4%	9.6%	0.8%
VA5	0.0%	0.0%	0.0%	0.0%	70.0%

Table 48 Compounded 7 month TPM: laser-ranibizumab

	From				
To	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
VA1	37.1%	27.8%	18.6%	11.8%	2.7%
VA2	53.9%	58.8%	52.7%	42.1%	11.2%
VA3	8.6%	12.7%	26.0%	35.1%	13.6%
VA4	0.4%	0.8%	2.7%	11.0%	0.8%
VA5	0.0%	0.0%	0.0%	0.0%	71.7%

Table 49 Compounded 7 month TPM: laser-dexamethasone

	From				
To	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
VA1	27.4%	12.2%	4.9%	2.0%	0.3%
VA2	60.1%	66.5%	35.2%	16.9%	3.0%
VA3	11.8%	19.9%	53.0%	39.8%	7.7%
VA4	0.6%	1.4%	6.8%	41.3%	0.5%
VA5	0.0%	0.0%	0.0%	0.0%	88.5%

These, in turn, imply the following odds ratios.

Table 50 2nd line odds ratios effectively applied within the model between cycles 7 and 13

	Odds ratios compared to 2nd line aflibercept									
	2nd line ranibizumab					2nd line dexamethasone				
	VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**
VA1	96%	93%	90%	88%	86%	62%	34%	21%	13%	11%
VA2	103%	104%	98%	93%	91%	133%	144%	48%	26%	22%
VA3	104%	105%	110%	108%	97%	147%	180%	353%	132%	51%
VA4	104%	107%	111%	117%	99%	160%	196%	298%	665%	64%
VA5	103%	104%	106%	106%	109%	134%	151%	178%	186%	329%

The above can be interpreted as the odds ratios that would have to be applied to the compound seven month laser-aflibercept aflibercept rescue TPM of Table 47 to arrive at the modelled patient distribution in the laser-ranibizumab arm or the laser dexamethasone arm at the end of the first year.

These implied cycle seven to 13 odds ratios are very different from those that are applied each 4-week cycle within the model. The effects are somewhat more dramatic for 2nd line dexamethasone. There is a far lesser chance of improvement and a far greater chance of worsening. This also applies for 2nd line ranibizumab, though with less force.

The odds ratios of the NMA apply to a six month period. The implied six or seven month odds ratios of the model should be aligned with these. It appears that they are not and that the compounding of the odds ratios within the model somewhat biases the analyses against 2nd line ranibizumab and against 2nd line dexamethasone. This argues for a model based upon six month TPMs rather than monthly TPMs.

Appropriate sources of QoL values in visual disorders

The company response to clarification question B8 cites the NICE DSU TSD No.8[93] as stating that "the EQ-5D is probably not appropriate for assessing the impact of … some specific forms of visual impairment". The TSD document bases this conclusion on the review of Tosh et al94 and there is no further discussion of this other than the statement as to the appropriateness of the EQ-5D for some specific forms of visual impairment. This study has been superseded by the NIHR HTA report by Longworth et al[95] which the company states found that "EQ-5D … *is likely to be inappropriate for studies of … some visual impairment".*

The NIHR HTA report has undertaken a rather wider and more formal analysis of the EQ-5D and other generic QoL measures across a range of conditions. The report assesses the performance of generic measures according to:

- "*construct validity, the extent to which the measure differentiated between groups defined according to severity..;*
- *convergent validity, the strength of association between the EQ-5D and other measures of HRQL or clinical severity assessed using correlation coefficients or statistical significance and regression methods;*
- *responsiveness, the extent (size and statistical significance) to which EQ-5D shows change where change has been observed using other HRQL or clinical measures; and*
- *reliability, the extent to which the EQ-5D shows no change where no change in health has been observed using other measures*."

The visual impairment aspects are summarised as: *"Most of the 31 studies considered in this review found a worsening of utility values as visual impairment increases. Most evidence was found for the EQ-5D. Nearly all studies found significant differences between patients with the condition and a control group without it. Studies comparing EQ-5D scores across severity groups were more mixed, with most finding little or no difference between groups defined by clinical measures of visual impairment. No studies reported evidence on reliability for any of the measures. Three studies only allowed assessment of responsiveness and these identified changes consistent with an effective intervention, but differences were statistically significant in only two of three studies. The assessment of convergent validity was more concerning, with several studies not demonstrating a statistically significant correlation with clinical measures."*

In short, EQ-5D QoL was typically found to worsen with BCVA and was often more responsive to the effects of an intervention. Consequently, it is not obvious to the ERG that the VIBRANT EQ-5D data should be entirely rejected or that the Czoski-Murray QoL function should necessarily be the preferred choice.

The NIHR HTA report concludes that *"The systematic review established that EQ-5D … performance varied according to aetiology for vision".* There is no more in the summary about which aetiologies the EQ-5D is a good measure for and which it is a bad measure for. The NIHR HTA report does not recommend superior sources to the EQ-5D for QoL in visual disorders.

As far as the ERG can ascertain, the measure of responsiveness in the NIHR HTA report is the correlation between the individual patient clinical measure and EQ-5D score. While not expert in the area, the ERG also notes that the EQ-5D social tariff is a step function. It seems possible that the quality of life improvements associated with improvements in the BCVA of the WSE may typically be too small for many patients to cause them to cross the boundaries of the EQ-5D between, for example, some problems and no problems. No change in QoL will be recorded among these patients and the EQ-5D will be unresponsive among them. However, for the patients that do cross the boundaries of the EQ-5D, the inferred change in their QoL will probably be somewhat larger than the actual change in their QoL. The EQ-5D will be too

responsive among this group of patients. Nevertheless, when averaged across all patients, the responsiveness of the EQ-5D may be a more reasonable reflection of the average change in QoL. This would seem to raise the possibility of the EQ-5D being responsive at the trial level provided the sample was of a reasonable size even if it is not responsive at the level of the individual patient.

QoL: WSE as a function of BSE: evidence

Most NICE assessments of treatments for visual disorders have assumed that a change in the BCVA of the WSE has 30% the QoL impact of the same change in the BCVA of the BSE. For the TA274 ranibizumab for treating diabetic macular oedema, the ERG constructed a variety of scenarios, with a given change in the BCVA of the WSE being assumed to have 0%, 15%, 30%, 50%, 75% and 100% the QoL impact of the parallel change in the BCVA of the BSE.

The AC for the ranibizumab assessment preferred the 30% scenario, but, as far as the ERG is aware, this was more a practical decision and not based upon any particular evidence. At the time of the TA274 ranibizumab for treating diabetic macular oedema, the only real data available on this was that of Brown.[96]

Brown et al[96] employed time-trade off TTO and standard gamble (SG) to assess the HRQoL among 325 US patients with impaired vision of at least 20/40 in at least one eye. There were 78 patients with good vision of 20/20 to 20/25 in one eye. These patients were subdivided by the BCVA in the fellow eye into 5 groups with TTO and SG being applied to them, resulting in the following patient distribution and HRQoL estimates.

Table 51 HRQoL by BCVA in WSE for those with good vision in BSE: Brown et al 1999

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

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

The RESONATE EQ-5D data appear to correspond reasonably to those of Brown et al above in the sense of most patients having a fairly good BCVA in their BSE. The BCVA of the BSE is typically in either VA1 or VA2, with it only being the BCVA of the WSE that drops below this.

To the extent that the EQ-5D analyses of the RESONATE data are reliable, the coefficients on the BCVA of the WSE and the BCVA of the BSE of the linear models can be compared.

Table 52 RESONATE EQ-5D QoL coefficients on BCVAs of WSE and BSE

	WSE	BSE
OLS	[redacted]	[redacted]
Fixed effects	[redacted]	[redacted]
Random effects	[redacted]	[redacted]

There is a reasonable congruence between the models in terms of the impact of the BSE upon QoL with a coefficient of around [redacted]. This may seem quite small when compared with the values available in the literature as reviewed by the ERG below.

However, it seems that the great majority of the VIBRANT BSE data relate to vision in the VA1 to VA2 range. It may be that changes in BSE vision in this range have a lesser effect than when the BCVA of the BSE is somewhat worse.

There is no obvious pattern between the two coefficients, other than the WSE having a smaller QoL impact than the BSE. Whether this supports the Brown et al[96] data, which appear to show that changes in the BCVA of the WSE have very little impact upon QoL, is questionable. The above may argue for sensitivity analyses that reduce the WSE proportion to less than 30%.

QoL: WSE as a function of BSE: model implementation

The model applies a QoL decrement for a given change in the BCVA of the WSE as a percentage of the QoL decrement associated with the same change in the BCVA of the BSE.

However, given an input of X% within the model, this is implemented as 1/(1+(1/X%)). The ERG does not understand the rationale for this, but it results in the following Y% being applied within the model.

Table 53 WSE QoL impact as percentage BSE QoL

Input X%	Applied Y%
15%	13%
30%	23%
43%	30%

In the light of this, a sensitivity analysis increasing the input percentage to 43% is justified.

QoL: additional values from the literature

The submission has concentrated upon Czoski-Murray et al[86] to the exclusion of other papers within the literature that have been used in previous NICE assessments, most notably Brown.[96]

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

Table 54 Czoski-Murray HRQoL values

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

This resulted in two regression equations, one controlling for age and the other not. These were also compared with similar regression equations derived from a patient survey among ARMD patients undertaken by Espallargues et al,[97] co-authored with Czoski-Murray. Espallargues et al[97] measured TTO, HU13 and EQ-5D among 209 UK ARMD patients and related these to the VA of the BSE. Valuation of the EQ-5D data was based upon the UK social tariff, while valuation of the HU13 index was apparently based upon the VAS and standard gamble conducted among a sample of the Canadian public. The regression models reported below are only reported in Czoski-Murray.[86]

Table 55 Czoski-Murray HRQoL models

	Lens study		Survey of ARMD patients					
Method	**TTO (n=311)**		**TTO (n=203)**		**HUI3 (n=206)**		**EQ-5D (n=207)**	
Models	**coef**	**s.e.**	**coef**	**s.e.**	**coef**	**s.e.**	**coef**	**s.e.**
Not controlling for Age								
Constant	0.828	0.039	0.753	0.038	0.479	0.033	0.745	0.027
VA LogMAR	-0.359	0.045	-0.087	0.031	-0.140	0.027	-0.027	0.023
Adjusted R^2	0.171		0.032		0.110		0.002	
Controlling for Age								
Constant	0.860	0.068	1.737	0.217	1.078	0.198	0.753	0.164
VA LogMAR	-0.368	0.046	-0.036	0.032	-0.109	0.028	-0.027	0.024
Age	-0.001	0.002	-0.013	0.013	-0.008	0.003	0.000	0.002
Adjusted R^2	0.172		0.121		0.147		0.003	

Czoski-Murray noted that the coefficient from TTO values obtained from the lenses study within the model not correcting for age was *"over four times the size of the patients' own TTO coefficients and 13 times the coefficient for the EQ-5D"*. In other words, for a given LogMAR change in the BCVA of the BSE, the Lens TTO coefficient suggests this will have four times the HRQoL impact compared to the coefficient estimated using the TTO among ARMD patients. Czoski-Murray also noted that controlling for age *"increased the differences between the coefficients on the VA for the TTO values".* Consequently, if the EQ-5D is thought unresponsive to visual disorders, the TTO results among the patients of Espallargues et al may suggest that the TTO estimates of Czoski-Murray are too high.

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

Brown[96] subdivided the BSEs into 12 BCVA groups, with TTO and SG suggesting the following HRQoL values.

Table 56 HRQoL by BCVA in BSE: Brown 1999

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

Brown also used the above to estimate quality of life as a function of the decimalised Snellen resulting in QoL = 0.514 + 0.370 * VA. This imposes a non-linearity in terms of QoL as a function of the ETDRS letters.

The Czoski-Murray and the Brown data can be summarised as below, with the values for Brown ETDRS letters 60 and 55, 45 and 40 and 30 being taken as a linear average of the adjacent values due to there being no immediate read across from the values in Brown. The values of Brown can also be made linear in the ETDRS by simplistically connecting the best and the worst values.

Table 57 Czoski-Murray and Brown TTO QoL values

ETDRS	Snellen	LogMAR	C-M	Brown 99	Brown equ.	Brown linear
90	20/15	-0.1	0.832		1.007	0.949
85	20/20	0.0	0.795	0.920	0.884	0.920
80	20/25	0.1	0.758	0.870	0.810	0.891
75	20/32	0.2	0.721	0.840	0.745	0.862
70	20/40	0.3	0.685	0.800	0.699	0.832
65	20/50	0.4	0.648	0.770	0.662	0.803
60	20/63	0.5	0.611	*0.737*	0.631	0.774
55	20/80	0.6	0.574	*0.703*	0.607	0.745
50	20/100	0.7	0.537	0.670	0.588	0.715
45	20/125	0.8	0.501	*0.667*	0.573	0.686
40	20/160	0.9	0.464	*0.663*	0.560	0.657
35	20/200	1.0	0.427	0.660	0.551	0.628
30	20/250	1.1	0.390	*0.645*	0.544	0.598
25	20/320	1.2	0.353	0.630	0.537	0.569
20	20/400	1.3	0.317	0.540	0.533	0.540

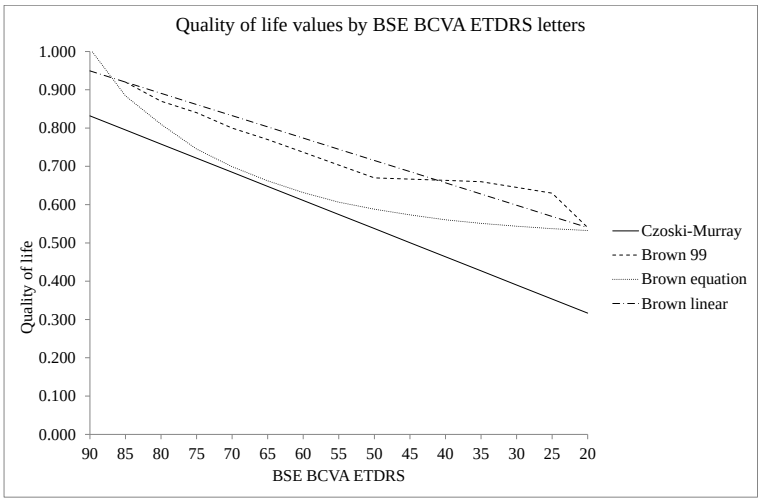

Figure 6 Czoski-Murray and Brown TTO QoL values

The slopes of the Czoski-Murray function and the rather crude ERG linear interpolation of Brown are not so different: -0.368 compared to -0.292.

Given the comparison with the patients' TTO estimates of Espallargues et al, there may be suspicion that the TTO estimates of the Czoski-Murray et al experimental

lenses study may be too large. As a consequence, a sensitivity analysis that applies the rather crudely ERG derived ETDRS coefficient of -0.292 will be considered.

QoL: RESONATE Tobit model

The company's argument largely centres on which RESONATE EQ-5D model should be used on the basis of the R^2. It may be sensible to take into account other considerations, such as the repeated measures nature of the data. However, at clarification, the company supplied the R^2 values for the Tobit model. For both the linear modelling and the logarithmic modelling, while still low, these are superior to the other models, at [redacted] compared to [redacted] for the OLS model. The company was asked to supply the bilateral QoL functions for each model and largely did so, but did not do so for the Tobit model. As a consequence, the ERG has not explored this further.

QoL: additional data from RESONATE and VIVID/VISTA

There are also the coefficients from the company analysis of the VIVID/VISTA EQ-5D data that the company submitted for the TA346 aflibercept for treating DMO. The OLS log(WSE BCVA) coefficient was [redacted] while that for the log(BSE BCVA) was [redacted]. Both were statistically significant. Patient BMI was also included in the DMO regressions, possibly as a proxy for the likelihood of the diabetes comorbidities, although these might also be expected to be correlated with BCVAs. The corresponding coefficients in the RESONATE data are [redacted] and [redacted]. The coefficients are not identical, but there is some similarity.

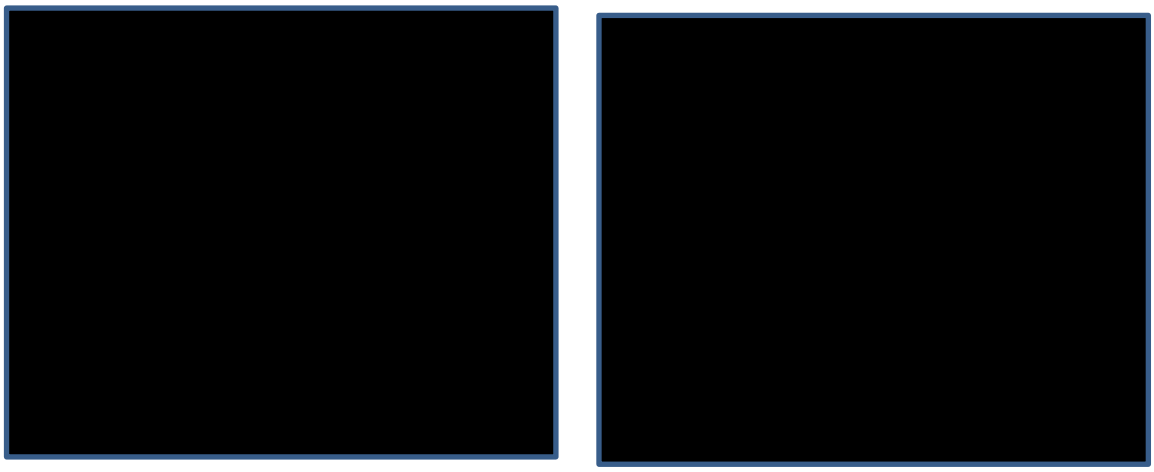

Figure 7 Scatterplots of changes in BCVA and changes in EQ-5D QoL

The company has also supplied scatter plots of the change in the BCVA of the WSE against the change in the EQ-5D QoL and also of the change in the BCVA of the BSE against the change in the EQ-5D QoL, as below.

It seems likely that the above data define eyes as being the WSE or the BSE by their status at baseline. A reasonable proportion of study eyes, around [redacted], crossed over from being the WSE to being the BSE with this being most common in the aflibercept-laser arm at [redacted]. This complicates interpretation of the above scatter plot, and the ERG should have formulated the clarification request to take cross over into account.

Nevertheless, there is no strong pattern of evidence for changes in QoL being a function of changes in the BCVA of the BSE, let alone a function of changes in the BCVA of the WSE, despite the regression coefficients on both the BCVA of the BSE and the BCVA of the WSE typically being statistically significant.

An aspect that is somewhat surprising is the number of patients estimated to lose vision in their BSE over the course of RESONATE, albeit relatively few patients lose more than 10 letters. The general tendency for the majority of patients was to gain letters in their BSE. Unless the above takes into account cross over, it appears that the non-study eyes also typically gained visual acuity over the course of RESONATE.

The ERG did ask the company to supply regressions of changes in EQ-5D QoL against changes in BCVA of the WSE and the BSE. The company replied that there was not enough time for addressing this request despite the required data sets being available as outlined in the scatter plots above.

Cycle length

There is a general inconsistency within the model as to whether the cycle length is four weeks, hence 52/13, or is a month of 52/12. The first year is typically taken to be 52/13 with subsequent years being 52/12. However, discounting assumes that the first year is based upon 52/12, which, in itself, has only a very marginal impact upon results.

The ERG remains slightly concerned about whether the remainder of the model is aligned with 52/13 for the first year and 52/12 for the remainder of the time horizon. This applies particularly in the modelling of the non-study eye where the incidence of fellow eye involvement is every 12th cycle and the duration of treatment of the first year of treatment for these newly incident fellow eyes is only 12 cycles rather than the 13 of the fellow eye.

An area where the model becomes unaligned as a result of this is in the number of injections. The patient cohort of the first year runs for the first 13 cycles of the model. The number of injections over these 13 cycles for e.g. aflibercept is taken to be the number of injections in year 1, nine injections, divided by twelve to give 0.75 per calendar month with this then being applied to each of the first 12 four week cycles. The last four week cycle of the 1st year has one twelfth of the number of injections in year two, 4.15 injections, applied to it. This appears to be incorrect and also appears to cascade down through the cohort flow calculations. It is difficult to estimate precisely what effect this has upon the modelling and it is not possible to correct the company model for this. The ERG's impression is that it increases the uncertainty around the estimates of the direct drug costs.

For the first year of the model, the possibility of rescue medication is only applied to the last five cycles. It appears more correct to apply this to the last six cycles of this period, particularly since the model divides the total number of injections during this period by six to arrive at the monthly amount.

A curiosity within the company model structure is that there is some attempt to correct for the above in cycle nine of the model when most cross over occurs within the aflibercept arm. The number of laser administrations is set equal to one rather than one sixth of the six monthly amount. This attempted correction is not applied consistently and accounts for some of the differences between the company model and the ERG rebuild, but it has little effect.

Fellow eye incidence

The annual incidence of fellow eye involvement of 2.5% is only applied for four years within the modelling, which may tend to underestimate the costs and benefits of fellow eye involvement. This argues for a sensitivity analysis around this.

Mortality

The mortality risk for those with one eye or two eyes in VA5 for the first six cycles of the model is incorrectly averaged over the first 26 cycles of the model. During the decline phase, the one eye VA5 mortality increase is not applied.

Due to the Markov model extending beyond the mortality calculations, the model also applies no mortality from the 398th cycle, although patients are aged 96 by this point and few remain alive[r].

Probabilistic modelling

The ERG is surprised by the apparent non-linearity of the model in the light of the company's submission using means and standard errors, and, where standard errors are not available, ±20% of the mean value. The probabilistic cost effectiveness estimates are somewhat better than the deterministic estimates due to much lower cost estimates. Within the timeframe for this appraisal, the ERG has not been able to identify the source of this non-linearity.

A number of the inputs to the model appear to be implemented probabilistically. Many of these are correctly treated as being deterministic such as the discount rates. Others can be argued to be by assumption, hence, perhaps, not suitable for probabilistic modelling; e.g. the numbers of injections from year 2 onwards.

It may not be reasonable to treat other inputs as being deterministic; e.g. the starting age of the cohort with the model showing some non-linearity. This non-linearity is not particularly dramatic: across two simulations with a starting age of 52 years and 78 years the average cost effectiveness estimate for aflibercept-laser compared to laser-

[r] Corrected in the *Mortality* worksheet by making cells B414:K517 be of the same format as the cells above, only indexing R17:R138, and setting the probabilities of death for those age 110+ equal to 1.

aflibercept is £15,786 per QALY compared with an estimate of £15,362 per QALY for a starting age of 65 years.

A number of variables have probabilistic sampling turned off, while for others, where probabilistic sampling might be expected and was allowed for within the model, have been subsequently hard coded to be constant.

Table 58 Model variables in parameter hub not sampled probabilistically

Variables	Method
Baseline age	Sampling turned off
Blindness RR mortality	Variable hard coded
Proportion FE treated	Variable hard coded
Proportion injections requiring separate monitoring visit	Sampling turned off
Eye examination cost	Sampling turned off
FA cost	Sampling turned off
Number of treatments	Sampling turned off
Monitoring visits	Sampling turned off
Laser adverse event rates	Sampling turned off

The most obvious elements that should not be treated deterministically within the probabilistic modelling are the clinical effectiveness estimates for aflibercept-laser and laser-aflibercept. The company confirmed at clarification that these elements are treated deterministically within the probabilistic modelling due to the company being unaware of any methods that enable probabilistic sampling of the output of the R MSM package.

In the opinion of the ERG, there is little point in undertaking probabilistic modelling if the clinical effectiveness estimates upon which all the modelling rests are not implemented probabilistically. Given the NICE TAPs methods guide and the validation section 5.2.11 above, this may further argue for basing the TPMs on patient count data rather than deriving them using the R MSM package. Basing the TPMs on patient count data should also align the model results from those using the shift-tables approach, obviating the need for probabilistic sampling of the shift tables. There are

well established methods for probabilistic sampling of TPMs based upon patient count data.

Minor issue: discontinuation rates

There appears to be a minor error in the calculation of the monthly discontinuation percentage. This is given as ((1+n/N) ^ (1/12) – 1) when ERG calculations suggest it should be (1 – (1-n/N) ^ (1/12)). The method slightly underestimates the discontinuation percentage. It is also based upon 12 cycles within the year, when the first year lasts for 13 cycles. This also applies to the calculation of SAE rates.

Minor issue: TPMs: discontinuations and deaths

Within the TPMs the discontinuations and deaths are assumed to all occur among those remaining in their original health state; i.e. the probability of discontinuations and the probability of death is in effect subtracted from the principal diagonal. This may tend to exaggerate the differences between the treatment arms.

Minor issue: SAE QALYs

It appears that the QALY decrements associated with cataract and IOP are not discounted and that the QALY decrement for cataract is also applied to IOP in the study eye.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

In the light of the results of the RETAIN study, the revised ERG base case for the comparison of aflibercept-laser with laser-aflibercept assumes that after year five, 30% of patients will require an annual average of 3.2 anti-VEGF administrations. This is arbitrarily assumed to be required for a further five years, with this duration being varied in sensitivity analyses to 0 years and 10 years. The literature review did not find any evidence for ongoing dexamethasone use and it is consequently difficult to make reasonable assumptions for this comparison. For this reason, the ERG base case assumes no ongoing year 6+ dosing for the comparisons of laser-aflibercept, laser-ranibizumab and laser-dexamethasone and only introduces these as sensitivity analyses for the comparison of laser-aflibercept and laser-ranibizumab.

Based upon expert opinion, the ERG has revised the company's economic model to:

- Assume quarterly monitoring for 1st year laser based upon expert opinion[s]
- Assume 80% of administration visits can double as monitoring visits[t]
- Assume 100% of fellow eye involvement will be treated[u]

The ERG has also revised the model to:

- Correct indexing for fellow eye costing[v]
- Correct 1st year indexing of rescue costs[w]
- Correct referencing for laser costs in aflibercept-laser[x]
- Assume the same administration costs for laser as for anti-VEGF[y]
- Correct the mortality averaging during the first 7 cycles of the model[z]
- Apply ongoing mortality for cycles 396+, as previously outlined
- Revise dosing inputs to take into account discontinuations and cross-over, as previously outlined. Note that the ERG has not revised the dosing for dexamethasone due to time constraints.
- Anti-VEGF dosing for years 6+ of 3.2 annual administrations for 30% of patients for 5 years, implemented as previously outlined
- Not apply the cataract QALY decrement to IOP, by simply setting this to zero in the summary of results.
- Include fellow eye SAE disutilities[aa]

The ERG has undertaken the following sensitivity analyses:

- SA01: Apply the R MSM derived TPMs for the comparison of aflibercept-laser with laser-aflibercept
- SA02: Apply the 8 studies median ORs of gaining at least 15 letters of 1.08 for ranibizumab and 0.40 for dexamethasone[bb]

[s] Implemented in the *Tx_Input* worksheet by setting L135=4
[t] Implemented in the *Executive_Summary* worksheet by setting cell C29=80%
[u] Implemented in the *PH* worksheet by setting G15=1
[v] Implemented in the markov worksheets by having e.g. cell LH125 refer to cell LC124 rather than cell LC125
[w] Implemented in the markov worksheets by setting cell LB118=1
[x] Implemented in the *Markov-aflibercept* worksheet by having e.g. cell LF121 refer to cell KB121 rather than cell KB120
[y] Implemented in the *Cost_Input* worksheet by setting cell C27=0 and G27=G26
[z] Implemented in the *Mortality* worksheet by setting cell J7=average(J17:J23) and K7=average(K17:K23)
[aa] Implemented in the *QALYs* worksheet in cells E16:H16 by adding the relevant RF95 to RE95.

- SA03: Revise the quality of life percentage for the WSE to be 15%[cc]
- SA04: Revise the quality of life percentage for the WSE to be 43%[dd]
- SA05: Revise the quality of life function to have a coefficient of -0.292[ee]
- SA06: Revise the quality of life to be the VIBRANT EQ-5D OLS linear model[ff]
- SA07: Revise the quality of life to be the VIBRANT EQ-5D random effects linear model[gg]
- SA08: Anti-VEGF dosing for years 6+ lasting 0, 5 and 10 years, as previously outlined
- SA09: Anti-VEGF dosing for years 6+ of an annual 2.0 doses, as previously outlined
- SA10: Ranibizumab having one less administration than aflibercept during year 1, as previously outlined
- SA11: Only BCVA VA2 being treated for the comparison of aflibercept-laser with laser aflibercept[hh]
- SA12: Only BCVA VA3 to VA5 being treated for the comparison of aflibercept-laser with laser aflibercept[ii]

The ERG was not able to run the model probabilistically because the main clinical inputs to the economic model have not been implemented probabilistically and could not be amended.

Aflibercept-laser compared with laser-aflibercept

The ERG revised base case is presented below.

[bb] Implemented in the *Tx_Input* worksheet by setting L19:N19 and L28:N28 to the relevant values
[cc] Implemented in the *Utility_regression_models* worksheet by setting cell D25=15%
[dd] Implemented in the *Utility_regression_models* worksheet by setting cell D25=42.85%
[ee] Implemented in the *Utility_regression_models* worksheet by setting cell D13=-0.292
[ff] Implemented in the *Utility_regression_models* worksheet by copying the relevant values into cells D27:H31
[gg] Implemented in the *Utility_regression_models* worksheet by copying the relevant values into cells D27:H31
[hh] Implemented in the *Shift_Tables* worksheet by copying the values supplied at clarification into cells D7:H20, U13:Y20, D25:H38 and U31:Y38
[ii] Implemented in the *Shift_Tables* worksheet by copying the values supplied at clarification into cells D7:H20, U13:Y20, D25:H38 and U31:Y38

Table 59 ERG revised base case: aflibercept-laser compared with laser-aflibercept

	Aflibercept-laser			Laser-aflibercept		
	SE	**NSE**	**Total**	**SE**	**NSE**	**Total**
1st line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net						[redacted]
QALYs BCVA			[redacted]			[redacted]
QALYs cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs			[redacted]			[redacted]
Net QALYs						[redacted]
ICER						£27,259

Aflibercept-laser is estimated to result in an additional [redacted] net cost but to also yield an additional [redacted] QALYs, resulting in a cost effectiveness estimate of £27,259 per QALY.

The results of the univariate sensitivity analyses are presented in Table 60.

Table 60 ERG sensitivity analyses: aflibercept-laser compared with laser-aflibercept

	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	£27,259
SA01: R MSM TPMs	[redacted]	[redacted]	£23,847
SA02: 8 study NMA	[redacted]	[redacted]	n.a.
SA03: 15% WSE QoL	[redacted]	[redacted]	£31,581
SA04: 43% WSE QoL	[redacted]	[redacted]	£24,891
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£34,656
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£47,850
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£70,394
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	£16,801
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	£31,624
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	£23,337
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	n.a.
SA11: VA2 shift tables	[redacted]	[redacted]	£43,566
SA12: VA3, VA4 + VA5 shift tables	[redacted]	[redacted]	£23,804

Applying the R MSM derived TPMs improves the cost effectiveness estimate by a reasonable amount to £23,847 per QALY.

As expected, the alternative sources of quality of life values tend to worsen the cost effectiveness of aflibercept-laser compared with laser-aflibercept. The exception to this is the sensitivity analysis SA04, which revises the WSE QoL impact to 43% of that of the BSE within the formula 1/(1+(1/43%)) = 30%. and improves the cost effectiveness estimate to £24,891 per QALY.

The other sensitivity examined in the above is the duration and dosing among the 30% assumed to require ongoing anti-VEGF treatment. Assuming no dosing from year six onwards reduces the net costs quite considerably and improves the cost effectiveness estimate to £16,801 per QALY, while assuming it applied for 10 years, even with ongoing discontinuations, worsens the cost effectiveness estimate to £31,624 per QALY. If this ongoing dosing is 2.0 administrations for five years among those requiring it, the cost effectiveness estimate improves to £23,337 per QALY.

The VIBRANT patient group was broadly equally split between those with their study eye in VA2 and those with their study eye in VA3, VA4 or VA5, though the numbers in VA4 and VA5 were quite small. Applying the subgroup specific shift tables data suggests a worse cost effectiveness among those with their study eye inVA2 compared to those with their study eye in VA3, VA4 or VA5.

Laser followed by alternative 2nd line rescue treatments

The ERG revised base case is shown in Table 61.

Table 61 ERG revised base case: laser followed by alternative 2nd line rescue

	Laser-aflibercept			Laser-ranibizumab			Laser-dexamethasone		
	SE	**NSE**	**Total**	**SE**	**NSE**	**Total**	**SE**	**NSE**	**Total**
1st line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net						[redacted]			[redacted]
QALYs BCVA			[redacted]			[redacted]			[redacted]
QALYs cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs			[redacted]			[redacted]			[redacted]
Net QALYs						[redacted]			[redacted]
ICER						DOM			£18,542

For the revised base case, laser-aflibercept is cheaper than laser-ranibizumab, due mainly to only the aflibercept PAS having been applied in the above. It is also estimated to yield a small net gain of [redacted] QALYs, resulting in it being estimated to dominate laser-ranibizumab.

For the comparison with dexamethasone, due to the higher number of aflibercept administrations laser-aflibercept is estimated to result in an additional net cost of

[redacted]. The QALY gain is somewhat larger at [redacted] QALYs, resulting in a cost effectiveness estimate of £18,542 per QALY.

The results of the univariate sensitivity analyses are shown in Table 62.

Table 62 ERG sensitivity analyses: laser followed by alternative 2nd line rescue

	vs laser-ranibizumab			vs laser-dexamethasone		
	ΔCosts	ΔQALYs	ICER	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	DOM	[redacted]	[redacted]	£18,542
SA01: R MSM TPMs	[redacted]	[redacted]	n.a.	[redacted]	[redacted]	n.a.
SA02: 8 study NMA	[redacted]	[redacted]	£204k	[redacted]	[redacted]	£20,969
SA03: 15% WSE QoL	[redacted]	[redacted]	DOM	[redacted]	[redacted]	£21,468
SA04: 43% WSE QoL	[redacted]	[redacted]	DOM	[redacted]	[redacted]	£17,162
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	DOM	[redacted]	[redacted]	£23,518
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	DOM	[redacted]	[redacted]	£32,846
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	DOM	[redacted]	[redacted]	£48,815
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.	[redacted]	[redacted]	n.a.
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	DOM	[redacted]	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	DOM	[redacted]	[redacted]	n.a.
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	DOM	[redacted]	[redacted]	n.a.
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	DOM	[redacted]	[redacted]	n.a.

As for the base case, the QALY differences between laser-aflibercept and laser-ranibizumab are relatively small. SA02 that applies the eight study NMA results sees laser-ranibizumab confer slightly more QALYs, but given the net costs the cost effectiveness of laser-ranibizumab compared to laser-aflibercept is poor at £204k per QALY.

The range of sensitivity analyses of SA08 and SA09 are better seen as the base cases for the comparison with laser-ranibizumab but consistency of approach and a lack of data for ongoing dexamethasone treatment led to the above presentation.

The eight study NMA has a relatively muted impact upon the cost effectiveness estimate for laser-aflibercept compared with laser-dexamethasone, though it does push it above £20k per QALY. The alternative sources of quality of life estimates typically worsen the cost effectiveness estimates, again pushing the cost effectiveness

estimate above £20k per QALY. It is only the VIBRANT EQ-5D estimates that push it above £30k per QALY.

5.5 Conclusions of the cost effectiveness section

Possible biases within the economic model inputs and modelling are:

- No consideration of bevacizumab.
- The VIBRANT trial assuming LOCF for missing data. Drop-outs during VIBRANT were quite high. Given the rapid initial increase in BCVA in the aflibercept-laser arm compared with the laser-aflibercept arm, any tendency for rebound to baseline among drop-outs could have a bigger effect in the aflibercept-laser arm. It might be possible to explore an assumption of rebound to baseline as a scenario analysis.
- The aflibercept dosing in the VIBRANT trial differed between the arms. In the aflibercept-laser arm for the 1st six months it was monthly and for the 2nd six months bi-monthly: a maximum of 10 doses. In the laser-aflibercept arm for the 1st three months of rescue aflibercept it monthly and for the 2nd three months it was bi-monthly. Therefore, the benefits of 2nd line rescue aflibercept in the laser-aflibercept arm may have been underestimated compared to the benefits of 1st line aflibercept in the aflibercept-laser arm due to:
  - Dosing for the first six months of 2nd line rescue aflibercept being less than for the first six months of 1st line aflibercept.
  - There being no second six months dosing of 2nd line rescue aflibercept compared to there being a second six months dosing of 1st line aflibercept.
- The results from the R MSM derived TPMs not being aligned with that of the shift tables approach for the comparison of aflibercept-laser with laser-aflibercept. In the opinion of the ERG, this argues for using either the shift tables approach or TPMs based upon patient count data as have been used in previous NICE technology assessments in visual disorders.
- The six month odds ratios of the NMA applying to 1st line treatments, but the model necessarily applies them to 2nd line rescue treatments.
- The six month odds ratios being applied to 4-weekly TPMs. These are then compounded seven times. This appears to exaggerate the differences between the treatments. This exaggeration increases the more the odds ratio differs from one, so is particularly serious for the comparison with dexamethasone. This may largely invalidate these comparisons. In the opinion of the ERG, this

argues for applying a single six month TPM for rescue aflibercept in the laser-aflibercept arm, applying the odds ratios to this and making some simple interpolation for the cycles between month six and month 12 of the model.

- The company model not adjusting dosing for cross-over to rescue therapy within the model or for discontinuations. The ERG has attempted to correct the model for this, but given the model structure it is difficult to do so reliably. This also needs to take into account the discontinuation rates, the modelled rates not being obviously aligned with anything in the clinical effectiveness section.
- The company not reporting the results of its expert survey for dosing and monitoring for years 6+ of the model. The RETAIN trial suggests that there is a requirement for ongoing anti-VEGF dosing, among perhaps as many as half the patient population.
- The probabilistic modelling typically suggesting cost estimates, which are somewhat lower than those of the deterministic estimates. This applies strongly in the aflibercept-laser arm, still quite strongly in the laser-aflibercept arm but less strongly in the laser-ranibizumab arm and the laser-dexamethasone arm. Consequently, the probabilistic modelling improves the cost effectiveness estimates. The reasons for this are not intuitive, and the ERG has not identified why this occurs.
- The probabilistic modelling has not implemented the main clinical inputs to the model, the TPMs and shift tables, probabilistically. This is due to the company being unaware of any method to do so for R MSM derived TPMs or for the shift tables. In the opinion of the ERG, this suggests using TPMs derived from patient count data as have been used in previous NICE technology assessments for visual conditions, for which there are well established sampling methods.

Uncertainties within the economic model and the modelling are:

- A complicated model structure that is difficult to reliably correct and to amend to incorporate other elements.
- The model cycle length flips between 52/13 weeks and 52/12 weeks with the model elements appearing to not be entirely lined up between the two.

- Whether there would be any difference in dosing between aflibercept and ranibizumab.
- What proportion of patients requires ongoing dosing with anti-VEGFs, at what dose and for how long.
- What proportion of patients requires ongoing dosing with dexamethasone, at what dose and for how long.
- What the most appropriate source for quality of life values is and whether there is a general over-reliance upon the experimental lenses study of Czoski-Murray.
- What the quality of life impact of a loss in BCVA in the worse seeing eye is compared to the quality of life impact of the same loss in BCVA in the better seeing eye.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG has revised the model in a number of ways, a full account of which is given in section 5.4 in Chapter 5. The main changes made by the ERG are:

- Revise dosing to take into account cross-over and discontinuations. Note that the dosing for dexamethasone has not been revised by the ERG due to time constraints.
- Apply the shift tables for the comparison of aflibercept-laser with laser-aflibercept.
- Assume additional ongoing anti-VEGF dosing of 3.2 per year for five years for 30% of the patient population for the base case for the comparison of aflibercept-laser and laser aflibercept. Due to a lack of data for dexamethasone, this is only included as a sensitivity analysis for the comparison of laser-aflibercept with laser-ranibizumab.
- Include SAEs for fellow eyes involvement, with it being assumed that all fellow eye involvement is treated.
- Assume quarterly monitoring for laser during the first year.

For the comparison of aflibercept-laser with laser-aflibercept this results in net costs of [redacted] and a net gain of [redacted] QALYs, so a cost effectiveness estimate of £27,259 per QALY.

Applying the R MSM TPMs rather than the shift tables improves the cost effectiveness estimate to £23,847 per QALY.

Assuming that the WSE QoL impact is 15% that of the BSE worsens the cost effectiveness estimate to £31,581 per QALY, while an assumption of 43% improves it to £24,891 per QALY. The other possible sources for quality of life values worsen the cost effectiveness estimates to be above £30k per QALY.

Assuming that all BRVO has resolved by year six with no further treatments being required improves the cost effectiveness estimate to £16,801 per QALY, while

assuming that the ongoing treatment is required for 10 years worsens the cost effectiveness estimate to £31,624 per QALY.

For the comparison of laser-aflibercept with laser-ranibizumab, net savings of [redacted] are estimated. In all that follows, it should be borne in mind that these analyses include the price discount available through the aflibercept patient access scheme but not the price discount available through the ranibizumab patient access scheme. The odds ratio of 0.93 for gaining letters also causes laser-aflibercept to be estimated to be superior, yielding a net [redacted] QALYs. As a consequence, laser-aflibercept is estimated to dominate laser-ranibizumab.

Applying the eight studies NMA odds ratio for gaining letters of 1.08 causes laser-ranibizumab to be clinically superior to laser-aflibercept, with a gain of [redacted] QALYs. Nonetheless, laser-ranibizumab still costs substantially more and the cost effectiveness of laser-ranibizumab compared to laser-aflibercept is estimated to be £204k per QALY.

The alternative sources of quality of life estimates tend to reduce the gain from laser-aflibercept over laser-ranibizumab but as it is still cost saving it remains dominant.

Assuming that 30% of patients remain unresolved at six years with a need for ongoing dosing with anti-VEGFs increases the cost savings associated with laser-aflibercept and so it remains dominant over laser-ranibizumab. This is not altered by assuming that ranibizumab requires 1 fewer injections than aflibercept during the first year of treatment.

For the comparison of laser-aflibercept with laser-dexamethasone, net costs of [redacted] are balanced by net gains of [redacted] QALYs resulting in a cost effectiveness estimate of £18,542 per QALY.

Applying the eight studies NMA odds ratio for gaining letters of 0.40 reduces the net gain to [redacted] QALYs and so worsens the cost effectiveness estimate to £20,969 per QALY. The VIBRANT EQ-5D data also somewhat reduce the net gain, pushing the cost effectiveness estimate to over £30k per QALY.

The VIBRANT trial assumed LOCF for drop-outs. The drop-out rate was quite high. Any tendency for drop-outs to rebound to baseline might worsen the clinical and cost effectiveness estimates for aflibercept-laser compared with laser-aflibercept. Whether it is reasonable to conduct a scenario analysis of rebound to baseline is debatable.

The VIBRANT trial dosing for 1st line aflibercept in the aflibercept-laser arm was both more frequent and of longer duration than for 2nd line rescue aflibercept in the laser-aflibercept arm. The full clinical benefits of rescue aflibercept may not have been realised in the laser-aflibercept arm. This may have depressed the clinical effectiveness estimate in the laser-aflibercept arm to below what would be realised in clinical practice.

7 Overall conclusions

The current submission focuses on a phase III RCT, VIBRANT, sponsored by the company (Bayer Pharma), which compared aflibercept 2mg (91 participants) with grid laser photocoagulation (90 participants). No other head-to-head trials assessing aflibercept versus ranibizumab or dexamethasone intravitreal implant were identified. The company conducted a systematic review of the literature review to identify RCTs investigating the efficacy and safety of aflibercept versus other active treatments in adults with visual impairment due to BRVO in order to conduct an indirect comparison. Nine eligible studies were deemed suitable for inclusion. The company, after assessment of heterogeneity, excluded five of these nine studies. The four remaining studies were included in the base case network meta-analysis. The excluded studies were included in sensitivity analyses.

The primary outcome in VIBRANT was the proportion of patients gaining ≥15 letters from baseline to week 24 in BCVA. Secondary and additional efficacy outcomes included the change from baseline in BCVA score at week 24, the change from baseline in central retinal thickness, perfusion status, retinal ischaemia and the retinal fluid status. Aflibercept was shown to be superior to laser photocoagulation with higher proportions of participants achieving these outcomes (see Table 10 ‘Summary of the results of the VIBRANT study’ in Chapter 4). The results of a number of subgroup analyses were consistent with the results of the overall trial population.

With the exception of injection-related TEAEs, which were higher in participants receiving aflibercept, the incidence of ocular and non-ocular TEAEs was balanced across intervention groups.

The results of the NMA suggested that aflibercept had similar performance to ranibizumab when considering the proportion gaining at least 15 BCVA letters and that aflibercept performed favourably when compared with dexamethasone.

The company’s systematic review of clinical evidence was generally well-conducted and used appropriate methodology. There were some concerns, however, about the

transparency of the assumptions used, including the exclusion of five studies from the base-case results due to clinical heterogeneity.

With regard to the cost-effectiveness analyses, the main differences of opinion between the company and the ERG are whether:

- Bevacizumab should have been considered.
- The TPMs should be based upon individual patient count data as in previous NICE assessments in visual disorders.
- Six month odds ratios should be applied to four-weekly TPMs. If not, this largely invalidates the comparisons with laser-ranibizumab and laser-dexamethasone.
- Dosing inputs to the model should be adjusted for cross-over and discontinuations.
- Some BRVO will not have resolved by year six resulting in further ongoing treatment.
- The probabilistic modelling should implement the main clinical inputs from VIBRANT probabilistically.

The main uncertainties within the economics and the modelling are:

- Whether there would be any difference in dosing between aflibercept and ranibizumab.
- What proportion of patients requires ongoing dosing with anti-VEGFs, at what dose and for how long.
- What proportion of patients requires ongoing dosing with dexamethasone, at what dose and for how long.
- What the most appropriate source for quality of life values is and whether there is a general over-reliance upon the experimental lenses study of Czoski-Murray.
- What the quality of life impact of a loss in BCVA in the worse seeing eye is compared to the quality of life impact of the same loss in BCVA in the better seeing eye.

Elements that were uncertain and that the ERG could not quantify are:

- The VIBRANT trial assumed LOCF for drop-outs. The drop-out rate was quite high. Any tendency for drop-outs to rebound to baseline might worsen the clinical and cost effectiveness estimates for aflibercept-laser compared to laser-aflibercept. Whether it is reasonable to conduct a scenario analysis of rebound to baseline is debatable.
- The VIBRANT trial dosing for 1st line aflibercept in the aflibercept-laser arm was both more frequent and of longer duration than for 2nd line rescue aflibercept in the laser-aflibercept arm. The full clinical benefits of rescue aflibercept may not have been realised in the laser-aflibercept arm. This may have depressed the clinical effectiveness estimate in the laser-aflibercept arm to below what would be realised in clinical practice.

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 the clinical effectiveness of these treatments and would inform cost-effectiveness.

Future RCTs should include primary and secondary outcomes measured at longer-term time points (6 months is insufficient especially considering that many patients still require anti-VEGF treatment 3 and 4 years after initiation) and should evaluate efficacy and cost-effectiveness of treatments in patients with or without macular/foveal ischaemia. Comparisons with laser photocoagulation would still be pertinent, especially new forms of laser such as subthreshold micropulse laser.

Future clinical trials should evaluate efficacy and cost-effectiveness of new treatments compared with laser photocoagulation based on CRT because, in thinner retinas (i.e. less than 400 micrometres), as demonstrated by the TA346 on aflibercept for treating diabetic macular oedema, laser treatment may be a more cost-effective alternative.

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Appendices

Appendix 1 Long term follow-up of anti-VEGF treatment

MEDLINE Search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 22nd March 2016 >

Search Strategy:

1	Retinal Vein Occlusion/ (3242)
2	retinal vein occlusion.ti,kw. (2261)
3	1 or 2 (3682)
4	Vascular Endothelial Growth Factor A/ai [Antagonists & Inhibitors] (5611)
5	anti vegf.ti. (667)
6	ranibizumab.ti,rn,sh. (2288)
7	bevacizumab.ti,rn,sh. (8972)
8	(aflibercept or eyelea).ti,rn. (541)
9	(avastin or lucentis).ti. (537)
10	or/4-9 (13555)
11	3 and 10 (491)
12	follow up studies/ (537769)
13	follow up.tw, (698352)
14	long term.tw. (590979)
15	12 or 13 or 14 (1447981)
16	11 and 15 (222)

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 21 April 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 **Inclusion of the nine identified studies in the network meta-analysis (page 9)**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 9, 62, 66 In the base case efficacy comparison four studies were included in a network meta-analysis. Five studies were excluded from the basecase network as they were considered to have clinically relevant between-study heterogeneity that could bias the comparison. It is commented in the ERG report that Bayer could have attempted to fully explore the impact of other results in sensitivity analyses, including those of the full network of eligible studies, which were often less favourable to aflibercept but with overlapping credible intervals.	Please remove the statements indicating that the suggested analyses were not conducted and that the inclusion of all nine studies was not explored.	The ERG report actually presents the results of the analyses which it says are missing (page 97 first bullet of the ERG report). There was a variation from the NICE template that might explain the confusion. According to the template, scenario analyses should be presented in sections 5.8.8 and 5.8.9. In the submission scenario analyses were presented in section 5.9.3 – we apologise for this incorrect deviation from the template. The NMA sensitivity analyses were presented in table 38 of the submission whereby the 5 excluded studies were included in the evidence network. The analysis showed that there was no evidence of a difference between aflibercept and ranibizumab in all sensitivity analyses conducted, however, whether the median OR point estimate favoured aflibercept (OR<1) or ranibizumab (OR >1) was dependent on the inclusion/exclusion of the RABAMES study. The OR most in favour of ranibizumab (least in favour of aflibercept) was used in a cost-effectiveness scenario analysis - see table 120 and table 121 and figures 67-70 of the submission. The results indicate that in the comparison exploring aflibercept first-line versus laser followed by ranibizumab, aflibercept as a first-line treatment option remained cost-effective (ICER £9,632).	The ERG acknowledges that the scenario analyses in section 5.9.3 including all trials were missed, but agrees with the company that it would have been clearer if these results had been mentioned at an earlier point within the submission. It remains the opinion of the ERG, however, that these analyses could have been used as the base-case results, or that the implications of using these results in the cost-effectiveness analyses could have been given much higher prominence within the report. The ERG statements indicating that the suggested analyses were not conducted and that the inclusion of all nine studies was not explored have now been removed (see Erratum document).

		The results of the comparison comparing aflibercept and ranibizumab, both as second-line treatment options, showed that the cost-effectiveness result was very sensitive to the point estimate of relative efficacy. In this scenario aflibercept changed from being less costly and more effective (basecase) to less costly and less effective i.e. in the southeast quadrant of the cost-effectiveness plane.	

Issue 2 **Application of the OR to each monthly transition matrix**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 7, 98, 111-114, 135, 136, 142 The ERG comments that the six-month odds ratio [from the network meta-analysis] is applied to the four-weekly transition probability matrices and that as this is	Remove any references to the application of the OR to each cycle being incorrect and exaggerating the differences between treatments	The MSM package works by fitting transition probabilities to the entire dataset and then outputting transition matrices corresponding to the chosen cycle length, in this case 4-weekly. Had a different cycle length been chosen the transition matrices generated from the MSM would have been automatically adjusted accordingly by the MSM package. From the calculations on page 111-114 it appears as if the ERG has applied the odds ratio directly to the transition probabilities which is not correct and has led to the erroneous conclusion of 'compounding'. To generate comparator transition matrices using the odds ratio and VIBRANT data we applied the log odds ratios to the log odds associated with each transition and then back transformed to the natural scale to get treatment specific transition matrices (a full description of the method is in section 5.3.2.3.1of the submission). In order to demonstrate that no 'compounding' has taken place and no advantage conferred on aflibercept we have generated a 6-month transition matrix for the second 6 months of the model (as suggested by the ERG) for aflibercept, ranibizumab and dexamethasone. We have then compared the distribution of the study eyes across the 5 VA health states when using this	No factual error identified. No revision required. The ERG cannot check the data, which underlies Table 1, that the company has presented at error check. The issue is also not about the R MSM derived 4-weekly TPMs for rescue aflibercept in the

done for each 4-weekly cycle it exaggerates ('compounds') the differences between the treatments and may largely invalidate the comparisons with laser-ranibizumab and laser-dexamethasone.

The ERG comments that this argues for six month TPMs being used for the second 6 months of the first year of the model.

We believe there has been some confusion concerning how the transition matrices for comparator treatments were calculated and that the ERG conclusions are not correct.

6-month matrix with the distribution using the 4-weeky transition matrices as used in the submission. The tables below show the distribution of patients at 52 week (i.e. cycle 13).

As can be seen the distribution of patients when applying the OR to the 6-month VIBRANT transition matrices is virtually identical to the distribution when using 4-weekly transitions as per the submission.

Please note that the distribution of patients across the 5 visual acuity health states at cycle 13 does not sum to 1. This is because the starting point for this analysis was 6 months and included only those patients who had switched to a second-line treatment and who had not discontinued or died – see the Markov trace tab in the Excel model Y118:AC118 (uploaded separately in order for the ERG to be able to verify the results. Please note that in order to verify the results the user needs to select 'MSM' in the executive summary tab as the source of efficacy for both aflibercept and comparator treatment).

We also request that the ERG consider the results of the scenario analysis (section 5.9.3.1 of the submission) in which aflibercept and ranibizumab are considered to be of equivalent efficacy. By definition, in an assumption of equivalent efficacy there is no advantage for either treatment other than attributed to position in the treatment pathway (first or second-line) and differences in cost. In this scenario the ICER for aflibercept first-line versus laser followed by ranibizumab was £9,259 and for 'laser followed by aflibercept' versus 'laser followed by ranibizumab' there were cost-savings attributed to the aflibercept arm (see tables 118 and 119 of the submission).

Table 1. 13th cycle patient distribution using 4-weekly versus 6-monthly transition matrices

	VA1	VA 2	VA 3	VA 4	VA 5
Aflibercept patient distribution at cycle 13 (study eye)					
6 month TPs	0.1421	0.2927	0.0929	0.0099	0.0216
4 week TPs	0.1421	0.2927	0.0929	0.0099	0.0216

laser-aflibercept arm. The ERG does not question these TPMs and accepts that they are 4-weekly TPMs.

Within the *Transition_Mix* worksheet the odds ratios are applied to 4-weekly aflibercept TPMs: e.g. the odds ratio between cell D37 and cell N37 is 0.93. Cell D37 and cell N37 are 4-weekly probabilities within 4-weekly TPMs. As far as the ERG can ascertain these are applied 7 times within the model, being within cells AB29:AF33 of the TPMs of cells AB29:AR45 of the relevant Markov worksheets.

In order to derive the 4-weekly TPMs for ranibizumab and dexamethasone the odds ratios are applied as per the company method,

Difference	*0.0000*	*0.0000*	*0.0000*	*0.0000*	*0.0000*
Ranibizumab patient distributions at cycle 13 (study eye)					
6 month TPs	0.1363	0.2925	0.0968	0.0115	0.0222
4 week TPs	0.1345	0.2936	0.0981	0.0110	0.0221
Difference	*0.0018*	*-0.0011*	*-0.0012*	*0.0005*	*0.0000*
Dexamethasone patient distributions at cycle 13 (study eye)					
6 month TPs	0.0772	0.2818	0.1439	0.0289	0.0274
4 week TPs	0.0619	0.2771	0.1619	0.0310	0.0273
Difference	*0.0153*	*0.0047*	*-0.0180*	*-0.0021*	*0.0001*

which results in the TPMs of Table 18 of the ERG report. It is these 4-weekly TPMs of Table 18 that the ERG has compounded 7 times to arrive at the TPMs of Tables 48 and 49 of the ERG report, while the TPM of table 47 is derived by compounding the rescue aflibercept TPM of Table 17 of the ERG report.

The company avoids addressing the central point of what the implied 6 month odds ratios are from the repeated (7 times) application of the TPMs of cells C37:H42 and cells M37:R42. This is presented in a clear fashion in Tables 46 to 50 of the ERG report. The company is familiar with matrix multiplication but does not contradict the derivation of Table 50.

			The ERG is open to the company providing further evidence that Table 50 of the ERG report is incorrect or that the ERG has incorrectly assumed that the probabilities of the TPMs of the *Transition_Mix* worksheet e.g. cells D37 and N37 are applied 7 times within the model. This requires that the company cross check that the derivation of Tables 47 to 49 of the ERG report; i.e. does applying these TPMs to any patient distribution result in the same patient distribution as applying the TPMs of Tables 17 and 18 seven times. And if Tables 47 to 49 are correct whether they imply the ORs of Table 50 of the ERG report.

Issue 3 **Incorporating uncertainty in the aflibercept first-line versus laser followed by aflibercept comparison.**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 7, 72 The comments from the ERG in relation to PSA and uncertainty in efficacy read as though no PSA comparisons have incorporated uncertainty in efficacy. However, only <u>one</u> comparison did not incorporate uncertainty in efficacy i.e. aflibercept first-line versus laser followed by aflibercept. This analysis used the actual transitions observed from the VIBRANT trial.	Inclusion of the PSA results incorporating uncertainty in efficacy for the aflibercept first-line versus laser followed by aflibercept analysis.	In the PSA's for the comparisons against ranibizumab and dexamethasone uncertainty in efficacy was incorporated by applying a distribution to the ORs for achieving ≥15 letters from baseline. Sampling from the OR distribution improved/worsened the transition probability matrices for the comparator treatments relative to aflibercept – see table 92 of the submission and section 5.9.2 of the submission. As the ERG states, methods for sampling from patient count data are available and we could have used these methods to incorporate uncertainty into the efficacy in the aflibercept first versus laser followed by aflibercept comparison. We have now conducted this analysis. The actual distribution of patients between health states (shift tables) were used as the basis for the analysis. The Dirichlet distribution, as suggested by Briggs et al (1), has been used in order to incorporate uncertainty in efficacy for both laser and aflibercept. All other uncertainty was as per the submission. The Dirichlet distribution (multivariate generalisation of the beta distribution) was used with parameters set to equal the number of categories in the multinomial distribution (i.e. 25). The results are presented in table 2 below with table 3 (table 128 from the submission) included for comparison. Also included is the scatterplot and CEAC curve. The PSA estimate of cost-effectiveness is in line with the PSA results for the other comparisons with the estimate being slightly, but not meaningfully more favourable than the deterministic result. In order for the ERG to verify the results the economic model has been uploaded separately (please note that to run the analysis the source of efficacy needs to be selected as 'shift tables' from the executive summary tab for both treatments).	No error identified. No revision required. It is incorrect to state that only one comparison did not incorporate uncertainty in efficacy. All comparisons of 2nd line rescue treatments do not either despite the ORs being implemented probabilistically. The company acknowledged this at clarification stating that "*In terms of the MSM package we are not aware of any methods to test the transition matrices for aflibercept and laser probabilistically*". These transition matrices are the main clinical input for these comparisons.

Table 2. Probabilistic results: comparison 1c – aflibercept first-line versus laser followed by aflibercept (using shift tables)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.713	[redacted]				
LSR followed by AFL	[redacted]	13.709	[redacted]	[redacted]	0.0043	[redacted]	17,492

Table 3. Deterministic results: comparison 1c – aflibercept first-line versus laser followed by aflibercept (shift tables)

Technologies	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£)
AFL first-line	[redacted]	13.716	[redacted]				
LSR followed by AFL	[redacted]	13.712	[redacted]	[redacted]	0.0043	[redacted]	17,976

Figure 1. Scatterplot: comparison 1c – aflibercept first-line versus laser followed by aflibercept (shift tables)

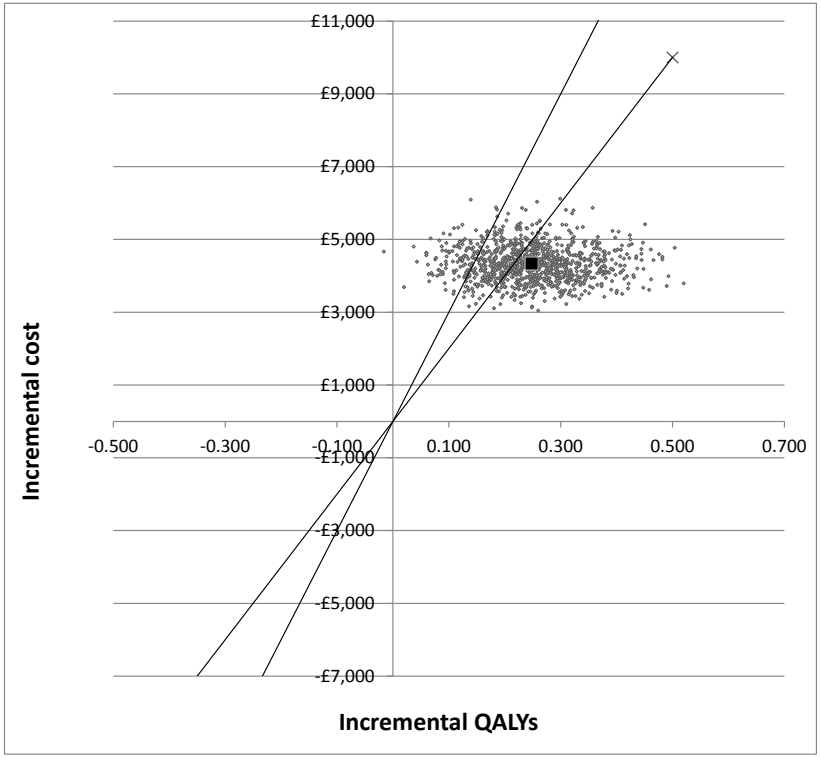
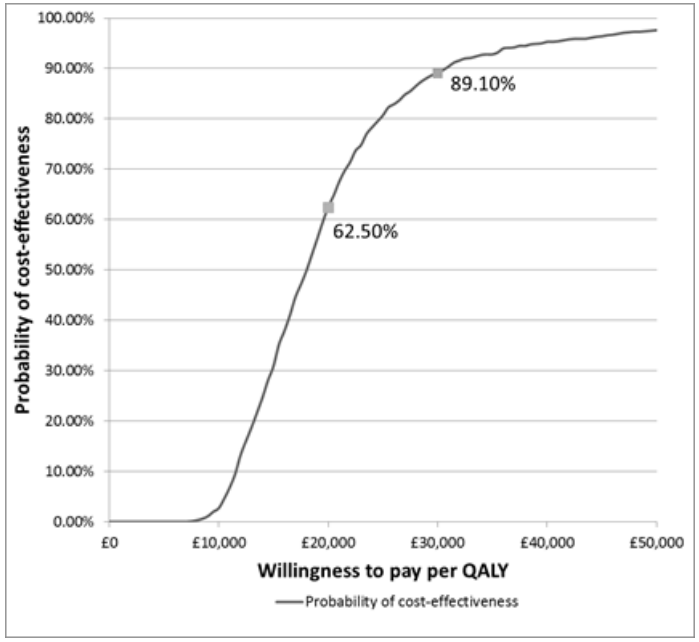


Figure 2. CEAC: comparison 1c – aflibercept first-line versus laser followed by aflibercept



1) Briggs A. Decision modelling for health economic evaluation. 1st ed. USA: Oxford University Press; 2006.

Issue 4 **Reference to the RESONATE study**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 85, 107-110 References to a trial named RESONATE throughout the submission whereas no such trial has been presented	Please check that a direct swap of 'RESONATE' to 'VIBRANT' can be made throughout the report.	The pivotal trial presented in the submission for aflibercept was the VIBRANT study and no information on a trial named RESONATE has been presented. It appears that references to RESONATE should be references to VIBRANT.	The company is correct that all references to RESONATE should be to VIBRANT. References to RESONATE have now been checked and corrected throughout the report (see Erratum document).

Issue 5 **Results of the physician survey for the combined time period of year 6+ were not presented in the submission**

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>Page 7

One of the ERGs listed main concerns was that the results of the physician survey for the year 6+ time frame were not presented.</td>
<td>None proposed. We have provided the information for transparency</td>
<td>The statement is correct as the physician survey results for the combined time period of year 6+ were not presented. We acknowledge that there was a lack of transparency in these results not being available in the submission. The decision was made that the information for years 1-5 from the survey were the most reliable as ranibizumab had been available for coming up to five years at the time of the survey. Consequently there was no actual experience on the use of anti-VEGF treatments beyond this timepoint.

The year 6+ annual treatment/monitoring results from the physician survey are shown in table 4

Table 4.
<table>
<tr><th></th><th>Estimated average number of injections/laser procedures, per affected eye, per patient</th><th>Estimated average number of monitoring visits, per affected eye, per patient</th></tr>
<tr><td>Aflibercept</td><td>0.15</td><td>0.6</td></tr>
<tr><td>Ranibizumab</td><td>0.18</td><td>0.79</td></tr>
<tr><td>Laser</td><td>0.03</td><td>0.56</td></tr>
</table>
</td>
<td>No error identified. No revision required.</td>
</tr>
</table>

		<table><tr><td>Dexamethasone</td><td>0.07</td><td>0.63</td></tr></table> Given the possibility that a small number of patients might require injections beyond year 6 a sensitivity analysis, as conducted by the ERG is appropriate. However, we consider that the sensitivity analysis conducted by the ERG might better reflect treatment in years 6+ if some changes were made (see issue 6).	

Issue 6 **The ERGs assumption of 30% of patients requiring 3.2 injections each year from year 6 – year 10 (page 9)**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9, 128, 129 Based on data from the RETAIN study, the ERG have assumed that 30% of patients may require an additional 3.2 injections for each of the years 6 to 10. This injection rate is too high and actually represents an increase in treatment rate relative to year 5. Also, a decreasing injection requirement over time has not been	Revision of the analysis to incorporate • a reduced rate of injections relative to year 5 rather than an increase • resolution of BRVO in years 6-10 and therefore a decreasing need for injections in each year relative to the year before	The physician survey indicated a decreasing need for injections over time (table 80 of the submission). In addition, the RETAIN study shows a decreasing need for injections over the duration of the study. Assuming 30% of patients require a continuous and ongoing 3.2 injections per year for each of the years 6 to 10 does not account for ongoing resolution in this patient group. The physician survey estimated an average rate of injections of 0.58 (for ranibizumab) in year 5. Using an assumption of 30% requiring 3.2 injections represents an average of 0.96 injections which is actually an increase from year	No error identified. No revision required. The ERG report is explicit about the difficulty of incorporating the year 6+ dosing within the submitted model. This is because the placeholder for this in the submitted company model is not operative. This greatly limits the analyses that the ERG can undertake with the ERG report stating on page 104 "*The ERG is aware that this modelling is imperfect. However, considering the submitted model structure, it is all that could feasibly be done*". The ERG cannot revise the model to

considered. In addition, we are not sure if the ERG intended to only apply the costs of extra injections without also incorporating the benefit of added injections i.e. maintenance of stable vision in their analyses. Physicians would only continue to monitor and treat if there was a benefit to doing so. Given the above we consider that the analysis conducted by the ERG over-presents the costs and does not capture the benefits of treatment beyond year 6.	• the benefit of treatment i.e. stable vision from years 6-10 if treatment continues to be given.	5 as estimated from the physician survey. The RETAIN study (n=34) is biased in that patients who were less were those who were most likely to stay in the study. The paper states that "…in general, patients did not leave the trial early because they were doing poorly, but rather because they were no longer receiving injections…". We believe that the proportion of patients who might require further treatment is therefor likely to be an overestimate. In the economic analysis presented in the submission an assumption of stable vision was used whilst the population was still being monitored and treated as needed. Physicians would only continue to monitor and treat if there was a benefit to doing so. If monitoring and treatment is continuing beyond year 5 as suggested by the ERG it is reasonable to assume the aim of this treatment would be to maintain vision. It would seem appropriate therefore, in any sensitivity analysis extending treatment beyond year 5, to match treatment with a continuation of efficacy i.e. stable vision.	incorporate stable visual acuity. However, if stable visual acuity were also assumed for rescue aflibercept and rescue ranibizumab, and perhaps also among those receiving 1st line laser, who did not require 2nd line rescue anti-VEGF, the impact of this is likely to be muted. The 3.2 dosing is higher than the year 5 figure and indeed the year 3 and year 4 figure of the company's expert survey. Given that these are real world data from RETAIN, this argues for an additional sensitivity analysis that increases the anti-VEGF dosing in years 3, 4 and 5. The ERG will prepare additional sensitivity analyses around this for the AC meeting. Note that the modelled proportion requiring treatments is conditioned by the company estimates for discontinuation rates, so the proportion on treatment continues to decline.

Issue 7 ERGs 'correction' to the number of injections in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 107-110 The ERG presents calculations showing the	Could the ERG check that the 'corrections' have been applied equally to both arms of the ERG	We took a standard approach to the implementation of treatment i.e. the total treatment for a period of time was divided across the cycles. However, reviewing the ERG calculations we agree that this approach has led to an underestimation of	No error identified. No revision required. The main concern is around the

<table>
<tr>
<td>model estimates slightly fewer treatments in comparison to the VIBRANT study.

We agree that the model estimates slightly fewer treatments relative to the VIBRANT trial but this underestimation is evident for both treatment arms.

We have tried to follow what the ERG have done based on the ERG report and the ERG model, in order to understand the impact on the ICER. On review of the ERG model we think that the ‘corrections’ outlined in the ERG report have not been applied equally to both arms for years 2-5 of the model.

Using the description of the ‘correction’ in the ERG report we have implemented the changes in the model (to both arms), to the best of our understanding and can only see a relatively small impact on the</td>
<td>model. If, as we suspect the impact on the ICER is relatively small we would ask that consideration be given to whether this should be listed as a main concern.</td>
<td>the number of treatments in both arms.

Using the results from the ERGs calculations from tables 44 and 45 of the ERG report it is evident that the model underestimates treatment with aflibercept equally in both arms (see table 5). There is a small overestimation of laser treatment in the aflibercept to laser arm and overestimate in the laser to aflibercept arm. To understand the impact of the ERG ‘corrections’ we have implemented them (for both arms), to the best of our understanding, according to the description in the ERG report. Our results are presented in table 6. As far as we can see there is a relatively small effect on the ICER.

Table 5.
<table><tr><th></th><th colspan="2">Aflibercept to laser</th><th colspan="2">Laser to aflibercept</th></tr><tr><th></th><th>AFL</th><th>Laser</th><th>Laser</th><th>AFL</th></tr><tr><td>Treatment as per VIBRANT (table 44 of ERG report)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>As per model (table 45 of ERG report</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Difference</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td>
<td>year 1 dosing, but there remain concerns around the year 2-5 dosing. This is a main structural concern as it means that any changes to discontinuation rates within the model require dosing inputs to be adjusted. The derivation of the company inputs for discontinuation rates within the model remains unclear.</td>
</tr>
</table>

ICERs. Our concern is that this being described as a main concern might be overstating its impact.

Table 6.

Comparison	Submitted ICER	ICER using ERG revisions of dosing	Difference
1a- aflibercept 1st line versus laser followed by ranibizumab	£8,939	£8,351	-£588
1c- aflibercept 1st line versus laser followed by aflibercept	£15,365	£15,570	+£205
2a- laser followed by aflibercept versus laser followed by ranibizumab	Dominant	Dominant	NA

Aberdeen HTA Group

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

Erratum

Completed 01 May 2016

This report was commissioned by
the NIHR HTA Programme as
project number **15/64/13**.

Contains CIC/AIC

This document is intended to replace pages 9, 62, 66, 85, 107, 108, 110, 117, 123, and 124 of the original ERG assessment report for *Aflibercept for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion*, which contained a few minor inaccuracies. On pages 9, 62 and 66 we have deleted an ERG's comment that was not correct and on the remaining pages we have amended a wrong reference to an included trial.

The amended pages follow in order of page number below.

Only one odds ratio from the clinical effectiveness section, with a point estimate favouring aflibercept over ranibizumab, was used in the cost-effectiveness results.

With regard to the cost-effectiveness evidence, weaknesses and areas of uncertainty have been summarised in section 1.5 above.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has revised the model in a number of ways, a full account of which is given in Chapter 5, section 5.4, below. The main changes made by the ERG are:

- Revise dosing to take into account cross-over and discontinuations. Note that the dosing for dexamethasone has not been revised by the ERG due to time constraints.
- Apply the shift tables for the comparison of aflibercept-laser with laser-aflibercept.
- Assume additional ongoing anti-VEGF dosing of 3.2 per year for five years for 30% of the patient population for the base case for the comparison of aflibercept-laser and laser aflibercept. Due to a lack of data for dexamethasone, this is only included as a sensitivity analysis for the comparison of laser-aflibercept with laser-ranibizumab.
- Include SAEs for fellow eyes involvement, with it being assumed that all fellow eye involvement is treated.
- Assume quarterly monitoring for laser during the first year.

For the comparison of aflibercept-laser with laser-aflibercept this results in net costs of [redacted] and a net gain of [redacted] QALYs, so a cost effectiveness estimate of £27,259 per QALY.

Applying the R MSM TPMs rather than the shift tables improves the cost effectiveness estimate to £23,847 per QALY.

source of data for the BRIGHTER study. The company confirmed that this was sourced from either the Novartis NMA or from an abstract by Mones.[57]

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

Nine eligible studies were identified but five were excluded from the base-case analyses because of their lack of similarity to VIBRANT. Of the four studies included in the base-case NMA, only one was available as a full text peer-reviewed publication while all five excluded

studies were available as full text peer-reviewed publications. Although the ERG agrees that these five excluded trials have important clinical differences compared to VIBRANT, they could have been considered eligible for inclusion according to the inclusion criteria specified in NICE's final scope. The ERG does, however, note that using the DIC statistic the NMA models including only four studies did seem to provide considerably better model fit than the full models.

The company's NMA used the recommended WinBUGS programs included in the NICE Decision Support Unit Technical Support Document 2 (DSU TSD 2). Results were only presented for two of the possible pairwise comparisons in the network: ranibizumab 0.5 mg versus aflibercept and dexamethasone versus aflibercept. Two other ranibizumab arms were included in the network (ranibizumab 0.5 mg plus laser and ranibizumab 0.3 mg plus laser) but no comparison with aflibercept was reported. The company presented results for both fixed and random effects models and using both mean and median as the summary statistic. Ninety-five percent credible intervals were provided.

The NMA was restricted to two outcomes and only analyses at six months were considered. This is reasonable given that after six months VIBRANT allowed aflibercept rescue treatment in the laser arm, but it means that data at 12 months, which suggested a more modest difference between aflibercept and laser, were not considered. Other studies within the network also allowed rescue treatment, but at variable time points.

4.6 Conclusions of the clinical effectiveness section

The ERG believes that the methods used in the systematic review and network meta-analysis (NMA) were generally appropriate and correctly applied. When conducting the NMA the company used the recommended WinBUGS programs from the NICE DSU TSD 2.

The principal concerns relate to the transparency of the assumptions used. The company excluded five studies from the review of clinical evidence. Although the ERG agrees that there is clinical heterogeneity between these studies and VIBRANT, the ERG is of the opinion that these studies meet the inclusion criteria specified in the NICE's final scope and a more transparent approach would have been to include these studies in the primary analyses. The reasons for exclusion did not appear to be pre-specified. Data for two of the four remaining studies were taken from a conference poster presented by a rival company. The ERG also noted that the four excluded studies were all of small sample size (<100 participants per treatment arm).

Apart from excluding some of the eligible studies, the company has also taken a number of other decisions: to use median instead of mean in the NMA, to use fixed effect rather than random effects models in the NMA, to use gaining ≥ 15 letters as the principal outcome measure and to use only data at 6 months. Although individually these decisions are reasonable and justifiable, the results used in the economic model had a point estimate favouring aflibercept over ranibizumab.

It is worth noting that if other assumptions had been made (as those made by Novartis),[58, 74] a point estimate favouring ranibizumab could have been obtained, although credible intervals were very wide with considerable overlap with the company's results.

blindness as shown by the minimal estimates for the costs of blindness. As a consequence, for modelling purposes, this may not be a particular concern.

When reviewing the QoL values, as will be outlined later, it should be borne in mind that the model only requires health states for the BSE in VA1 and in VA2. The VIBRANT EQ-5D data are also presumably largely limited to this. Hence, it makes little sense to examine the values extrapolated to the bilateral health states of VA5-VA5 as these are both largely outside the VIBRANT EQ-5D data and not applied within the model. Any sense check should concentrate upon the health states for the BSE in VA1 and in VA2.

Due to the VIBRANT EQ-5D data being panel data, it may make more sense to apply the random effects EQ-5D models. The company outlines that repeated measures were considered within this, with the subject being the random intercept, but that the OLS had a superior R^2. The R^2 appears virtually identical to the ERG, though, as the company also noted, the coefficients on BCVA of the BSE were significant for the OLS modelling but not for the random effects modelling.

Table 26 VIBRANT EQ-5D Random effects model coefficients

	Linear model		Log. model	
	coef	**p-value**	**coef**	**p-value**
Constant	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
BCVA BSE	[redacted]	[redacted]	[redacted]	[redacted]
BCVA WSE	[redacted]	[redacted]	[redacted]	[redacted]

For a 65 year old, this results in the following estimates.

Drop-out rates were quite high in both arms: 6 (7%) at 6 months and an additional 12 (13%) at 1 year to give a total of 18[a] (20%) in the aflibercept-laser arm and 9 (10%) at 6 months and an additional 6 (7%) at 1 year to give a total of 14[b] (16%) in the laser-aflibercept arm. It seems likely that many of these patients, and possibly the majority, will not have resolved when they drop out. Drop-outs were handled by using the Last Observation Carried Forward (LOCF) approach.

Since many, if not most, will not have resolved by the time they drop out there may be some unobserved rebound among these patients. Given the different immediate treatment effects and the different administration schedules, the size of this rebound may differ between the arms. There are reasons to believe that this rebound among drop outs may be bigger in the aflibercept-laser arm than in the laser-aflibercept arm, particularly among patients discontinuing before 6 months.

The results of Farinha et al[12] may, if anti-VEGF dosing was sub-optimal, provide support of an assumption of BCVA rebounding towards baseline among drop-outs.

While any rebound among drop-outs is unobservable, the drop-out rates may be a cause for concern when measuring relative treatment effects. The only immediately obvious alternative assumption to LOCF of rebound to baseline might have quite a large impact upon results and might have been worthwhile for the company to have explored.

Dosing: VIBRANT versus model

At clarification, the company provided the following number of treatment administrations for VIBRANT. These can be converted to the mean number of doses per patient. For simplicity, the ERG has simply divided them by the number of patients in the arm at baseline. Hence, the 2nd line treatment numbers appear too low when compared with, for example, the 4.40 doses of 2nd line rescue aflibercept since the denominator, for this 4.40 is the number of patients who received 2nd line rescue aflibercept.

[a] Note that one patient who dropped out had metastatic breast cancer while another had pelvic abscess and small bowel obstruction.

[b] Note that among the 14 one patient died.

Table 44 VIBRANT treatment administrations per patient year 1

	VIBRANT number of treatments				VIBRANT mean number of treatments			
	AFLI-LASE		LASE-AFLI		AFLI-LASE		LASE-AFLI	
	AFLI	LASE	LASE	AFLI	AFLI	LASE	LASE	AFLI
Week 0	91		90		1.00		1.00	
Week 4	[redacted]		[redacted]		[redacted]		[redacted]	
Week 8	[redacted]		[redacted]		[redacted]		[redacted]	
Week 12	[redacted]		[redacted]		[redacted]		[redacted]	
Week 16	[redacted]		[redacted]		[redacted]		[redacted]	
Week 20	[redacted]		[redacted]		[redacted]		[redacted]	
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The values in the electronic model are based upon the number on treatment multiplied by a month treatment rate: e.g. 9 / 12 = 0.75 for aflibercept. This is an area where the model and VIBRANT diverge, with VIBRANT having a 4 week treatment schedule and the model having a monthly treatment schedule[c] for costing purposes. The values reported below have been corrected for apparent errors in indexing.

[c] In other words in the *Markov-Aflibercept* worksheet the 9.00 injections of cell LE100 are spread out over the 12 cells of LE112:LE123

administrations into account would require the number of aflibercept administrations to only be increased to 9.60[d] to arrive at a year 1 total mean of 8.99 aflibercept treatments. This will be the default value for the revised ERG base case.

Similarly, to get the mean number of treatments to tally with the inputted mean values during the first year of the model requires that the number of 1st line laser administrations be set equal to 2.55.[e] This may seem a large increase but it should be borne in mind that the majority of patients in the laser-aflibercept arm received 2nd line rescue aflibercept. Thus, the model suggests that few patients remain in 1st line laser from the 6th month, but the number of 1st line laser administrations per cycle is averaged over the first 12 months of the model.

The numbers of 2nd line rescue laser, aflibercept and ranibizumab administrations also appear to need to be set equal to 0.3, 5.6 and 5.6.[f] The number of 2nd line rescue dexamethasone administrations differ as the value is not based upon trial values but is rather by assumption. The model average within the cohort flow appears to be broadly in line with that assumed.

Similar considerations apply to the subsequent years mean numbers of treatment due to discontinuations. The mean values that are inputted to the model are not the mean per prevalent patient at the start of the year. It can be argued that the year 2, 3, 4 and 5 aflibercept numbers of administrations should be increased in the model inputs from 4.15, 2.61, 1.12 and 0.58 to 4.40, 2.75, 1.20, 0.60. If so, the number of year 2, 3, 4 and 5 laser administrations should be correspondingly increased from 1.12, 0.36, 0.12 and 0.03 to 1.18, 0.38, 0.13 and 0.03.

The above dosing is specific to the company assumed discontinuation rates. Therefore, there should not be any sensitivity analyses around discontinuation rates without a parallel consideration of how dosing inputs should be revised to result in model averages that reflect the VIBRANT trial and additional assumptions.

[d] Implemented in the *Tx_Input* worksheet by setting cell G39=9.60.
[e] Implemented in the Tx_Input worksheet by setting cell G60=2.55.
[f] Implemented in the *Tx_Input* worksheet by setting cell G92=0.30, G81=5.60 and G50=5.60.

Table 51 HRQoL by BCVA in WSE for those with good vision in BSE: Brown et al 1999

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

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

The VIBRANT EQ-5D data appear to correspond reasonably to those of Brown et al above in the sense of most patients having a fairly good BCVA in their BSE. The BCVA of the BSE is typically in either VA1 or VA2, with it only being the BCVA of the WSE that drops below this.

To the extent that the EQ-5D analyses of the VIBRANT data are reliable, the coefficients on the BCVA of the WSE and the BCVA of the BSE of the linear models can be compared.

Table 52 VIBRANT EQ-5D QoL coefficients on BCVAs of WSE and BSE

	WSE	BSE
OLS	[redacted]	[redacted]
Fixed effects	[redacted]	[redacted]
Random effects	[redacted]	[redacted]

There is a reasonable congruence between the models in terms of the impact of the BSE upon QoL with a coefficient of around [redacted]. This may seem quite small when compared with the values available in the literature as reviewed by the ERG below.

lenses study may be too large. As a consequence, a sensitivity analysis that applies the rather crudely ERG derived ETDRS coefficient of -0.292 will be considered.

QoL: VIBRANT Tobit model

The company's argument largely centres on which VIBRANT EQ-5D model should be used on the basis of the R^2. It may be sensible to take into account other considerations, such as the repeated measures nature of the data. However, at clarification, the company supplied the R^2 values for the Tobit model. For both the linear modelling and the logarithmic modelling, while still low, these are superior to the other models, at [redacted] compared to [redacted] for the OLS model. The company was asked to supply the bilateral QoL functions for each model and largely did so, but did not do so for the Tobit model. As a consequence, the ERG has not explored this further.

QoL: additional data from VIBRANT and VIVID/VISTA

There are also the coefficients from the company analysis of the VIVID/VISTA EQ-5D data that the company submitted for the TA346 aflibercept for treating DMO. The OLS log(WSE BCVA) coefficient was [redacted] while that for the log(BSE BCVA) was [redacted]. Both were statistically significant. Patient BMI was also included in the DMO regressions, possibly as a proxy for the likelihood of the diabetes comorbidities, although these might also be expected to be correlated with BCVAs. The corresponding coefficients in the VIBRANT data are [redacted] and [redacted]. The coefficients are not identical, but there is some similarity.

Figure 7 Scatterplots of changes in BCVA and changes in EQ-5D QoL

The company has also supplied scatter plots of the change in the BCVA of the WSE against the change in the EQ-5D QoL and also of the change in the BCVA of the BSE against the change in the EQ-5D QoL, as below.

It seems likely that the above data define eyes as being the WSE or the BSE by their status at baseline. A reasonable proportion of study eyes, around [redacted], crossed over from being the WSE to being the BSE with this being most common in the aflibercept-laser arm at [redacted] This complicates interpretation of the above scatter plot, and the ERG should have formulated the clarification request to take cross over into account.

Nevertheless, there is no strong pattern of evidence for changes in QoL being a function of changes in the BCVA of the BSE, let alone a function of changes in the BCVA of the WSE, despite the regression coefficients on both the BCVA of the BSE and the BCVA of the WSE typically being statistically significant.

An aspect that is somewhat surprising is the number of patients estimated to lose vision in their BSE over the course of VIBRANT, albeit relatively few patients lose more than 10 letters. The general tendency for the majority of patients was to gain letters in their BSE. Unless the above takes into account cross over, it appears that the non-study eyes also typically gained visual acuity over the course of VIBRANT.

The ERG did ask the company to supply regressions of changes in EQ-5D QoL against changes in BCVA of the WSE and the BSE. The company replied that there was not enough time for addressing this request despite the required data sets being available as outlined in the scatter plots above.

Cycle length

There is a general inconsistency within the model as to whether the cycle length is four weeks, hence 52/13, or is a month of 52/12. The first year is typically taken to be 52/13 with subsequent years being 52/12. However, discounting assumes that the first year is based upon 52/12, which, in itself, has only a very marginal impact upon results.

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

Additional sensitivity analyses in light of the company's response to the factual accuracy check

Produced by Aberdeen HTA Group

Date completed 03 May 2016

Contains CIC/AIC

During factual accuracy check the company highlighted that the base case anti-VEGF dosing among those remaining on anti-VEGF treatment during years 3, 4 and 5 of 2.75, 1.20 and 0.60 injections is inconsistent with the 3.2 annual injections assumed by the ERG for those who are unresolved and remain on anti-VEGF treatment during years 6+.

The values for years 3, 4 and 5 are drawn from the company's expert survey. This asked respondents:

> *Please indicate in the table below the average number of treatments that you would typically administer per eye, per patient, per year, based on the patients with BRVO that you are currently treating and/or following-up.*

Since the average number of anti-VEGF injections is less than one in year 5, in the opinion of the ERG this may suggest that respondents have interpreted this average as being per the initially treated patient body as a whole rather than among those remaining on treatment at the start of the year. The values inputted to the model are the number of injections per patient remaining on treatment at the start of that year. This is a key element of the modelling that was not brought out in the ERG report, though it should be borne in mind that the values from the company's expert survey are averaged across respondents. But the above suggests that the values inputted to the model for those remaining on anti-VEGF treatment during years 3, 4 and 5 may be too low, even if the responses to the company's expert survey are the most appropriate values to use.

The 3.2 injections for those remaining on anti-VEGF therapy during years 6+ is drawn from RETAIN end of year 4 data. To align this real world data with the expert survey results, the model structure suggests that the annual number of anti-VEGF injections should not fall below that of the last inputted value, and for year 4 should not fall below 3.2 injections. The following dosing schedules for the anti-VEGFs are reasonable revisions to those of the original ERG report.

Table 1. Revised dosing schedule for anti-VEGFs given company error check

	Year 2	Year 3	Year 4	Year 5	Year 6+
As per ERG report Table 60	4.15	2.61	1.12	0.58	3.20
Revised ERG dosing	4.15	3.20	3.20	3.20	3.20
Revised ERG dosing for SA09	4.15	3.20	3.20	2.60	2.00

Applying these dosing schedules[a] revises the cost effectiveness estimates for aflibercept-laser compared with laser-aflibercept of Table 60 of the ERG report to be as follows.

Table 2. ICERs: Revised dosing for anti-VEGFs given company error check

	ΔCosts	ΔQALYs	ICER
Base case	[redacted]	[redacted]	£28,813
SA01: R MSM TPMs	[redacted]	[redacted]	£25,549
SA02: 8 study NMA	[redacted]	[redacted]	n.a.
SA03: 15% WSE QoL	[redacted]	[redacted]	£33,380
SA04: 43% WSE QoL	[redacted]	[redacted]	£26,309
SA05: Crude -0.292 Brown QoL	[redacted]	[redacted]	£36,631
SA06: VIBRANT EQ-5D OLS	[redacted]	[redacted]	£50,578
SA07: VIBRANT EQ-5D Rand. Eff.	[redacted]	[redacted]	£74,405
SA08a: No anti-VEGF yrs 6+	[redacted]	[redacted]	£18,355
SA08b: 5 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	n.a.
SA08c: 10 yrs anti-VEGF yrs 6+	[redacted]	[redacted]	£33,178
SA09: 2.0 per yr anti-VEGF yrs 6+	[redacted]	[redacted]	£24,709
SA10: Ranibizumab admin 1 less	[redacted]	[redacted]	n.a.
SA11: VA2 shift tables	[redacted]	[redacted]	£46,572
SA12: VA3, VA4 + VA5 shift tables	[redacted]	[redacted]	£25,005

As per previous analyses, the comparison of laser-aflibercept with laser ranibizumab is little affected by changes to the common anti-VEGF dosing assumptions. As a consequence, and due to time constraint, the ERG has not explored the revised dosing for this comparison or for the comparison with dexamethasone.

[a] Implemented in the *Tx_Input* worksheet by setting cells L52:L54=G83:G85=3.39, and for SA09 cells L54=G85=2.76.